JUSTIA

Amino acid sequences directed against envelope proteins of a virus and polypeptides comprising the same for the treatment of viral diseases

Jun 5, 2009 - Ablynx N.V.

The present invention relates in part to amino acid sequences that are directed against and/or that can specifically bind to an envelope protein of a virus, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences.

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Description

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. §371 of international application PCT/EP2009/056975, filed Jun. 5, 2009, which was published under PCT Article 21(2) in English, and claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application Ser. No. 61/059,055, filed Jun. 5, 2008, U.S. provisional application Ser. No. 61/092,991, filed Aug. 29, 2008, U.S. provisional application Ser. No. 61/139,130, filed Dec. 19, 2008, U.S. provisional application Ser. No. 61/144,653, filed Jan. 14, 2009, U.S. provisional application Ser. No. 61/172,914, filed Apr. 27, 2009, and U.S. provisional application Ser. No. 61/174,108, filed Apr. 30, 2009, the disclosures of which are incorporated by reference herein in their entireties.

FIELD OF THE INVENTION

The present invention relates to amino acid sequences that are directed against and/or that can specifically bind to an envelope protein of a virus, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences (also referred to herein as "amino acid sequences of the invention", "compounds of the invention", and "polypeptides of the invention", respectively).

The invention also relates to nucleic acids encoding such amino acid sequences and polypeptides (also referred to herein as "nucleic acids of the invention" or "nucleotide sequences of the invention"); to methods for preparing such amino acid sequences and polypeptides; to host cells expressing or capable of expressing such amino acid sequences or polypeptides; to compositions, and in particular to pharmaceutical compositions, that comprise such amino acid sequences, polypeptides, nucleic acids and/or host cells; and to uses of such amino acid sequences or polypeptides, nucleic acids, host cells and/or compositions, in particular for prophylactic, therapeutic or diagnostic purposes, such as the prophylactic, therapeutic or diagnostic purposes mentioned herein.

Other aspects, embodiments, advantages and applications of the invention will become clear from the further description herein.

BACKGROUND ART

Enveloped viruses assemble by budding at membranes of host cells (Compans et al. In *Comprehensive Virology*, Fraenkel and Wagner, eds. Plenum Press, New York 4: 179-252 (1975); Choppin and Compans, In *Comprehensive Virology*, Fraenkel and Wagner, eds. Plenum Press, New York 4: 96-178 (1975); Wagner, In *Comprehensive Virology*, Fraenkel and Wagner, eds. Plenum Press, New York 4:1-94 (1975)). During this process they acquire

an envelope which has a lipid bilayer, whose composition reflects that of the host membrane, glycoproteins that form projections or spikes on the surface of the virus particles, and non-glycosylated M-proteins which are associated with the interior surface of the lipid bilayer of the virus particle. The virion-associated proteins are virus specific.

One of the crucial steps in virus infection is the fusion between the virus membrane and the membrane of the host cell, which is mediated by viral glycoproteins, such as viral attachment proteins and viral fusion proteins.

This virus membrane fusion can take place either at the plasma membrane or at an intracellular location following virus uptake by endocytosis (Earp et al. *Curr. Topics Microbiol. Immunol.* 285, 25-66 (2005); Smith et al. *Science* 304, 237-242 (2004)). Viruses belonging to the Retroviridae, Paramyxoviridae, Herpesviridae, and Coronaviridae families typically initiate fusion in a pH-independent manner whereby the virion initially binds to cell surface receptors and subsequently the viral membrane fuses with the plasma membrane of the host cell at neutral pH.

A second, more complex route of entry is characterized by receptor-mediated such as clathrin-dependent, caveola-dependent uptake or non-clathrin-dependent, non-caveola dependent uptake (Smith et al. *Science* 304, 237-242 (2004); Sieczkarski et al. *Curr. Topics Microbiol. Immunol.* 285, 1-23 (2005)). Viruses that use such routes frequently have fusion reactions that require exposure to mildly acidic pH within organelles of the endocytic pathway (Helenius et al. *J. Cell Biol.* 84, 404-420 (1980)). Viruses belonging to the Orthomyxoviridae, Togaviridae, Rhabdoviridae, Bunyaviridae, and Arenaviridae families often require a low-pH-mediated event for efficient fusion of viral and host cellular membranes.

The determination of the atomic structure of complete ectodomains or core regions of many viral fusion proteins in their pre- and/or post-fusion states has revealed a large diversity of conformations. Nevertheless, in all the cases studied so far, the structural transition from a pre- to a post-fusion conformation leads to a stable hairpin conformation resulting in the positioning of the two membrane anchors, the transmembrane and the fusion peptide domains, at the same end of a trimeric elongated rod-like structure. Three different classes of viral fusion proteins have been identified to date based on their common post-fusion structural motifs (Table C-3) (Kielian et al. *Nat. Rev. Microbiol.* 4: 67-76 (2006); Weissenhorn et al. *FEBS Lett.* 581, 2150-2155 (2007)).

In their final, post-fusion state, class I viral fusion proteins are characterized by the interaction of the membrane-proximal C-terminal regions with the more N-terminal trimeric α-helical coiled-coil domains to form a trimer of hairpins that brings the fusion peptides and transmembrane domains together (Skehel et al. *Cell* 95: 871-874 (1998)). Importantly, for several class I proteins, peptides containing sequences of these C-terminal

or N-interacting regions can bind to the viral fusion protein and inhibit fusion and infection by preventing refolding to the final hairpin conformation (for review see Moore and Doms *Proc. Natl. Acad. Sci. USA.* 100: 10598-10602 (2003)). The final trimeric hairpin structure is often referred to as a six-helix bundle. The structures of two class I proteins have also been crystallographically determined with respect to their state prior to activation of fusion. For one protein, influenza virus hemagglutinin (HA), this initial state does not exhibit the six-helix bundle (Wilson et al. *Nature* 289: 366-373 (1981)), whereas for the other, simian parainfluenza virus 5 fusion (F) protein, a six-helix bundle is already present (Yin et al. *Proc. Natl. Acad. Sci. USA* 102: 9288-9293 (2005)), but this structure is not identical to the final bundle. In both cases, in transiting from their initial to their final state, the proteins undergo changes in secondary structure that cause parts of the protein, notably fusion peptides, to move long distances (Baker et al. *Mol. Cell* 3: 309-319 (1999). Chen et al. *Proc. Natl. Acad. Sci. USA* 96: 8967-8972 (1999)). Examples of virus families that express class I fusion proteins are the Orthomyxoviridae, the Paramyxoviridae, the Filoviridae, the Retroviridae and the Coronaviridae.

Viruses that are known to express class II proteins belong to the genus of alphaviruses (family Togaviridae) and to the family of Flaviviridae (Kielian et al. *Virology* 344: 38-47 (2006)). Alphaviruses and flaviviridae are small, spherical viruses containing plus-strand RNA genomes packaged with a capsid protein. The nucleocapsid is enveloped by a lipid bilayer containing the virus membrane fusion protein (alphavirus E1 or flavivirus E). In mature virions, alphavirus E1 is associated as a heterodimer with the viral E2 protein, whereas the flavivirus E protein is found as an E-E homodimer. Low pH causes a dramatic rearrangement of the fusion protein to the post-fusion conformation, dissociating its dimeric interactions and producing a target membrane-inserted homotrimer that is believed to drive the membrane fusion reaction. Although the alphavirus and flavivirus fusion proteins do not have detectable amino acid sequence similarity, they have remarkably similar secondary and tertiary structures, indicating their evolutionary relationship and leading to their classification as the inaugural members of the class II virus fusion proteins (Lescar et al. Cell 105: 137-148 (2001)). The neutral pH (i.e. pre-fusion) structures of the fusion protein ectodomains have been determined for the alphavirus Semliki Forest virus (SFV; Lescar et al. Cell 105: 137-148 (2001)) and the flaviviruses TBE, DV2, and DV3 (Rey 375: 291-298 (1995); Modis Proc. Natl. Acad. Sci. USA 100: 6986-6991 (2003)). The proteins are elongated molecules composed almost entirely of β-strands and contain three domains: domain I, which is located centrally; domain II, which is located at one side of domain I and contains the target-membrane-interacting fusion peptide loop at its tip; and an Ig-like domain III, which is connected to the other side of domain I. Although not present in the ectodomain structure, in the full-length proteins the stem region and transmembrane anchor are found at the C-terminus of domain III, at the opposite end of the protein from the fusion loop. The fusion proteins are arranged with icosahedral symmetry

and lie tangential (almost parallel) to the virus membrane. The conformational changes of class II fusion proteins necessary to transit from the crystallographically determined initial state to the final state do not involve substantial changes in secondary structure. Instead, the domains of class II proteins rotate at "pivot points" so that large-scale movements bring fusion loops and transmembrane domains into proximity, forming trimers of hairpins composed of β-structures.

A third class of fusion proteins forms in its post-fusion state trimers of hairpins by combining two structural elements. Similar to class I fusion proteins, class III fusion proteins display a central α-helical trimeric core; however, each fusion domain exposes two fusion loops located at the tip of an elongated β-sheet revealing a striking convergence with class II fusion proteins (Roche et al. *Science* 313: 187-191 (2006); Heldwein et al. *Science* 313: 217-220 (2006)). Examples of virus families that express class III fusion proteins are the Rhabdoviridae and the Herpesviridae.

Up to now, neutralizing antibodies have been crucial for protection against diseases associated with enveloped viruses. In principle, such antibodies can act against both free virus and against infected cells. The most marked antiviral activity of antibodies and the activity that is most important for antibody-mediated protection is the neutralization of free virus particles. The antiviral activity towards free virus particles can be achieved by binding of the antibody to a specific target on the virion surface, such as an envelope protein which can result in the inhibition of viral infection (neutralization) and/or in the triggering of effector systems that can lead to viral clearance. Antibodies that are specifically directed against infected cells can also mediate several antiviral activities. Fc-mediated effector systems can lead to cell lysis or clearance by antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). The inhibition of viral replication inside cells by the binding of antibodies to viral molecules that are expressed at the membrane of the cells, presumably through signalling mechanisms, has also been described, particularly for viral infection of neurons (Fujinami et al. *Nature* 279: 529-530 (1979); Levine et al. *Science* 254: 856-860 (1991)). Antibodies can also inhibit the release of viruses from infected cells (Gerhard et al. *Curr. Top. Microbiol. Immunol.* 260: 171-190 (2001)) and the cell-cell transmission of viruses (Pantaleo et al. *Eur. J. Immunol.* 25: 226-231 (1995); Burioni et al. *Proc. Natl. Acad. Sci. USA* 91: 355-359 (1994)). Neutralizing antibodies tend to be effective against both infected cells and free virus particles because they bind to envelope molecules that are presented on infected cells as well as on virions. However, non-neutralizing antibodies might also be effective against infected cells by binding to molecules that are expressed on infected cells, but not on virions, for example the M2 protein of influenza virus (Fiers et al. *Virus Research* 103 (1-2): 173-176 (2004)). Okuno et al. (1993, J. Virol. 67: 2552-2558) describe a monoclonal antibody (MAb C179) that binds to the stem region of HA and inhibits the fusion activity of HA resulting in virus neutralization and inhibition of cell fusion.

Clinically, antibody therapy using polyclonal and monoclonal antibodies (mAbs) is effectively used as prophylaxis against varicella, hepatitis A, hepatitis B, rabies (Montano-Hirose et al. *Vaccine* 11: 1259-1266 (1993) and Schumacher et al. *Vaccine* 10: 754-760 (1992)), and respiratory syncytial virus infections (Sawyer *Antiviral Res.* 47: 57-77 (2000)). Within the last 10 years, two antibodies have been licensed for a viral indication, RespiGam and Synagis®, both for prevention of respiratory syncytial virus infection. RespiGam is a human plasma derived antibody and Synagis® is a humanized monoclonal antibody, the first such antibody to be licensed for an infectious disease indication. CytoGam for prevention of cytomegalovirus infection in kidney transplant patients has recently been granted an expanded indication to include use in lung, liver, pancreas and heart transplant patients. Antibody-based therapy for human patients with influenza is up to now little explored. Nabi-HB is a human plasma derived antibody marketed to treat HBV acute or perinatal exposure. However, it has been shown that specific monoclonal antibodies can confer prophylactic and therapeutic protection against influenza in mice (Smirnov et al. *Arch Virol.* 145: 1733-1741 (2000); Renegar et al. *J Immunol.* 173: 1978-1986 (2004); Palladino et al. *J Virol.* 69: 2075-2081 (1995)). Humanized mouse mAbs and equine F(ab')2 fragments specific for hemagglutinin H5 protein of the influenza virus have also been used for efficacious prophylaxis and therapy in the mouse model (Lu et al. *Respir Res.* 7: 43 (2006); Hanson et al. *Respir Res.* 7: 126 (2006)).

Antibody fragments, such as F(ab')2 fragments, Fab fragments (Lamarre et al. *J. Immunol.* 154: 3975-3984 (1995); Thullier et al. *J. Biotechnol.* 69: 183-190 (1999); Schofield et al. *J. Gen. Virol.* 78: 2431-2439 (1997); Barbas et al. PNAS 89:10164 (1992); Crowe et al. PNAS 91: 1386 (1994); Prince et al. JVI 64: 3091 (1990)) and single chain Fv fragments (Mason et al. *Virology* 224: 548 (1996)) have also proven to be successful in neutralizing a variety of enveloped viruses both in vitro and in vivo in animal models (predominantly in mice).

Variable domains derived from camelid species heavy chain antibodies have been generated against the nucleoprotein of Marburg virus (Sherwood et al. al. *J. Infect. Dis.* 196 (2): S213-219 (2007)), against p15 matrix protein of porcine retroviruses (Dekker et al. *J. Virol.* 77 (22): 12132-12139 (2003)), against the HBsAg of human Hepatitis B virus (Serruys et al. 12th *International Symposium on Viral Hepatitis and Liver Disease* (2006); Serruys et al. *Novel compounds & strategies to combat pathogenic microorganisms* (*poster*) (2006); Serruys et al. *The Molecular Biology of Hepatitis B Viruses* (*poster*) (2007); Serruys *New insights in HBV diversity, pathogenesis, diagnosis and treatment* (*oral presentation*) (2007); Serruys *NBC-12: Single-domain intrabodies inhibit Hepatitis B virus replication in mice* (*oral presentation*) (2008)), against vaccinia virus (Goldman et al. *Anal. Chem.* 78 (24): 8245-8255 (2006)), and against gp120 of HIV-1 (Forsman et al. *Abstract EU-WHO Neut Workshop*, Italy, March 2007) in some cases resulting in effective blocking of viral replication or neutralization in vitro and/or in vivo (in a mouse model).

The prior art discussed hereabove clearly indicates that the development of effective and potent antiviral drugs remains a major scientific challenge. Only for a minority of viral infections, there is currently an effective prophylactic and/or therapeutic compound available.

However, these currently existing antiviral drugs, have numerous side-effects, such as nausea, vomiting, skin rashes, migraine, fatigue, trembling, and, more rarely, epileptic seizures.

Also, the mutability and resultant adaptability of viruses present an enormous difficulty to the design of antiviral strategies that are effective over the long term. While drug design has gained from advances in the molecular understanding of viral growth processes, many initially potent drugs lose their efficacy over time because of the emergence of drug-resistant strains. When mutations arise that attenuate or compensate for the inhibitory effect of the drug, virus strains that carry such mutations gain a growth advantage and are subsequently selected for in the viral population.

Hence, for the majority of currently known human viral diseases there is an urgent need for a potent antiviral drugs that can be used for effective treatment and prevention of these diseases. In addition, a need exists for alternative and improved antiviral drugs over the presently existing drugs with regard to efficacy and/or potency (over the long term), overcoming currently encountered disadvantages, such as for instance undesired side-effects and viral evasion/viral escape.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide amino acid sequences that are directed against and/or that can specifically bind to an envelope protein of a virus. The amino acid sequences according to the present invention, that are directed against and/or specifically binding to an envelope protein of a virus, can generally be used to modulate, and in particular to inhibit and/or to prevent the viral-mediated biological pathways in which an envelope protein of a virus and/or a viral receptor are involved. In particular, the amino acid sequences of the present invention can be used to neutralize a virus (as defined herein) and/or to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein).

More specifically, the amino acid sequences according to the present invention may neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place) and/or in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place).

Accordingly, amino acid sequences of the present invention that neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place), are said herein to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell. Furthermore, amino acid sequences of the present invention that neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place), are said herein to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell.

Accordingly, the amino acid sequences of the present invention can modulate and in particular inhibit and/or prevent viral entry and/or viral replication in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway(s); preferably, the amino acid sequences of the present invention can modulate and in particular inhibit and/or prevent viral entry in a target host cell by binding to an envelope protein of a virus, such that virion aggregation is induced and/or virion structure is destabilized and/or virion attachment to a target host cell is modulated, inhibited and/or prevented (for instance by modulating and/or inhibiting and/or preventing the interaction between the envelope protein of a virus and a viral receptor and/or between the envelope protein of a virus and a target host cell or by competing with said envelope protein for binding to said viral receptor and/or said target host cell) and/or viral fusion with said target host cell is modulated, inhibited and/or prevented (for instance at the target host cell membrane or within an endosomal and/or lysosomal compartment of said target host cell), for example by preventing said envelope protein of a virus from undergoing a conformational change. Alternatively, the amino acid sequences of the present invention can modulate and in particular inhibit and/or prevent viral replication (as defined herein) in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway; preferably, the amino acid sequences of the present invention can modulate and in particular inhibit and/or prevent viral replication in a target host cell by binding to an envelope protein of a virus, such that transcription and/or translation of the viral genome is affected, inhibited and/or prevented and/or viral packaging and/or the formation of functional virions is affected, inhibited and/or prevented and/or budding of nascent virions from the target host cell membrane is reduced, inhibited and/or prevented.

As such, the polypeptides and compositions of the present invention can be used for the prevention and treatment (as defined herein) of viral diseases. Generally, “viral diseases” can be defined as diseases and disorders that are caused by one or more viruses; in particular viral diseases may be diseases that can be prevented and/or treated, respectively, by suitably administering to a subject in need thereof (i.e. having the disease or disorder or

at least one symptom thereof and/or at risk of attracting or developing the disease or disorder) of either an amino acid sequence, polypeptide or composition of the invention (and in particular, of a pharmaceutically active amount thereof) and/or of a known anti-viral compound against an envelope protein of a virus or a viral-mediated biological pathway in which an envelope protein of a virus and/or its viral receptor is involved (and in particular, of a pharmaceutically active amount thereof). Examples of such viral diseases will be clear to the skilled person based on the disclosure herein, and for example include the following diseases and disorders (caused by the following viruses): AIDS (caused by HIV), AIDS Related Complex (caused by HIV), Aseptic meningitis (caused by HSV-2), Bronchiolitis (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)]), California encephalitis (caused by California encephalitis virus), Chickenpox (caused by Varicella zoster virus), Colorado tick fever (caused by Colorado tick fever virus), Common cold (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)] or Parainfluenza virus), Conjunctivitis (caused by e.g. Herpes simplex virus), Cowpox (caused by vaccinia virus), Croup (caused by e.g. parainfluenza viruses 1 to 3), Cytomegalovirus Infection (caused by cytomegalovirus), Dengue fever (caused by dengue virus), Eastern equine encephalitis (caused by EEE virus), Ebola hemorrhagic fever (caused by Ebola virus), encephalitis and chronic pneumonitis in sheep (caused by Visna virus), encephalitis (caused by Semliki Forest virus), Gingivostomatitis (caused by HSV-1), Hantavirus hemorrhagic fever/Hantaan-Korean hemorrhagic fever (caused by Hantavirus), Hepatitis (caused by Hepatitis virus), Genital herpes (caused by HSV-2), Herpes labialis (caused by HSV-1), neonatal herpes (caused by HSV-2), Genital HSV (caused by Herpes simplex virus), Infectious mononucleosis (caused by e.g. Epstein-Barr virus), Influenza (Flu) (caused by influenza viruses A, B and C [Influenza viruses, diseases caused by influenza viruses and pharmaceuticals to treat these diseases are reviewed by Subbarao et al. *Nat. Rev. Immunol.* 7: 267-278 (2007)]), Japanese encephalitis virus (caused by JEE virus), Keratoconjunctivitis (caused by HSV-1), Lassa fever, Leukemia and lymphoma (caused by e.g. Human T cell leukemia virus or Moloney murine leukemia virus), Lower respiratory tract infections (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)] or Sendai virus), Measles (caused by rubeola virus), Marburg hemorrhagic fever (caused by Marburg virus), Molluscum contagiosum (caused by Molluscum), Mononucleosis-like syndrome (caused by CMV), mumps (caused by mumps virus), Newcastle disease (caused by avian paramoxyvirus 1), Norovirus, Orf (caused by Orfvirus), Pharyngitis (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)], Influenza Virus [Influenza viruses, diseases caused by influenza viruses and pharmaceuticals to treat these diseases are reviewed by Subbarao et al. Nat. Rev. Immunol. 7: 267-278 (2007)], Parainfluenza virus and Epstein-Barr virus), Pneumonia (viral) (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed

by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)] or CMV), Progressive multifocal leukencephalopathy, Rabies (caused by Rabies virus [rabies virus and diseases caused by rabies are reviewed by Woldehiwet Z. *Res. Vet. Sci.* 73: 17-25 (2002) and Dietzschold et al. *J. Virol.* 56: 12-18 (1985)]), Roseola (caused by HHV-6), Rubella (caused by rubivirus), SARS (caused by a human coronavirus), Shingles (caused by Varicella zoster virus), Smallpox (caused by Variola virus), St. Louis encephalitis (caused by SLE virus), Strep Throat (caused by e.g. RSV [RSV virus and diseases caused by RSV are reviewed by Ogra P. *Paediatric Respiratory Reviews* 5: S119-S126 (2004)], Influenza Virus [Influenza viruses, diseases caused by influenza viruses and pharmaceuticals to treat these diseases are reviewed by Subbarao et al. *Nat. Rev. Immunol.* 7: 267-278 (2007)], Parainfluenza virus, Epstein-Barr virus), Sindbis fever (Sindbis virus), Temporal lobe encephalitis (caused by HSV-1), Urethritis (caused by Herpes simplex virus), Vesicular stomatitis (caused by vesicular stomatitis virus), Viral encephalitis, Viral gastroenteritis, Viral meningitis, Viral pneumonia, Western equine encephalitis (caused by WEE virus), West Nile disease, Yellow fever (caused by Yellow Fever virus), and Zoster (caused by Varicella zoster virus). The amino acid sequences, polypeptides and compositions according to the invention can be used to treat any of the foregoing viral diseases. Other examples of such viral diseases will be clear to the skilled person; for instance, the amino acid sequences, polypeptides and compositions according to the invention can be used to treat any of the viral diseases that are disclosed in the handbook "Fields Virology", 5^{th} edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

Accordingly, the amino acid sequences, polypeptides and compositions of the present invention can be used for the prevention and treatment of viral diseases which are characterized by viral-mediated biological pathway(s) in which an envelope protein of a virus and/or a viral receptor are involved.

In particular, the amino acid sequences, polypeptides and compositions of the present invention can be used for the prevention and treatment of viral diseases characterized by any viral-mediated biological pathway(s) in which an envelope protein of a virus and/or a viral receptor are involved. However, preferably, the amino acid sequences, polypeptides and compositions of the present invention can be used for the prevention and treatment of viral diseases characterized by viral entry in a target host cell, such as virion attachment to a target host cell and/or viral fusion with a target host cell. Also preferably, the amino acid sequences, polypeptides and compositions of the present invention can be used for the prevention and treatment of viral diseases characterized by viral replication in a target host cell, such as viral transcription and/or viral translation and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane.

Some specific, but non-limiting examples of such uses are:

- Amino acid sequences and polypeptide of the invention against hemagglutinin H5, and pharmaceutical compositions comprising the same, may be used in the prevention and treatment of influenza (flu), pharyngitis, strep throat, common cold and respiratory tract infections;
- Amino acid sequences and polypeptide of the invention against hRSV, and pharmaceutical compositions comprising the same, may be used in the prevention and treatment of lower respiratory tract infections, bronchiolitis, common cold, pharyngitis, viral pneumonia and strep throat;
- Amino acid sequences and polypeptide of the invention against rabies, and pharmaceutical compositions comprising the same, may be used in the prevention and treatment of rabies, brain inflammation and (acute) encephalitis;

Other examples of such uses will be clear to the skilled person based on the disclosure herein.

Thus, without being limited thereto, the amino acid sequences, polypeptides and compositions of the invention can for example be used to prevent and/or to treat all diseases and disorders that are currently being prevented or treated with known anti-viral compounds that can modulate viral-mediated biological pathway(s) in which an envelope protein of a virus and/or a viral receptor are involved, such as those mentioned in the prior art cited above. It is also envisaged that the amino acid sequences, polypeptides and compositions of the invention can be used to prevent and/or to treat all diseases and disorders for which treatment with such anti-viral compounds is currently being developed, has been proposed, or will be proposed or developed in future. In addition, it is envisaged that, because of their favourable properties as further described herein, the amino acid sequences, polypeptides and compositions of the present invention may be used for the prevention and treatment of other diseases and disorders than those for which these known anti-viral compounds are being used or will be proposed or developed; and/or that the amino acid sequences, polypeptides and compositions of the present invention may provide new methods and regimens for treating the diseases and disorders described herein.

Other applications and uses of the amino acid sequences and polypeptides of the invention will become clear to the skilled person from the further disclosure herein.

Generally, it is an object of the invention to provide pharmacologically active agents, as well as compositions comprising the same, that can be used in the diagnosis, prevention and/or treatment of viral diseases and of the further diseases and disorders mentioned herein; and to provide methods for the diagnosis, prevention and/or treatment of such diseases and

disorders that involve the administration and/or use of such agents and compositions.

In particular, it is an object of the invention to provide such pharmacologically active agents, compositions and/or methods that have certain advantages compared to the agents, compositions and/or methods that are currently used and/or known in the art. These advantages will become clear from the further description below.

More in particular, it is an object of the invention to provide therapeutic proteins that can be used as pharmacologically active agents, as well as compositions comprising the same, for the diagnosis, prevention and/or treatment of viral diseases and of the further diseases and disorders mentioned herein; and to provide methods for the diagnosis, prevention and/or treatment of such diseases and disorders that involve the administration and/or the use of such therapeutic proteins and compositions.

Accordingly, it is a specific object of the present invention to provide amino acid sequences that are directed against (as defined herein) an envelope protein of a virus, in particular against an envelope protein of a virus that is able to infect a warm-blooded animal, more in particular against an envelope protein of a virus that is able to infect mammalians, and especially against an envelope protein of a virus that is able to infect humans; and to provide proteins and polypeptides comprising or essentially consisting of at least one such amino acid sequence.

In particular, it is a specific object of the present invention to provide such amino acid sequences and such proteins and/or polypeptides that are suitable for prophylactic, therapeutic and/or diagnostic use in a warm-blooded animal, and in particular in a mammal, and more in particular in a human being.

More in particular, it is a specific object of the present invention to provide such amino acid sequences and such proteins and/or polypeptides that can be used for the prevention, treatment, alleviation and/or diagnosis of one or more diseases, disorders or conditions associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor (such as the diseases, disorders and conditions mentioned herein) in a warm-blooded animal, in particular in a mammal, and more in particular in a human being.

It is also a specific object of the invention to provide such amino acid sequences and such proteins and/or polypeptides that can be used in the preparation of pharmaceutical or veterinary compositions for the prevention and/or treatment of one or more diseases, disorders or conditions associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor (such as the diseases, disorders and conditions mentioned herein) in a warm-blooded animal, in particular in a mammal, and more in particular in a human being.

In the invention, generally, these objects are achieved by the use of the amino acid sequences, proteins, polypeptides and compositions that are described herein.

In general, the invention provides amino acid sequences that are directed against (as defined herein) and/or can specifically bind (as defined herein) to an envelope protein of a virus; as well as compounds and constructs, and in particular proteins and polypeptides, that comprise at least one such amino acid sequence. Preferably, said envelope protein of a virus against which the amino acid sequences and polypeptides of the invention are directed against and/or specifically bind to may be encoded by the viral genome, i.e. may be a viral-specific envelope protein. Alternatively, said envelope protein of a virus may also not be encoded by the viral genome but may for instance be encoded by the genome of "a target host cell of said virus" (as further defined herein). Furthermore, said envelope protein of a virus is preferably a membrane protein, which is bound to or attached to and/or embedded in and/or crosses the bi-lipid membrane layer of the viral envelope of said virus. In another preferred but non-limiting aspect, said envelope protein of a virus against which the amino acid sequences and polypeptides of the invention are directed and/or which is specifically bound by the amino acid sequences and/or polypeptides of the invention may be a glycoprotein. Alternatively, said envelope protein may be a non-glycosylated protein.

More in particular, the invention provides amino acid sequences that can bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein; as well as compounds and constructs, and in particular proteins and polypeptides, that comprise at least one such amino acid sequence.

In particular, amino acid sequences and polypeptides of the invention are preferably such that they:

- bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles);
  and/or such that they:
- bind to an envelope protein of a virus with a k_{on}-rate of between $10^2\ M^{-1}s^{-1}$ to about $10^7\ M^{-1}s^{-1}$, preferably between $10^3\ M^{-1}s^{-1}$ and $10^7\ M^{-1}s^{-1}$, more preferably between $10^4\ M^{-1}s^{-1}$ and $10^7\ M^{-1}s^{-1}$, such as between $10^5\ M^{-1}s^{-1}$ and $10^7\ M^{-1}s^{-1}$;
  and/or such that they:
- bind to an envelope protein of a virus with a k_{off} rate between $1\ s^{-1}$ ($t_{1/2}$=0.69 s)

and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, a monovalent amino acid sequence of the invention (or a polypeptide that contains only one amino acid sequence of the invention) is preferably such that it will bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

Some preferred IC50 values for binding of the amino acid sequences or polypeptides of the invention to an envelope protein of a virus will become clear from the further description and examples herein.

For binding to an envelope protein of a virus, an amino acid sequence of the invention will usually contain within its amino acid sequence one or more amino acid residues or one or more stretches of amino acid residues (i.e. with each "stretch" comprising two or more amino acid residues that are adjacent to each other or in close proximity to each other, i.e. in the primary or tertiary structure of the amino acid sequence) via which the amino acid sequence of the invention can bind to an envelope protein of a virus, which amino acid residues or stretches of amino acid residues thus form the "site" for binding to an envelope protein of a virus (also referred to herein as the "antigen binding site").

The amino acid sequences provided by the invention are preferably in essentially isolated form (as defined herein), or form part of a protein or polypeptide of the invention (as defined herein), which may comprise or essentially consist of one or more amino acid sequences of the invention and which may optionally further comprise one or more further amino acid sequences (all optionally linked via one or more suitable linkers). For example, and without limitation, the one or more amino acid sequences of the invention may be used as a binding unit in such a protein or polypeptide, which may optionally contain one or more further amino acid sequences that can serve as a binding unit (i.e. against one or more other targets than the envelope protein of a virus, to which the amino acid sequences of the invention specifically bind to and/or are directed against), so as to provide a monovalent, multivalent or multispecific polypeptide of the invention, respectively, all as described herein. Such a protein or polypeptide may also be in essentially isolated form (as defined herein).

The amino acid sequences and polypeptides of the invention as such preferably essentially consist of a single amino acid chain that is not linked via disulphide bridges to any other amino acid sequence or chain (but that may or may not contain one or more intramolecular disulphide bridges. For example, it is known that NANOBODIES® (V_{HH} sequences)—as described herein—may sometimes contain a disulphide bridge between CDR3 and CDR1 or FR2). However, it should be noted that one or more amino acid sequences of the invention

may be linked to each other and/or to other amino acid sequences (e.g. via disulphide bridges) to provide peptide constructs that may also be useful in the invention (for example Fab' fragments, $F(ab')_2$ fragments, ScFv constructs, "diabodies" and other multispecific constructs. Reference is for example made to the review by Holliger and Hudson, Nat Biotechnol. 2005 September; 23(9):1126-36).

Generally, when an amino acid sequence of the invention (or a compound, construct or polypeptide comprising the same) is intended for administration to a subject (for example for therapeutic and/or diagnostic purposes as described herein), it is preferably either an amino acid sequence that does not occur naturally in said subject; or, when it does occur naturally in said subject, in essentially isolated form (as defined herein).

It will also be clear to the skilled person that for pharmaceutical use, the amino acid sequences of the invention (as well as compounds, constructs and polypeptides comprising the same) are preferably directed against an envelope protein of a virus that is able to infect humans; whereas for veterinary purposes, the amino acid sequences and polypeptides of the invention are preferably directed against an envelope protein of a virus that is able to infect the species to be treated, or at least cross-reactive with an envelope protein of a virus that is able to infect the species to be treated.

Furthermore, an amino acid sequence of the invention may optionally, and in addition to the at least one binding site for binding against an envelope protein of a virus, contain one or more further binding sites for binding against other antigens, proteins or targets.

The efficacy of the amino acid sequences and polypeptides of the invention, and of compositions comprising the same, can be tested using any suitable in vitro assay, cell-based assay, in vivo assay and/or animal model known per se, or any combination thereof, depending on the specific disease or disorder involved. Suitable assays and animal models will be clear to the skilled person, and for example include a Biacore assay; epitope mapping e.g. by using monoclonal antibodies which recognize known epitopes; cell based neutralization assays for the different virus strains (e.g. virus neutralization assay for influenza as described in Vanlandschoot et al. *Virol.* 212: 526-534 (1995) and Vanlandschoot et al. J. Gen. Virol. 79: 1781-1791 (1998) or Rapid Fluorescent Focus Inhibition Test (RFFIT) for rabies as described in Standard procedure from WHO Laboratory Techniques in Rabies, (1996)); in vitro inhibition of cell to cell spread (Dietzschold et al. *J. Virol.* 56: 12-18 (1985)); cell-cell fusion inhibition assay (Vanlandschoot et al. J. Gen. Virol. 79: 1781-1791 (1998)); plaque assay to examine resistance or sensitivity to antibody (Vanlandschoot et al. J. Gen. Virol. 79: 1781-1791 (1998)); investigate ADEI in macrophage cell lines and primary macrophages and compare infection rates with and without pre-incubation of the virus with antibodies and amino acid sequences and polypeptides of the invention (Tirado et al. *Viral Immunol.* 16: 69-86

(2003)); retroviral and lentiviral pseudotypes of replication-competent virus to study neutralizing antibody responses to H5N1 viral infection (Temperton et al. Emerg. Infect. Dis. 11: 411-416 (2005)); cotton rat model for studies on RSV (Murphy et al. *Virus Res.* 11: 1-15 (1988)); in vivo screening of neutralizing capacity of rabies infection by intracerebral inoculation in mice; validation of the use of amino acid sequences and polypeptides according to the invention for post-exposure prophylaxis (Schumacher et al. *Vaccine* 10: 754-760 (1992)); assessment of the therapeutic potential of amino acid sequences and polypeptides of the invention to treat an ongoing viral brain infection; Ferret model for H5N1 infection (Yen et al. *J. Virol.* 81: 6890-6898 (2007)); assessment of the prophylactic and therapeutic potential of amino acid sequences and polypeptides of the invention to treat influenza-infected mice (Simmons et al. *Plos Medicine* 4 (5): 928-936); as well as the assays and animal models used in the experimental part below and in the prior art cited herein.

Also, according to the invention, amino acid sequences and polypeptides that are directed against an envelope protein of a virus that is able to infect a first species of warm-blooded animal may or may not show cross-reactivity with an envelope protein of a virus that is able to infect one or more other species of warm-blooded animal. For example, amino acid sequences and polypeptides directed against an envelope protein of a virus that is able to infect humans may or may not show cross reactivity with an envelope protein of a virus that is able to infect one or more other species of primates (such as, without limitation, monkeys from the genus *Macaca* (such as, and in particular, cynomolgus monkeys (*Macaca fascicularis*) and/or rhesus monkeys (*Macaca mulatta*)) and baboon (*Papio ursinus*)) and/or with an envelope protein of a virus that is able to infect one or more species of animals that are often used in animal models for diseases (for example mouse, rat, rabbit, pig or dog), and in particular in animal models for diseases and disorders associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor (such as the species and animal models mentioned herein). In this respect, it will be clear to the skilled person that such cross-reactivity, when present, may have advantages from a drug development point of view, since it allows the amino acid sequences and polypeptides against an envelope protein of a virus that is able to infect humans to be tested in such disease models.

More generally, amino acid sequences and polypeptides of the invention that are cross-reactive with two or more homologous envelope proteins of a virus that is able to infect multiple species of mammal will usually be advantageous for use in veterinary applications, since it will allow the same amino acid sequence or polypeptide to be used across multiple species. Thus, it is also encompassed within the scope of the invention that amino acid sequences and polypeptides directed against an envelope protein of a virus that is able to infect one species of animal (such as amino acid sequences and polypeptides against an envelope protein of a virus that is able to infect humans) can be used in the treatment of

another species of animal, as long as the use of the amino acid sequences and/or polypeptides provide the desired effects in the species to be treated.

The present invention is in its broadest sense also not particularly limited to or defined by a specific envelope protein of a virus or a specific class, category or type of envelope proteins of a virus against which the amino acid sequences and polypeptides of the invention are directed. For example, the amino acid sequences and polypeptides may be directed against any envelope protein of a virus. Virus envelope proteins are known in the art and for example include but are not limited to: the F protein of RSV virus, the G protein of RSV virus, the SH protein of RSV virus, the M protein of RSV virus, the M2 protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

The amino acid sequences and polypeptides of the invention may be directed against any of the foregoing viral envelope proteins. Other examples of viral envelope proteins will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may be directed against any of the viral envelope proteins that are disclosed in the handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

However, it is generally assumed and preferred that the amino acid sequences and polypeptides of the invention are preferably directed against an envelope protein of a virus, wherein said envelope protein is a viral attachment protein (as further defined herein); and/or a viral fusion protein (as further defined herein); and/or a viral attachment protein and a viral fusion protein (as further defined herein).

Thus, in one preferred, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are directed against and/or specifically bind to an envelope protein of a

virus, which is a viral attachment protein (as further defined herein). Viral attachment proteins are known in the art and for example include but are not limited to: the G protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, and the E protein of West Nile virus.

The amino acid sequences and polypeptides of the invention may be directed against any of the foregoing viral attachment proteins. Other examples of viral attachment proteins will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may be directed against any of the viral attachment proteins that are disclosed in the handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

The structural and functional features and mechanisms of action of a variety of viral attachment proteins are known in the art and are for example described in detail in the following literature: "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

It is assumed to be understood that a particular functional viral attachment protein (as defined herein) can be expressed in its functional form or can be expressed in the form of a (non-active) precursor protein. In the case that said particular functional viral attachment protein is expressed as a (non-active) precursor protein, it may be post-translationally processed and/or modified (for example by cleavage with one or more enzymes, such as proteases) within the target host cell (as defined herein) of the virus (for instance in specialized organelles such as the trans-Golgi compartment), resulting in a functional attachment protein and optionally at least one other main protein moiety. After said functional attachment protein and optionally said at least one other main protein moiety have been formed, these may either remain attached to each other (such as via covalent bounds, for instance by one or more disulfide bridges, or via non-covalent bounds, for instance by forming a protein complex) or these may be separated from each other; in both cases however (remaining attached to each other or being separated from each other) either only the resulting functional attachment protein or both the resulting functional attachment protein and the optionally at least one other main protein moiety may be directly involved in the attachment process between the virion and its target host cell (as defined herein) (for instance by binding to a particular viral receptor that is expressed on the surface of said target host cell). However, it is preferred that only the resulting

functional attachment protein is directly involved in the attachment process between the virion and its target host cell (for instance by binding to a particular viral receptor that is expressed on the surface of said target host cell). Examples of such functional attachment proteins that are formed by post-translational modification include but are not limited to the gp120 protein of HIV-1 virus and the HA1 protein of influenza. It is however not excluded that said formed at least one other main protein moiety is involved (either directly or indirectly) in the attachment process between the virion and its target host cell (as defined herein) and/or that said formed at least one other main protein moiety is involved (either directly or indirectly) in another process (such as for instance fusion of said virion with its target host cell) that is part of the process of infection and/or replication of said virion.

In another, non-limiting, preferred aspect, the amino acid sequences and polypeptides of the invention are directed against and/or specifically bind to an envelope protein of a virus, which is a viral fusion protein (as further defined herein).

Viral fusion proteins are known in the art and for example include but are not limited to: the F protein of RSV virus, the HA protein of Influenza A virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

The amino acid sequences and polypeptides of the invention may be directed against any of the foregoing viral fusion proteins. Other examples of viral fusion proteins will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may be directed against any of the viral fusion proteins that are disclosed in the handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

The structural and functional features and mechanisms of action of a variety of viral fusion proteins are known in the art and are for example described in detail in the following literature: Baker et al. *Mol. Cell* 3: 309-319 (1999); Chen et al. *Proc. Natl. Acad. Sci. USA* 96:

8967-8972 (1999); Earp et al. *Curr. Topics Microbiol. Immunol.* 285, 25-66 (2005); Heldwein et al. *Science* 313: 217-220 (2006); Helenius et al. *J. Cell Biol.* 84, 404-420 (1980); Kielian et al. *Nat. Rev. Microbiol.* 4: 67-76 (2006); Lescar et al. Cell 105: 137-148 (2001); Modis Proc. Natl. Acad. Sci. USA 100: 6986-6991 (2003); Moore and Doms *Proc. Natl. Acad. Sci. USA.* 100: 10598-10602 (2003); Rey 375: 291-298 (1995); Roche et al. *Science* 313: 187-191 (2006); Sieczkarski et al. *Curr. Topics Microbiol. Immunol.* 285, 1-23 (2005); Smith et al. *Science* 304, 237-242 (2004); Skehel et al. *Cell* 95: 871-874 (1998); Weissenhorn et al. *FEBS Lett.* 581, 2150-2155 (2007); Wilson et al. *Nature* 289: 366-373 (1981) and Yin et al. *Proc. Natl. Acad. Sci. USA* 102: 9288-9293 (2005); Handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

It is assumed to be understood that a particular functional viral fusion protein (as defined herein) can be expressed in its functional form or can be expressed in the form of a (non-active) precursor protein. In the case that said particular functional viral fusion protein is expressed as a (non-active) precursor protein, it may be post-translationally processed and/or modified (for example by cleavage with one or more enzymes, such as proteases) within the target host cell (as defined herein) of the virus (for instance in specialized organelles such as the trans-Golgi compartment), resulting in a functional fusion protein and optionally at least one other main protein moiety. After said functional fusion protein and optionally said at least one other main protein moiety have been formed, these may either remain attached to each other (such as via covalent bounds, for instance by one or more disulfide bridges, or via non-covalent bounds, for instance by forming a protein complex) or these may be separated from each other; in both cases however (remaining attached to each other or being separated from each other) either only the resulting functional fusion protein or both the resulting functional fusion protein and the optionally at least one other main protein moiety may be directly involved in the fusion process between the virion and its target host cell (as defined herein) (for instance by binding to membrane components of said target host cell). However, it is preferred that only the resulting functional fusion protein is directly involved in the fusion process between the virion and its target host cell (for instance by binding to membrane components of said target host cell). Examples of such functional fusion proteins that are formed by post-translational modification include but are not limited to the gp41 protein of HIV-1 virus and the HA2 subunit of HA protein of influenza. It is however not excluded that said at least one other main protein moiety is involved (either directly or indirectly) in the fusion process between the virion and its target host cell and/or that said at least one other main protein moiety is involved (either directly or indirectly) in another process (such as for instance attachment of said virion to its target host cell) that is part of the process of infection and/or replication of said virion.

Also, in another preferred, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are directed against and/or specifically bind to an envelope protein of a virus, which is a viral attachment protein and a viral fusion protein (as further defined herein).

Viral envelope proteins that are both viral attachment proteins and viral fusion proteins are known in the art and for example include but are not limited to: the HA protein of influenza A virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, and the E1 protein of Sindbis virus. The amino acid sequences and polypeptides of the invention may be directed against any of the foregoing viral envelope proteins that are both viral attachment proteins and viral fusion proteins. Other examples of viral envelope proteins that are both viral attachment proteins and viral fusion proteins will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may be directed against any of the viral envelope proteins that are both viral attachment proteins and viral fusion proteins and are disclosed in the handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

The structural and functional features and mechanisms of action of a variety of envelope proteins that are both viral attachment proteins and viral fusion proteins are known in the art and are for example described in detail in the following literature: handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

A particular functional viral envelope protein, which is both an attachment and a fusion protein, can be expressed in its functional form or can be expressed in the form of a (non-active) precursor protein. In the case that said particular functional viral attachment and fusion protein is expressed as a (non-active) precursor protein, it may be post-translationally processed and/or modified (for example by cleavage with one or more enzymes, such as proteases) within the target host cell (as defined herein) of the virus (for instance in specialized organelles such as the trans-Golgi compartment), resulting in a functional viral attachment and fusion protein and optionally at least one other main protein moiety. After said functional viral attachment and fusion protein and optionally said at least one other main protein moiety have been formed, these may either remain attached to each other (such as via covalent bounds, for instance by one or more disulfide bridges, or via non-covalent bounds, for instance by forming a protein complex) or these may be separated from each other; in both cases however (remaining attached to each other or

being separated from each other) either only the resulting functional viral attachment and fusion protein or both the resulting functional viral attachment and fusion protein and the optionally at least one other main protein moiety may be directly involved in the fusion process between the virion and its target host cell (for instance by binding to a particular viral receptor that is expressed on the surface of said target host cell and/or to membrane components of said target host cell). However, it is preferred that only the resulting functional viral attachment and fusion protein is directly involved in the fusion process between the virion and its target host cell (for instance by binding to a particular viral receptor that is expressed on the surface of said target host cell and/or to membrane components of said target host cell). It is however not excluded that said at least one other main protein moiety is involved (either directly or indirectly) in the fusion process between the virion and its target host cell (as defined herein) and/or that said at least one other main protein moiety is involved (either directly or indirectly) in another process (such as for instance only attachment of said virion to its target host cell or only fusion of said virion with its target host cell) that is part of the process of infection and/or replication of said virion.

The present invention is not particularly limited to or defined by a specific conformation and/or secondary and/or tertiary and/or quaternary structure of said envelope protein against which the amino acid sequences and polypeptides of the invention are directed. Thus, said envelope protein may be characterized by any conformation and/or secondary and/or tertiary and/or quaternary structure. For example, when an envelope protein of a virus exists in an activated conformation and in an inactive conformation or in a pre-fusion and post-fusion conformation or state, the amino acid sequences and polypeptides of the invention may bind to either one of these conformations, or may bind to both these conformations (i.e. with an affinity and/or specificity which may be the same or different).

Also, for example, the amino acid sequences and polypeptides of the invention may bind to a conformation of an envelope protein of a virus in which it is bound to a binding partner (as further defined herein), may bind to a conformation of an envelope protein of a virus in which it not bound to a binding partner, or may bind to both such conformations (again with an affinity and/or specificity which may be the same or different).

More specifically, said envelope protein may be characterized by a pre-fusion conformational state (as further defined herein) and/or an intermediate conformational state (as further defined herein) and/or a post-fusion conformational state (as further defined herein). In particular, said envelope protein, which is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state may be a viral attachment protein; alternatively and more preferably, said envelope protein, which is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state may be a

viral fusion protein (as defined herein); also, said envelope protein, which is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state may be a viral attachment protein and a viral fusion protein.

In cases wherein said at least one fusion protein is characterized by a pre-fusion conformational state, said pre-fusion conformational state may be a fusion protein trimer, such as for example (but not limited to) a trimer of hairpins or a six-helix bundle. When said pre-fusion conformational state of a viral fusion protein is a fusion protein trimer, three protein subunits are comprised in said protein trimer, which are preferably identical but also may be different from each other. Also, a particular protein subunit of said fusion protein trimer can either remain intact or uncleaved before, during and after the fusion process between a virion and its target host cell (as defined herein) or can be cleaved (for instance by one or more enzymes, such as proteases) before, during or after the fusion process to form at least two main protein moieties originating from said subunit of said protein trimer. In the case that said protein subunit of said fusion protein trimer is cleaved as described above, said at least two main protein moieties can either stay attached to each other (such as via covalent bounds, for instance by one or more disulfide bridges, or non-covalent bounds, for instance by forming a protein complex) or can be completely separate protein moieties, originating from the same subunit; in both cases however, either staying attached to each other or being completely separated from each other, it may be that only one, or at least two, or two or more or all of said main proteins moieties (originating from the same subunit of said fusion protein trimer) are directly involved in the fusion process between a virion and its target host cell (as defined herein). However, preferably, only one of said main proteins moieties (originating from the same subunit of said fusion protein trimer) is directly involved in the fusion process between a virion and its target host cell (as defined herein). Examples of such main protein parts that are directly involved in the fusion process between a virion and its target host cell include but are not limited to the F2 protein of RSV virus and the HA2 subunit of HA protein of influenza virus.

Examples of viral fusion proteins that are characterized by a pre-fusion conformational state, which is a fusion protein trimer, such as for example a trimer of hairpins or a six-helix bundle include but are not limited to Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.

Alternatively, said viral fusion protein may be characterized by a pre-fusion conformational

state (as defined herein), wherein said pre-fusion conformational state is a protein dimer (comprising two protein subunits), such as for example a fusion protein homodimer (comprising two identical protein subunits) or a protein heterodimer (comprising two different protein subunits). It is assumed to be understood that when said pre-fusion conformational state of a viral fusion protein is a protein dimer, such as a fusion protein homodimer or a protein heterodimer, that in said protein dimer (comprising two protein subunits) either both or only one of the two protein subunits of said protein dimer can be directly involved in the fusion process between a virion and its target host cell (as defined herein). Also, it is assumed to be understood that the two protein subunits of said protein dimer can either be attached to each other (such as for instance via covalent bounds or non-covalent bounds) or can be cleaved (for instance by one or more enzymes, such as proteases) to form two separate protein monomers before, during or after the fusion process between a virion and its target host cell.

Finally, said viral fusion protein may be characterized by a pre-fusion conformational state (as defined herein), wherein said pre-fusion conformational state is a fusion protein monomer.

Examples of viral fusion proteins that are characterized by a pre-fusion conformational state, which is a protein dimer, such as a fusion protein homodimer or a protein heterodimer, or a protein monomer include but are not limited to Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.

In cases wherein said at least one fusion protein is characterized by a post-fusion conformational state, said post-fusion conformational state may be a fusion protein trimer, such as for example (but not limited to) a trimer of hairpins or a six-helix bundle. More specifically, said post-fusion conformational state of viral fusion proteins may be a fusion protein trimer, which comprises an α-helical coiled coil and/or β-structures and/or an α-helical coiled coil and β-structures.

Examples of viral fusion proteins that are characterized by a post-fusion conformational state, which is a trimer of hairpins comprising an α-helical coiled coil include but are not limited to Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Human respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.

Examples of viral fusion proteins that are characterized by a post-fusion conformational

state, which is a trimer of hairpins comprising β-structures include but are not limited to Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.

Examples of viral fusion proteins that are characterized by a post-fusion conformational state, which is a trimer of hairpins comprising an α-helical coiled coil and β-structures include but are not limited to vesicular stomatitis virus G protein, rabies G protein and Herpes simplex virus gB protein.

The present invention thus generally provides amino acid sequences and polypeptides that may be directed to and/or may specifically bind to any conformation and/or secondary and/or tertiary and/or quaternary structure (where applicable) of said envelope protein.

In a first specific aspect, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state (as defined herein) of an envelope protein, which is a viral attachment protein (as defined herein), such as for example (but not limited to) amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state of a viral attachment protein, wherein said pre-fusion conformational state is characterized by a trimer of hairpins or a six-helical bundle; also, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the intermediate conformational state (as defined herein) of an envelope protein, which is a viral attachment protein; finally, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state (as defined herein) of an envelope protein, which is a viral attachment protein, such as for example (but not limited to) amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state of a viral attachment protein, wherein said post-fusion conformational state is characterized by a trimer of hairpins comprising an α-helical coiled coil or comprising an α-helical coiled coil and β-structures.

In this aspect of the invention, it is also encompassed that the amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state of said viral attachment protein; also, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the pre-fusion conformational state and to the post-fusion conformational state of said viral attachment protein; furthermore, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the intermediate conformational state and to the post-fusion conformational state of said viral attachment protein.

Furthermore, it is encompassed in this specific aspect of the present invention that the

amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state and to the post-fusion conformational state of said viral attachment protein.

In a second specific and preferable aspect, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state (as defined herein) of an envelope protein, which is a viral fusion protein (as defined herein), such as for example (but not limited to) amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state of a viral fusion protein, wherein said pre-fusion conformational state is characterized by a trimer of hairpins or a six-helical bundle; also, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the intermediate conformational state (as defined herein) of an envelope protein, which is a viral fusion protein; finally, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state (as defined herein) of an envelope protein, which is a viral fusion protein, such as for example (but not limited to) amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state of a viral fusion protein, wherein said post-fusion conformational state is characterized by a trimer of hairpins comprising an α-helical coiled coil or comprising an α-helical coiled coil and β-structures.

In this aspect of the invention, it is also encompassed that the amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state of said viral fusion protein; also, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the pre-fusion conformational state and to the post-fusion conformational state of said viral fusion protein; furthermore, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the intermediate conformational state and to the post-fusion conformational state of said viral fusion protein.

Furthermore, it is encompassed in this specific aspect of the present invention that the amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state and to the post-fusion conformational state of said viral fusion protein.

In a third specific aspect, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state (as defined herein) of an envelope protein, which is both a viral attachment protein and a viral fusion protein (as defined herein), such as for example (but not limited to)

amino acid sequences and polypeptides that are directed to and/or specifically bind to the pre-fusion conformational state of an envelope protein, which is both a viral attachment protein and a viral fusion protein, wherein said pre-fusion conformational state is characterized by a trimer of hairpins or a six-helical bundle; also, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the intermediate conformational state (as defined herein) of an envelope protein, which is both a viral attachment protein and a viral fusion protein; finally, the present invention provides amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state (as defined herein) of an envelope protein, which is both a viral attachment protein and a viral fusion protein, such as for example (but not limited to) amino acid sequences and polypeptides that are directed to and/or specifically bind to the post-fusion conformational state of an envelope protein, which is both a viral attachment protein and a viral fusion protein, wherein said post-fusion conformational state is characterized by a trimer of hairpins comprising an α-helical coiled coil or comprising an α-helical coiled coil and β-structures.

In this aspect of the invention, it is also encompassed that the amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state of said envelope protein, which is both a viral attachment protein and a viral fusion protein; also, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the pre-fusion conformational state and to the post-fusion conformational state of said envelope protein, which is both a viral attachment protein and a viral fusion protein; furthermore, the amino acid sequences and polypeptides of the invention can be directed to and/or can specifically bind to the intermediate conformational state and to the post-fusion conformational state of said envelope protein, which is both a viral attachment protein and a viral fusion protein.

Furthermore, it is encompassed in this specific aspect of the present invention that the amino acid sequences and polypeptides can be directed to and/or can specifically bind to the pre-fusion conformational state and to the intermediate conformational state and to the post-fusion conformational state of said envelope protein, which is both a viral attachment protein and a viral fusion protein.

As further described herein, a polypeptide of the invention may be bivalent and/or multivalent (as defined herein) and contain two or more amino acid sequences of the invention that are directed against an envelope protein of a virus. Generally, such polypeptides will bind to an envelope protein of a virus with increased avidity compared to a single amino acid sequence of the invention. It has also been observed that such polypeptides show (synergistically) increased binding, competition, and/or in vitro and/or in vivo neutralization of different genotypes, subtypes, escape mutants and/or strains of a

virus.

Such a polypeptide may for example comprise two amino acid sequences of the invention that are directed against the same antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus (which may or may not be an interaction site); or such a polypeptide may be biparatopic and/or multiparatopic (as defined herein) and comprise at least one "first" amino acid sequence of the invention that is directed against a first antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus (which may or may not be an interaction site); and at least one "second" amino acid sequence of the invention that is directed against a second antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of said envelope protein of a virus, wherein said second antigenic determinant, epitope, part, domain, subunit or conformation is different from the first (and again may or may not be an interaction site). Preferably, in such "bi- and/or multiparatopic" polypeptides of the invention, at least one amino acid sequence of the invention is directed against an interaction site (as defined herein), although the invention in its broadest sense is not limited thereto.

It is thus also within the scope of the invention that, where applicable, a polypeptide of the invention can bind to two or more antigenic determinants, epitopes, parts, domains, subunits or conformations of an envelope protein of a virus. In such a case, the antigenic determinants, epitopes, parts, domains or subunits of said envelope protein of a virus to which the amino acid sequences and/or polypeptides of the invention bind may be essentially the same (for example, if an envelope protein of a virus contains repeated structural motifs or occurs in a multimeric form) or may be different (and in the latter case, the amino acid sequences and polypeptides of the invention are said to be "bi- and/or multiparatopic" and may bind to such different antigenic determinants, epitopes, parts, domains, subunits of said envelope protein of a virus with an affinity and/or specificity which may be the same or different). Accordingly, bi- or multiparatopic polypeptides of the present invention are directed against and/or specifically bind to at least two epitopes of an envelope protein of a virus, and are for example (but not limited to) polypeptides that are directed against and/or can specifically bind to three or even more epitopes of the same envelope protein of a virus.

For example, and generally, a bivalent polypeptide of the invention may comprise two amino acid sequences of the invention directed against an antigenic determinant, epitope, part or domain of the viral envelope protein which may be suitably linked, for example via a suitable linker as further described herein. Preferably, such a bivalent polypeptide of the invention is further such that, when it binds to the viral envelope protein, it is capable of simultaneously binding to both antigenic determinants, epitopes, parts or domains (i.e. via the two amino acid sequences of the invention capable of binding to said antigenic

determinants, epitopes, parts or domains). Examples of such bivalent polypeptides of the invention will become clear from the further description herein. Also, a trivalent polypeptide of the invention may comprise three amino acid sequences of the invention directed against an antigenic determinant, epitope, part or domain of the viral envelope protein, and generally multivalent polypeptides of the invention may contain at least two amino acid sequences of the invention directed against an antigenic determinants, epitopes, parts or domains of the viral envelope protein. Generally, such bivalent, trivalent and multivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent, trivalent and multivalent polypeptides of the invention (for example, these bivalent, trivalent and multivalent polypeptides of the invention preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In one aspect of the invention, the amino acid sequences and (in particular) polypeptides of the invention are capable of binding to two or more antigenic determinants, epitopes, parts, domains of an envelope protein of a virus which are essentially the same. In this context, the amino acid sequences and polypeptides of the invention are also referred to as "multivalent (monospecific)" (such as e.g. "bivalent (monospecific)" or "trivalent (monospecific)", etc.) amino acid sequences and polypeptides. The multivalent amino acid sequences and polypeptides of the invention can be directed against any antigenic determinants, epitopes, parts, and/or domains of the envelope protein of a virus.

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention bivalent and are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein.

Generally, such a bivalent polypeptide of the invention may contain two amino acid sequences of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein). Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the

Synagis® binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis®.

In another preferred, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are bivalent and are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, The amino acid sequences and polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 423-436 of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein.

Generally, such a bivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the 101F binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as 101F.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of

competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the sialic acid binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the VN04-2 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as VN04-2.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of

competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb C179 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb C179.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are directed against the mAb 8-2 binding site (and preferably against an epitope located in the antigenic site IIa) on the G envelope protein of rabies and/or capable of competing with mAb 8-2 for binding to the G envelope protein.

Generally, such a bivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the mAb 8-2 binding site (and preferably an epitope located in the antigenic site IIa) on the G envelope protein and/or capable of competing with mAb 8-2 for binding to the G envelope protein. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the mAb 8-2 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are bivalent and are at least capable, upon binding to the G

envelope protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb 8-2.

In a preferred aspect, the amino acid sequences and (in particular) polypeptides of the invention are capable of binding to two or more different antigenic determinants, epitopes, parts, domains of an envelope protein of a virus. In this context, the amino acid sequences and polypeptides of the invention are also referred to as "multiparatopic" (such as e.g. "biparatopic" or "triparatopic", etc.) amino acid sequences and polypeptides. The multiparatopic amino acid sequences and polypeptides of the invention can be directed against any antigenic determinants, epitopes, parts, and/or domains of the envelope protein of a virus.

For example, and generally, a biparatopic polypeptide of the invention may comprise at least one amino acid sequence of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein and at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). Preferably, such a biparatopic polypeptide of the invention is further such that, when it binds to the viral envelope protein, it is capable of simultaneously binding to the first antigenic determinant, epitope, part or domain (i.e. via the at least one amino acid sequence of the invention capable of binding to said first antigenic determinant, epitope, part or domain) and binding to said second antigenic determinant, epitope, part or domain (i.e. via the at least one amino acid sequence of the invention capable of binding to said second antigenic determinant, epitope, part or domain). Examples of such biparatopic polypeptides of the invention will become clear from the further description herein. Also, a triparatopic polypeptide of the invention may comprise at least one further amino acid sequence of the invention directed against a third antigenic determinant, epitope, part or domain of the viral envelope protein (different from both the first and second antigenic determinant, epitope, part or domain), and generally multiparatopic polypeptides of the invention may contain at least two amino acid sequences of the invention directed against at least two different antigenic determinants, epitopes, parts or domains of the viral envelope protein. Generally, such biparatopic, triparatopic and multiparatopic polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic, triparatopic and multiparatopic polypeptides of the invention (for example, these biparatopic, triparatopic and multiparatopic polypeptides of the invention preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH}

sequences)).

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein, as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the at least one other antigenic determinant, epitope, part or domain on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis®.

In another preferred, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the

RSV F protein, as well as against at least one other antigenic determinant on the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 423-436 of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the 101F binding site and the at least one other antigenic determinant, epitope, part or domain on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as 101F.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic and are at least directed against the Synagis® binding site on the RSV F protein as well as against the 101F binding site on the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid

sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein. In another preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against region aa 423-436 of the RSV F protein. In another preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 423-436 of the RSV F protein. In another preferred aspect, the amino acid sequences and polypeptides of the invention are directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against the region aa 423-436 of the RSV F protein. In another preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against antigenic site IV-VI of the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as at least one amino acid sequence of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis® and 101F.

Again, the above biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention

(for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic with both paratopes directed against the Synagis® binding site on the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein (one paratope or both paratopes). In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against region aa 250-275 of the RSV F protein (one paratope or both paratopes).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic with both paratopes directed against the 101F binding site on the RSV F protein. The amino acid sequences and polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein (one paratope or both paratopes). In a preferred aspect, the amino acid sequences and polypeptides of the invention are directed against the region aa 423-436 of the RSV F protein (one paratope or both paratopes).

Again, the above biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind both binding sites; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on

the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the sialic acid binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the VN04-2 binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as VN04-2.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb C179 binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb C179.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the MAb 8-2 binding site on the G envelope protein of rabies and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as against at least one other antigenic determinant, epitope, part or domain on the G envelope protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for

binding to the G envelope protein, as well as at least one further amino acid sequence of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb 8-2 binding site and the at least one other antigenic determinant, epitope, part or domain on the G envelope protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the G envelope protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb 8-2.

Also, the polypeptides of the present invention may also be directed against and/or can specifically bind to at least one particular envelope protein of a virus and at least one further epitope of another target, which is different from said at least one particular envelope protein. For example (but not limited to), the polypeptides of the present invention may be directed against and/or can specifically bind to at least one particular envelope protein of a virus and at least one further epitope of a virus, for instance at least one further epitope of a viral protein, such as at least one further epitope of another particular viral envelope protein. Thus, the polypeptides according to the invention may be directed against and/or may specifically bind to at least two (or even more) epitopes of at least two different envelope proteins. Also, said at least one further epitope of a virus may or may not be involved in one or more of the viral-mediated biological pathways, in which an envelope protein of a virus and/or its viral receptor is involved; more specifically said at least one further epitope of a virus may or may not be involved in viral entry in a target host cell, such as virion attachment to a target host cell and/or viral fusion with a target host cell or said at least one further epitope of a virus may or may not be involved in viral replication in a target host cell, such as viral transcription and/or viral translation and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane.

Generally, bi-, and multivalent (as defined herein), bi-, and multispecific (as defined herein) and bi-, and multiparatopic (as defined herein) polypeptides according to the invention may be useful for the prevention and/or treatment of viral diseases by specifically binding

to at least one epitope of an envelope protein of a virus and at least one further epitope (which may or may not be different from said at least one epitope) of a target, wherein said target may or may not be different from said envelope protein.

Preferably, bi-, and multiparatopic polypeptides (as defined herein) according to the invention may be useful for the prevention and/or treatment of viral diseases by specifically binding to at least two (or even more) epitopes (which may be the same or different) on the same envelope protein of a virus.

Alternatively, the polypeptides of the present invention may be directed against and/or can specifically bind to at least one epitope of an envelope protein of a virus and at least one further epitope of another target, which is different from said particular envelope protein and which is for instance a further epitope of a virus, such as a further epitope of a viral protein or a further epitope of another particular viral envelope protein.

In another preferred aspect, the amino acid sequences and (in particular) polypeptides of the invention are capable of binding to three (different) antigenic determinants, epitopes, parts, domains of an envelope protein of a virus. In this context, the amino acid sequences and polypeptides of the invention are also referred to as "trivalent" (such as e.g. "trivalent triparatopic" or "trivalent biparatopic", "trivalent monoparatopic", etc.) amino acid sequences and polypeptides. The trivalent amino acid sequences and polypeptides of the invention can be directed against any antigenic determinants, epitopes, parts, and/or domains of the envelope protein of the virus.

For example, and generally, a trivalent polypeptide of the invention may comprise three amino acid sequences of the invention directed against the same antigenic determinant, epitope, part or domain of the viral envelope protein (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). A trivalent polypeptide of the invention may comprise two amino acid sequences of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, and at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent biparatopic". A trivalent polypeptide of the invention may comprise one amino acid sequence of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain and at least one amino acid sequence of the invention directed against a third antigenic

determinant, epitope, part or domain of the viral envelope protein different from the first and the second antigenic determinant, epitope, part or domain (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent triparatopic". A trivalent polypeptide of the invention may comprise two amino acid sequences of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, and at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein. Such a trivalent polypeptide of the invention may also be referred to as "trivalent bispecific". A trivalent polypeptide of the invention may also comprise one amino acid sequence of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of the same viral envelope protein different from the first antigenic determinant, epitope, part or domain and at least one amino acid sequence of the invention directed against a third antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent trispecific". A trivalent polypeptide of the invention may also comprise one amino acid sequence of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one amino acid sequence of the invention directed against a second antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein and at least one amino acid sequence of the invention directed against a third antigenic determinant, epitope, part or domain of a viral envelope protein different from the first and the second viral envelope protein (in which said amino acid sequences may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent trispecific".

Preferably, such a trivalent polypeptide of the invention is further such that, when it binds to the viral envelope protein, it is capable of simultaneously binding to the first antigenic determinant, epitope, part or domain (i.e. via the at least one amino acid sequence of the invention capable of binding to said first antigenic determinant, epitope, part or domain), binding to said second antigenic determinant, epitope, part or domain (i.e. via the at least one amino acid sequence of the invention capable of binding to said second antigenic determinant, epitope, part or domain) and binding to said third antigenic determinant, epitope, part or domain (i.e. via the at least one amino acid sequence of the invention capable of binding to said third antigenic determinant, epitope, part or domain). Examples of such trivalent polypeptides of the invention will become clear from the further

description herein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the two other antigenic determinants, epitopes, parts or domains on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa

250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and

in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis®.

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the 101F binding site and the two other antigenic determinants, epitopes, parts or domains on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of

the RSV F protein), as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the 101F binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the 101F binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as 101F.

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of

competing with Synagis for binding to the RSV F protein, as well as one amino acid sequence of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as one further amino acid sequence of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as two amino acid sequences of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F

protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain one amino acid sequence of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as two further amino acid sequences of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, one amino acid sequence of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. The amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the amino acid sequences and polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain one amino acid sequence of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against

region aa 250-275 of the RSV F protein), one further amino acid sequence of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as one further amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the Synagis® binding site, the 101F binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis® and/or 101F.

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the sialic acid binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus; and preferably

comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the sialic acid binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the sialic acid binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the

invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the VN04-2 binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the VN04-2 binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular)

polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the VN04-2 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as VN04-2.

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously

bind the MAb C179 binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb C179 binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb C179 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb C179.

In a preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise one amino acid sequence of the invention directed against the MAb 8-2 binding site on the G envelope protein of rabies and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as two amino acid sequences of the invention directed against another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain at least one amino acid sequence of the invention that is capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as two further amino acid sequences of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb 8-2 binding site and the two other antigenic determinants, epitopes, parts or domains on the G envelope protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise two amino acid sequences of the invention directed against the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as one amino acid sequence of the invention directed against another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain two amino acid sequences of the invention that are capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as one further amino acid sequence of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention

(for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb 8-2 binding site and the other antigenic determinant, epitope, part or domain on the G envelope protein; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and comprise three amino acid sequences of the invention directed against the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain three amino acid sequences of the invention that are capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; are preferably such that they can simultaneously bind the MAb 8-2 binding site; and preferably comprise single variable domains and more preferably NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the G envelope protein of rabies, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb 8-2.

Preferred bivalent and trivalent constructs of the invention are given in Tables C-6, Table A-2, Table A-4, Table A-5 and Table A-6.

Preferably, such bi-, tri-, and multivalent, bi-, tri-, and multispecific, and/or bi-, tri-, and multiparatopic polypeptides, as discussed hereabove, will bind to an envelope protein of a virus with increased avidity compared to a single amino acid sequence of the invention.

More specifically, bi-, tri-, and multiparatopic polypeptides and/or bi-, tri-, and multispecific polypeptides according to the invention may be useful in targeting multiple viral receptor binding sites on the same and on different envelope proteins, respectively, which can result in an increased potency of viral neutralization (as defined herein) compared to a single amino acid sequence of the invention. Also, bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be useful in binding different genotypes, different subtypes and/or different strains of

a certain virus. Also, bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be useful in preventing viral escape and/or viral evasion.

In a specific aspect of the invention, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H1N1. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1 as well as influenza subtype H3N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H1N1 as well as influenza subtype H3N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1 as well as influenza subtype H2N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H2N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H3N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H2N2 as well as influenza subtype H3N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1, influenza subtype H2N2, as well as influenza subtype H3N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind rabies genotype 1 as well as genotype 5. In yet another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against RSV and may bind different escape mutants of RSV (such as e.g. described in Lopez et al. 1998, J. Virol. 72: 6922-6928) and/or one or more escape mutants specific for antigen site II, specific for antigen site IV-VI or specific for the combination of both antigenic sites.

Finally, bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be useful in preventing and/or inhibiting viral infection and/or viral fusion of a virion with its target host cell (as defined herein) or may be useful in neutralizing a virus by inducing virion aggregation of said virus.

Generally, the amino acid sequences according to the present invention can be used to modulate, and in particular inhibit and/or prevent, the interaction between an envelope protein of a virus and a binding partner (e.g. viral receptor, target host cell, a particular cell membrane component or other binding partner, as applicable), and thus to modulate, and in particular inhibit, prevent or modulate viral-mediated biological pathway(s) in which an envelope protein of a virus and/or a viral receptor are involved. Thus, for example, when said envelope protein is part of a binding pair, the amino acid sequences and polypeptides may be such that they compete with the binding partner (e.g. viral receptor or other binding partner, as applicable) for binding to said envelope protein, and/or such that they (fully or partially) neutralize binding of the binding partner to the said envelope protein.

In this context, it is preferred that the amino acid sequences according to the invention can compete with a viral receptor of an envelope protein of a virus and/or with a target host cell for binding to said envelope protein.

When the amino acid sequences according to the invention compete with a target host cell for binding to said envelope protein, said amino acid sequences according to the invention may for example compete with particular cell membrane components of said target host cell, such as viral receptors, phospholipids, proteins, and/or glycoproteins, for binding to said envelope protein.

Viral receptors of enveloped proteins are known in the art and include but are not limited to the following examples: sialic acid, soluble (2,3) sialic acid, (2,6) sialic acid, CD4, CCR5, CXCR4, galactosylceramide, ACE2, HveA, CD155, ICAM-1, CAR, αv integrins, heparin sulphate proteoglycans, JAM-1, the Nicotinic Acetylcholine Receptor (AchR), the Neural Cell Adhesion Molecule (NCAM), and annexin II.

The amino acid sequences and polypeptides of the invention may compete with any of the foregoing viral receptors for binding to the envelope protein. Other examples of viral receptors will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may compete for binding to the envelope protein with any of the viral receptors that are disclosed in the handbook “Fields Virology”, 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

The amino acid sequences according to the present invention can generally be used to modulate, and in particular inhibit and/or prevent, the interaction between an envelope protein of a virus and a viral receptor and/or the interaction between an envelope protein of a virus and a target host cell.

When the amino acid sequences according to the invention modulate, and in particular

inhibit and/or prevent, the interaction between an envelope protein of a virus and a target host cell, said amino acid sequences according to the invention may for example modulate, and in particular inhibit and/or prevent, the interaction between an envelope protein of a virus and particular cell membrane components of said target host cell, such as viral receptors, phospholipids, proteins, and/or glycoproteins, for binding to said envelope protein.

In a preferred aspect, the amino acid sequences according to the present invention can generally be used to modulate, and in particular inhibit and/or prevent, the interaction between an envelope protein of a virus and a viral receptor. The amino acid sequences according to the present invention can generally be used to modulate, and in particular inhibit and/or prevent, the interaction between an envelope protein of a virus and a viral receptor wherein said interaction between an envelope protein and a viral receptor is chosen from the group consisting of the interaction of HA of influenza A virus with sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; the interaction of gp120 of HIV-1 virus with CD4; CCR5; CXCR4; and/or galactosylceramide; the interaction of S1 of SARS coronavirus with ACE2; the interaction of gD; gB; gC; the interaction of the heterodimer gH/gL of herpes simplex 1 virus and HveA; the interaction of VP1; VP2; VP3 of poliovirus 1 with CD155; the interaction of VP1; VP2; and/or VP3 of rhinovirus 3 with ICAM-1; the interaction of adenovirus 2 fibre with CAR; the interaction of adenovirus 2 penton base with αv integrins; sialic acid; (2,3) sialic acid; (2,6) sialic acid; and/or heparin sulphate proteoglycans; the interaction of σ1 of reovirus 1 with JAM-1; sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; and the interaction of G-protein of rabies virus with the Nicotinic Acetylcholine Receptor (AchR); and/or the Nueral Cell Adhesion Molecule (NCAM) (Thoulouze et al. 1998, J. Virol. 72: 7181-7190).

The amino acid sequences and polypeptides of the invention may generally be used to modulate, and in particular inhibit and/or prevent any of the foregoing interactions between an envelope protein of a virus and a viral receptor and/or between an envelope protein of a virus and particular cell membrane components of said target host cell, such as viral receptors, phospholipids, proteins, and/or glycoproteins.

Other examples of interactions between an envelope protein of a virus and a viral receptor will be clear to the skilled person; for instance, the amino acid sequences and polypeptides according to the invention may generally be used to modulate, and in particular inhibit and/or prevent any of the interactions between an envelope protein of a virus and a viral receptor that are disclosed in the handbook "Fields Virology", 5th edition (2007) by David M. Knipe, PhD; Peter M. Howley, MD; Diane E. Griffin, MD, PhD; Robert A. Lamb, PhD, ScD; Malcolm A. Martin, MD; Bernard Roizman, ScD; Stephen E. Straus, MD (ISBN-10: 0781760607; ISBN-13: 9780781760607).

In this context, the bi-, tri, and multiparatopic polypeptides according to the invention as described above, may compete with at least one, at least two or at least three (or even more) viral receptors of at least one or at least two (or even more) envelope proteins of a virus for binding to said envelope proteins.

Furthermore, the amino acid sequences and polypeptides according to the invention may also compete with at least one binding partner of an envelope protein of a virus (which is different from its natural viral receptor) for binding to said envelope protein. With at least one binding partner of an envelope protein is generally meant any molecule that is directed against and/or specifically binds to said envelope protein. For instance, a binding partner of an envelope protein can be an immunoglobulin, such as an antibody and can more specifically be a monoclonal antibody or any fragment thereof that can specifically bind said envelope protein. In this context, the amino acid sequences and polypeptides according to the invention may compete with a monoclonal antibody that is directed against and/or specifically binds to an envelope protein for binding to said envelope protein. For example, the amino acid sequences and polypeptides according to the invention may compete with the monoclonal antibody Synagis® (Zhao and Sullender J. Virol. 79: 396 (2005)) that is directed against and/or specifically binds to the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus for binding to said F-protein of RSV virus; and/or the amino acid sequences and polypeptides according to the invention may compete with the monoclonal antibody 9C5 (Krivitskaia et al., Vopr. Virusol. 44: 279 (1999)) that is directed against and/or specifically binds to the Fla site and/or the region comprising amino acid 389 of the F-protein of RSV virus for binding to said F-protein of RSV virus; and/or the amino acid sequences and polypeptides according to the invention may compete with the Fab fragment 101F (Wu et al., J. Gen Virol. 88: 2719 (2007)) that is directed against and/or specifically binds to amino acids 422 to 438 of the F-protein of RSV virus for binding to said F-protein of RSV virus; and/or the amino acid sequences and polypeptides according to the invention may compete with the monoclonal antibody VN04-2 (Hanson et al. Respiratory Research 7: 126 (2006)) that is directed against and/or specifically binds to the sialic acid binding site of the hemagglutinin H5 envelope protein of influenza virus for binding to said hemagglutinin H5 envelope protein; and/or the amino acid sequences and polypeptides according to the invention may compete with the monoclonal antibody C179 (Okkuno et al. J. Virol. 67: 255202558 (1993)) that is directed against and/or specifically binds to the stem region of the hemagglutinin H5 envelope protein of influenza virus for binding to said hemagglutinin H5 envelope protein; and/or the amino acid sequences and polypeptides according to the invention may compete with the monoclonal antibody MAb 8-2 or mAb 8-2 a mouse IgG2alpha (Montaño-Hirose et al. *Vaccine* 11(12):1259-1266 (1993)) that is directed against and/or specifically binds to the G envelope protein of rabies virus for binding to said G envelope protein.

In this context, the bi-, tri- and multiparatopic polypeptides according to the invention as

described above, may compete with at least one, at least two, at least three (or even more) binding partners of at least one, at least two, at least three (or even more) envelope proteins of a virus for binding to said envelope proteins, wherein said binding partners may be any molecules that are directed against and/or specifically bind to said envelope proteins, such as for instance, an immunoglobulin, such as an antibody and more specifically a monoclonal antibody or any fragment thereof that can specifically bind to said envelope protein. For instance, said bi-, tri- or multiparatopic polypeptides according to the invention may compete with the monoclonal antibody Synagis® (as described above) and/or the monoclonal antibody 9C5 (as described above) and/or the Fab fragment 101F Fab or any suitable combination thereof, for binding to the F-protein of RSV virus. Said bi-, tri- or multiparatopic polypeptides according to the invention may compete with VN04-2 and/or MAb C179 for binding the hemagglutinin H5 envelope protein of influenza virus. Said bi-, tri- or multiparatopic polypeptides according to the invention may compete with MAb 8-2 for binding to the G envelope protein of rabies virus.

The present invention is in its broadest sense also not particularly limited to or defined by a specific antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus against which the amino acid sequences and polypeptides of the invention are directed. For example, the amino acid sequences and polypeptides may or may not be directed against an "interaction site" (as defined herein).

However, it is generally assumed and preferred that the amino acid sequences and polypeptides of the invention are preferably directed against an interaction site (as defined herein), and in particular against at least one epitope of an envelope protein of a virus, such that at least one viral-mediated biological pathway in which an envelope protein of a virus and/or a viral receptor are involved is inhibited, prevented and/or modulated.

In particular, it is assumed and preferred that the amino acid sequences, polypeptides and compositions of the present invention are directed against at least one epitope of an envelope protein of a virus, such that viral entry in a target host cell (such as for instance virion attachment to a target host cell and/or viral fusion with a target host cell) and/or viral replication in a target host cell (such as for instance viral transcription and/or viral translation and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane) is inhibited, prevented and/or modulated.

The amino acid sequences and polypeptides may be directed against at least one epitope of an envelope protein of a virus that is surface-exposed or that is located in a cavity or cleft formed by an envelope protein of a virus. The amino acid sequences and polypeptides of the invention may be directed against an interaction site (as defined herein), and in particular against an epitope that is located in a cavity or cleft formed by a trimer of fusion

proteins (such as a fusion protein trimer that is a trimer of hairpins or a six-helix bundle) or a dimer of fusion proteins, wherein said fusion proteins can be in their pre-, intermediate, or post-fusion conformational state.

Furthermore, the amino acid sequences and polypeptides of the invention may also be directed against an epitope that is located in the stem region and/or in the neck region and/or in the globular head region of a fusion protein. Preferably, the amino acid sequences and polypeptides of the invention are directed against an epitope that is located in the stem region of a fusion protein, such as for instance against an epitope that is located in the region comprising one or more of the amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA; against an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA; against an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA; against an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA; or against an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA. Alternatively, the amino acid sequences and polypeptides of the invention may be directed against an epitope that is located in the globular head of a fusion protein (wherein said globular head may for example comprise a β-barrel-type structure or an immunoglobulin-type β-sandwich domain and a β-sheet domain).

Also, in particular, the amino acid sequences and polypeptides of the invention may preferably be directed against an interaction site, which is chosen from the group consisting of the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus, the F1a site and/or the region comprising amino acid 389 of the F-protein of RSV virus, amino acids 422 to 438 of the F-protein of RSV virus, sialic acid binding site of the H5 HA envelope protein of influenza virus, the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus (Thoulouze et al. 1998, J. Virol. 72: 7181-7190).

In one aspect of the invention the amino acids and polypeptides of the invention are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein. In particular, they may be directed against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein.

In another aspect of the invention the amino acids and polypeptides of the invention are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. In particular, they may be directed against

antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein.

In yet another aspect of the invention the amino acids and polypeptides of the invention are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect of the invention the amino acids and polypeptides of the invention are directed against the MAb 179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb 179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect of the invention the amino acids and polypeptides of the invention are directed against the MAb 8-2 binding site on G envelope protein of rabies virus and/or capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.

The amino acid sequences and polypeptides of the invention may also be directed against any epitope that is located in the C-terminal region of a fusion protein and/or in the N-terminal domain of a fusion protein and/or in or comprising the fusion peptide of a fusion protein and/or in the transmembrane domain of a fusion protein and/or in a α-helical coiled-coil of a fusion protein and/or in a β-structure of a fusion protein and/or in Domain I of a fusion protein and/or in Domain II of a fusion protein, such as for example in the fusion peptide of Domain II of a fusion protein, and/or in Domain III of a fusion protein, such as for example in the stem region at the C-terminus of Domain III of a fusion protein or in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.

Also, the amino acid sequences and polypeptides of the invention may be directed against any other epitope of an envelope protein of a virus (for instance any other epitope that is close to one of the aforementioned epitopes).

Thus, in one preferred, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are generally directed against any epitope or in particular against one of the above-mentioned epitopes of an envelope protein of a virus, and are as further defined herein. For example, said epitope may be present on an envelope protein of a virus that is chosen from the group consisting of the F protein of RSV virus, the G protein of RSV virus, the SH protein of RSV virus, the M protein of RSV virus, the M2 protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2, σ1 of Reovirus 1, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus,

the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

Accordingly, the amino acid sequences and polypeptides of the invention may be directed against any epitope that is present on an envelope protein of a virus, which is chosen from the group consisting of the F protein of RSV virus, the G protein of RSV virus, the SH protein of RSV virus, the M protein of RSV virus, the M2 protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the 51 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2, σ1 of Reovirus 1, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

It is also within the scope of the invention that, where applicable, an amino acid sequence of the invention can bind to two or more antigenic determinants, epitopes, parts, domains, subunits or conformations of said envelope protein of a virus. In such a case, the antigenic determinants, epitopes, parts, domains or subunits of said envelope protein of a virus to which the amino acid sequences and/or polypeptides of the invention bind may be essentially the same (for example, if said envelope protein of a virus contains repeated structural motifs or occurs in a multimeric form) or may be different (and in the latter case, the amino acid sequences and polypeptides of the invention may bind to such different antigenic determinants, epitopes, parts, domains, subunits of said envelope protein of a virus with an affinity and/or specificity which may be the same or different). Also, for example, when said envelope protein of a virus exists in an activated conformation and in

an inactive conformation or a pre-fusion and post-fusion conformation or state, the amino acid sequences and polypeptides of the invention may bind to either one of these conformations or states, or may bind to both these conformations or states (i.e. with an affinity and/or specificity which may be the same or different).

It is also expected that the amino acid sequences and polypeptides of the invention will generally bind to all naturally occurring or synthetic analogs, variants, mutants, alleles, parts and fragments of said envelope protein of a virus; or at least to those analogs, variants, mutants, alleles, parts and fragments of said envelope protein of a virus that contain one or more antigenic determinants or epitopes that are essentially the same as the antigenic determinant(s) or epitope(s) to which the amino acid sequences and polypeptides of the invention bind to said envelope protein of a virus (e.g. in wild-type viral envelope proteins). Again, in such a case, the amino acid sequences and polypeptides of the invention may bind to such analogs, variants, mutants, alleles, parts and fragments with an affinity and/or specificity that are the same as, or that are different from (i.e. higher than or lower than), the affinity and specificity with which the amino acid sequences of the invention bind to (wild-type) said envelope protein of a virus. It is also included within the scope of the invention that the amino acid sequences and polypeptides of the invention bind to some analogs, variants, mutants, alleles, parts and fragments of said envelope protein of a virus, but not to others.

In a specific aspect of the invention, the amino acid sequences are multivalent (such as bivalent or trivalent) and show improved affinity and/or improved cross-reactivity for different genotypes, subtypes, viral escape mutants and/or strains of a certain virus compared to the monovalent amino acid sequence. In one aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H1N1. In another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H3N2. In another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H1N1 as well as influenza subtype H3N2. In another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H2N2. Yet in another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H3N2. Yet in another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H2N2 as well as influenza subtype H3N2. Yet in another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H2N2. Yet in another aspect, the amino acid sequences are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1, influenza subtype H2N2 as well as influenza subtype H3N2. In another aspect, the amino acid sequences are directed against rabies virus and may bind

rabies genotype 1 as well as genotype 5. In yet another aspect, the amino acid sequences are directed against RSV and may bind different strains of RSV (such as e.g. Long, A-2 and/or B-1). In yet another aspect, the amino acid sequences are directed against RSV and may bind different escape mutants of RSV (such as e.g. described in Lopez et al. 1998, J. Virol. 72: 6922-6928) and/or escape mutants specific for antigen site II, antigen site IV-VI or the combination of both antigenic sites.

When said envelope protein of a virus exists in a monomeric form and in one or more multimeric forms, it is within the scope of the invention that the amino acid sequences and polypeptides of the invention only bind to said envelope protein of a virus in monomeric form, only bind to said envelope protein of a virus in multimeric form, or bind to both the monomeric and the multimeric form. Again, in such a case, the amino acid sequences and polypeptides of the invention may bind to the monomeric form with an affinity and/or specificity that are the same as, or that are different from (i.e. higher than or lower than), the affinity and specificity with which the amino acid sequences of the invention bind to the multimeric form.

For example, when the envelope protein of a virus exists in a monomeric form and in a trimeric forms, it is within the scope of the invention that the amino acid sequences and polypeptides of the invention only bind to said envelope protein of a virus in monomeric form, only bind to said envelope protein of a virus in trimeric form, or bind to both the monomeric and the trimeric form. Again, in such a case, the amino acid sequences and polypeptides of the invention may bind to the monomeric form with an affinity and/or specificity that are the same as, or that are different from (i.e. higher than or lower than), the affinity and specificity with which the amino acid sequences of the invention bind to the trimeric form.

Also, when said envelope protein of a virus can associate with other proteins or polypeptides to form protein complexes (e.g. with multiple subunits), it is within the scope of the invention that the amino acid sequences and polypeptides of the invention bind to said envelope protein of a virus in its non-associated state, bind to said envelope protein of a virus in its associated state, or bind to both.

In all these cases, the amino acid sequences and polypeptides of the invention may bind to such multimers or associated protein complexes with an affinity and/or specificity that may be the same as or different from (i.e. higher than or lower than) the affinity and/or specificity with which the amino acid sequences and polypeptides of the invention bind to said envelope protein of a virus in its monomeric and non-associated state.

Also, as will be clear to the skilled person, proteins or polypeptides that contain two or more amino acid sequences directed against said envelope protein of a virus may bind with higher avidity to said envelope protein of a virus than the corresponding monomeric amino

acid sequence(s). For example, and without limitation, proteins or polypeptides that contain two or more amino acid sequences directed against different epitopes of said envelope protein of a virus may (and usually will) bind with higher avidity than each of the different monomers, and proteins or polypeptides that contain two or more amino acid sequences directed against said envelope protein of a virus may (and usually will) bind also with higher avidity to a multimer (such as e.g. a trimer) of said envelope protein of a virus.

Generally, amino acid sequences and polypeptides of the invention will at least bind to those forms of said envelope protein of a virus (including monomeric, multimeric and associated forms) that are the most relevant from a biological and/or therapeutic point of view, as will be clear to the skilled person.

It is also within the scope of the invention to use parts, fragments, analogs, mutants, variants, alleles and/or derivatives of the amino acid sequences and polypeptides of the invention, and/or to use proteins or polypeptides comprising or essentially consisting of one or more of such parts, fragments, analogs, mutants, variants, alleles and/or derivatives, as long as these are suitable for the uses envisaged herein. Such parts, fragments, analogs, mutants, variants, alleles and/or derivatives will usually contain (at least part of) a functional antigen-binding site for binding against said envelope protein of a virus; and more preferably will be capable of specific binding to said envelope protein of a virus, and even more preferably capable of binding to said envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein. Some non-limiting examples of such parts, fragments, analogs, mutants, variants, alleles, derivatives, proteins and/or polypeptides will become clear from the further description herein. Additional fragments or polypeptides of the invention may also be provided by suitably combining (i.e. by linking or genetic fusion) one or more (smaller) parts or fragments as described herein.

In one specific, but non-limiting aspect of the invention, which will be further described herein, such analogs, mutants, variants, alleles, derivatives have an increased half-life in serum (as further described herein) compared to the amino acid sequence from which they have been derived. For example, an amino acid sequence of the invention may be linked (chemically or otherwise) to one or more groups or moieties that extend the half-life (such as PEG), so as to provide a derivative of an amino acid sequence of the invention with increased half-life.

In one specific, but non-limiting aspect, the amino acid sequence of the invention may be an amino acid sequence that comprises an immunoglobulin fold or may be an amino acid sequence that, under suitable conditions (such as physiological conditions) is capable of forming an immunoglobulin fold (i.e. by folding). Reference is inter alia made to the review

by Halaby et al. (1999, Protein Eng. 12: 563-71). Preferably, when properly folded so as to form an immunoglobulin fold, such an amino acid sequence is capable of specific binding (as defined herein) to said envelope protein of a virus; and more preferably capable of binding to said envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein. Also, parts, fragments, analogs, mutants, variants, alleles and/or derivatives of such amino acid sequences are preferably such that they comprise an immunoglobulin fold or are capable for forming, under suitable conditions, an immunoglobulin fold.

In particular, but without limitation, the amino acid sequences of the invention may be amino acid sequences that essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively); or any suitable fragment of such an amino acid sequence (which will then usually contain at least some of the amino acid residues that form at least one of the CDR's, as further described herein).

The amino acid sequences of the invention may in particular be an immunoglobulin sequence or a suitable fragment thereof, and more in particular be an immunoglobulin variable domain sequence or a suitable fragment thereof, such as light chain variable domain sequence (e.g. a V_L-sequence) or a suitable fragment thereof; or a heavy chain variable domain sequence (e.g. a V_H-sequence) or a suitable fragment thereof. When the amino acid sequence of the invention is a heavy chain variable domain sequence, it may be a heavy chain variable domain sequence that is derived from a conventional four-chain antibody (such as, without limitation, a V_H sequence that is derived from a human antibody) or be a so-called V_{HH}-sequence (as defined herein) that is derived from a so-called “heavy chain antibody” (as defined herein).

However, it should be noted that the invention is not limited as to the origin of the amino acid sequence of the invention (or of the nucleotide sequence of the invention used to express it), nor as to the way that the amino acid sequence or nucleotide sequence of the invention is (or has been) generated or obtained. Thus, the amino acid sequences of the invention may be naturally occurring amino acid sequences (from any suitable species) or synthetic or semi-synthetic amino acid sequences. In a specific but non-limiting aspect of the invention, the amino acid sequence is a naturally occurring immunoglobulin sequence (from any suitable species) or a synthetic or semi-synthetic immunoglobulin sequence, including but not limited to “humanized” (as defined herein) immunoglobulin sequences (such as partially or fully humanized mouse or rabbit immunoglobulin sequences, and in particular partially or fully humanized V_{HH} sequences or NANOBODIES® (V_{HH} sequences)), “camelized” (as defined herein) immunoglobulin sequences, as well as immunoglobulin sequences that have been obtained by techniques such as affinity maturation (for example,

starting from synthetic, random or naturally occurring immunoglobulin sequences), CDR grafting, veneering, combining fragments derived from different immunoglobulin sequences, PCR assembly using overlapping primers, and similar techniques for engineering immunoglobulin sequences well known to the skilled person; or any suitable combination of any of the foregoing. Reference is for example made to the standard handbooks, as well as to the further description and prior art mentioned herein.

Similarly, the nucleotide sequences of the invention may be naturally occurring nucleotide sequences or synthetic or semi-synthetic sequences, and may for example be sequences that are isolated by PCR from a suitable naturally occurring template (e.g. DNA or RNA isolated from a cell), nucleotide sequences that have been isolated from a library (and in particular, an expression library), nucleotide sequences that have been prepared by introducing mutations into a naturally occurring nucleotide sequence (using any suitable technique known per se, such as mismatch PCR), nucleotide sequence that have been prepared by PCR using overlapping primers, or nucleotide sequences that have been prepared using techniques for DNA synthesis known per se.

The amino acid sequence of the invention may in particular be a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a NANOBODY® (V_{HH} sequence) (as defined herein, and including but not limited to a V_{HH} sequence); other single variable domains, or any suitable fragment of any one thereof. For a general description of (single) domain antibodies, reference is also made to the prior art cited above, as well as to EP 0 368 684. For the term "dAb's", reference is for example made to Ward et al. (Nature 1989 Oct. 12; 341 (6242): 544-6), to Holt et al., Trends Biotechnol., 2003, 21(11):484-490; as well as to for example WO 06/030220, WO 06/003388 and other published patent applications of Domantis Ltd. It should also be noted that, although less preferred in the context of the present invention because they are not of mammalian origin, single domain antibodies or single variable domains can be derived from certain species of shark (for example, the so-called "IgNAR domains", see for example WO 05/18629).

In particular, the amino acid sequence of the invention may be a NANOBODY® (V_{HH} sequence) (as defined herein) or a suitable fragment thereof [Note: NANOBODY® (V_{HH} sequence), NANOBODIES® (V_{HH} sequences) and NANOCLONE® are registered trademarks of Ablynx N.V.] Such NANOBODIES® (V_{HH} sequences) directed against an envelope protein of a virus will also be referred to herein as "NANOBODIES® (V_{HH} sequences) of the invention".

For a general description of NANOBODIES® (V_{HH} sequences), reference is made to the further description below, as well as to the prior art cited herein. In this respect, it should

however be noted that this description and the prior art mainly described NANOBODIES® (V_{HH} sequences) of the so-called "V_H3 class" (i.e. NANOBODIES® (V_{HH} sequences) with a high degree of sequence homology to human germline sequences of the V_H3 class such as DP-47, DP-51 or DP-29), which NANOBODIES® (V_{HH} sequences) form a preferred aspect of this invention. It should however be noted that the invention in its broadest sense generally covers any type of NANOBODY® (V_{HH} sequence) directed against an envelope protein of a virus, and for example also covers the NANOBODIES® (V_{HH} sequences) belonging to the so-called "V_H4 class" (i.e. NANOBODIES® (V_{HH} sequences) with a high degree of sequence homology to human germline sequences of the V_H4 class such as DP-78), as for example described in WO 07/118670.

Generally, NANOBODIES® (V_{HH} sequences) (in particular V_{HH} sequences and partially humanized NANOBODIES® (V_{HH} sequences)) can in particular be characterized by the presence of one or more "Hallmark residues" (as described herein) in one or more of the framework sequences (again as further described herein).

Thus, generally, a NANOBODY® (V_{HH} sequence) can be defined as an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which one or more of the Hallmark residues are as further defined herein.

In particular, a NANOBODY® (V_{HH} sequence) can be an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which the framework sequences are as further defined herein.

More in particular, a NANOBODY® (V_{HH} sequence) can be an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- i) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the

Hallmark residues mentioned in Table B-2 below;
and in which:

- ii) said amino acid sequence has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences (indicated with X in the sequences of SEQ ID NO's: 1 to 22) are disregarded.

In these NANOBODIES® (V_{HH} sequences), the CDR sequences are generally as further defined herein.

Thus, the invention also relates to such NANOBODIES® (V_{HH} sequences) that can bind to (as defined herein) and/or are directed against an envelope protein of a virus, to suitable fragments thereof, as well as to polypeptides that comprise or essentially consist of one or more of such NANOBODIES® (V_{HH} sequences) and/or suitable fragments.

SEQ ID NO's 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) give the amino acid sequences of a number of V_{HH} sequences that have been raised against an envelope protein of a virus.

TABLE A-1 Preferred V_{HH} sequences or NANOBODY® (V_{HH} sequences)(also referred herein as a sequence with a particular name or SEQ ID NO: X, wherein X is a number referring to the relevant amino acid sequence): Name SEQ ID NO: Amino acid sequence LG202A10 126
EVQLVESGGGLVQAGDSLRLSCIDSGRTFSDYPIGWFRQAPGKEREFVAAI
YAIGGDVYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAIYSCAVASGG
GSIRSARRYDYWGRGTQVTVSS LG202A12 127
EVQLVESGGGLVQAGGSLRLSCAASGGTFSSYAMGWFRQAPGKERDFVSAI
TWSGGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADDQK
YDYIAYAEYEYDYWGQGTQVTVSS LG202A5 128
EVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI
NNIGEEAYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202A9 129
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWHN
DPNKNEYKGQGTQVTVSS LG202B10 130
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGDEVYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCTRDWYN
DPNKNEYKGQGTQVTVSS LG202B7 131
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGDEVYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCTRDWFD

DPNKNEYKGQGTQVTVSS LG202B8 132
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYWMSWVRQAPGKGLEWVSAI
SNSGGETYYADSVKGRFTISRDNAKNTLYLQMNSLRSEDTAVYYCTRDWHS
DPNKHEYRGQGTQVTVSS LG202B9 133
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNLGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWYD
DPNKNEYKGQGTQVTVSS LG202C1 134
KVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI
NNIGEEAYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202C11 135
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWHN
DPNKNEYKGQGTQVTVSS LG202C2 136
EVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI
NNIGEEAYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202C7 137
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYWMSWVRQAPGKGLEWVSAI
NNVGDETYYANSVKGRFTIARDNTKRTLYLQMNSLKSEDTAVYYCTRDWHS
EPNKYEYKGQGTQVTVSS LG202C8 138
EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSGI
SPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSLTL
TDSPDLRSQGTQVTVSS LG202C9 139
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGETYYADSVKGRFTISRDNAKNALYLQMNSLKSEDTAVYYCARDWYN
DPNKNEYKGQGTQVTVSS LG202D5 140
EVQLVESGGGLVQAGGSLRLSCAASGSTGSSTAMGWSRQAPGKQREWVASI
SSAGTIRYVDSVKGRFTISRDNAKNTGYLQMNSLKPEDTAVYYCYVVGNFT TYWGRGTQVTVSS
LG202D7 141 EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNLGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWYD
DPNKNEYKGQGTQVTVSS LG202D8 142
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGDEVYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCTRDWYN
DPNKNEYKGQGTQVTVSS LG202E11 143
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGDEVYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCTRDWYN
DPNKNEYKGQGTQVTVSS LG202E2 144
EVQLVESGGGLVQPGGSLRLSCAASGFTFGGYWMTWVRQAPGKGLEWVSSI
ANDGKSTYYVDSVKGRFSISRDNAKNTLYLQMNSLKSEDTAVYYCVRDWAS
DYAGYSPNSQGTQVTVSS LG202E5 145
EVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI

NNIGEETYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202E6 146
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAI
SWSGRTTYYADFVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLSP
GNEYGEMMEYEYDYWGEGTQVTVSS LG202E7 147
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGETYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAAYYCARDWYN
DPNKNEYKGQGTQVTVSS LG202F10 148
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNLGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWYD
DPNKNEYKGQGTQVTVSS LG202F12 149
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYWMSWVRQAPGKGLEWVSAI
NNVGGDTYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCARDWYN
DPNKNEYKGQGTQVTVSS LG202F3 150
EVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI
NNIGEEAYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202F4 151
EVQLVESGGDLVQPGGSLRLSCAASGFTFRGYWMTWVRQAPGKGLEWVSSI
NNIGEEAYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202F8 152
EVQLVESGGGLVQPGGSLRLSCAASGLIFSSYDMGWFRQAPGEERAFVGAI
SRSGDVRYVDPVKGRFTITRDNAKNTVYLQMNSLKPEDTAVYYCAADADGW
WHRGQAYHWWGQGTQVTVSS LG202G11 153
EVQLVESGGGLVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGETYYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAAYYCARDWYN
DPNKNEYKGQGTQVTVSS LG202G3 154
EVQLMESGGGLVQAGGSLRLSCAASGRTFSGYTMGWFRQAPGKGREWVAGI
SWSGDSTYYADSVKGRFTISREDAKNTVYLQMNSLKPGDTADYYCAAECAM
YGSSWPPPCMDWGQGTQVTVSS LG202G8 155
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNLGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWYD
DPNKNEYKGQGTQVTVSS LG202H2 156
EVQLVESGGDLVQPGGSLRLSCAASGFTFSGYWMTWVRQAPGKGLEWVSSI
NNIGEEVYYVDSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCVKDWAS
DYAGYSPNSQGTQVTVSS LG202H8 157
EVQLVESGGGSVQPGGSLRLSCAASGFTFRGYWMSWVRQAPGKGLEWVSAI
NNVGGDTYYADSVKGRFTISRDNAKNMLYLQMNSLKAEDTAVYYCARDWHN
DPNKNEYKGQGTQVTVSS LG191B9 158
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSSFMAWFRQVLGSDREFVGGI
SPGGRFTYYADSRKGRFTISGDNANNTVYLQMHSVKPEDTATYYCAADTQF

SGYVPKETNEYDYWGQGTQVTVSS LG191D3 159
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAV
SRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELT
NRNSGAYYYAWAYDYWGQGTQVTVSS LG192A8 160
EVQLVESGGGLVQAGGSLRLSCAASERTVIAYTMGWFRRAPGKERDFVAAM
NWNGGNTIYADSAKGRFTISRDNAKNTVYLQMNSLKAEDTAVYYCAARPRF
WGSYEYDYWGQGTQVTVSS LG192B1 161
EVQLVESGGGLVQPGGSLRLSCAASGLTFRNYAIGWFRQAPGKEREGVSCI
NSGGSITDYLDSVKGRFAISRDNAKSTVYLQMNSLKPEDTAVYYCATDLTS
SCPIYSGTDYWGKGTLVTVSS LG192C10 162
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SDTAYYADSVKGRFTISRDNAKNTVYLPMNSLKPEDTAVYYCAAAPKSWGT
WPLVADTRSYHFWGQGTQVTVSS LG192C4 163
EVQLVESGGGLVQAGGSLRLSCEASGRTFSSYAMVGWFRQAPGKEREFVAA
VTRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADS
TNRNSGAVYYSWAYDYWGQGTQVTVSS LG192C6 164
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TRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNRGAIYYTWAYDYWGQGTQVTVSS LG192D3 165
EVQLVESGGGLVQAGGSLRLSCATSGRTRSRYTMGWFRQAPGKEREFVAAI
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GTGYSDNYYSTSEEYDYWGQGTQVTVSS LG191E4 166
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YIYSDSLSERSYDYWGQGTQVTVSS LG192F2 167
EVQLVESGGGLVQAGGSLRLSCEASGRTFSPIAMGWFRQAPGKEREFVAVV
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LG192H2 169 EVQLVESGGGLVQAGGSLRLSCEASGRTFSNYAMGWFRQAPGKEREFVAVV
TRWSGGRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAWYYTWAYDHWGQGTQVTVSS LG20610B 170
EVQLVESGGGLVQAGGSLRLSCTASGRTFSSYAMGWFRQTPGKEREFVASI
SWIGKFTYYADSVKGRFTISGENAKNTVYLQMNSLKPEDTAVYYCAAKTLV
GVTTAFDRWGQGTQVTVSS LG20610C 171
EVQLVESGGGLVQTGGSLRLSCAASGRTFSSSFMAWFRQALGSDREFVGGI
SPGGRITYYADSRKGRFTISRDNANNTVYLQMDSLKPEDTATYYCAADTQY
SGVVLKESTDYDYWGQGTQVTVSS LG20610D 172
EVQLVESGGGLVQTGGSLRLSCAASGRTFSSSFMAWFRQALGSDREFVGGI

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SGVVLKESTDYDYWGQGTQVTVSS LG20610E 173
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VTTILWNYWGQGTQVTVSS LG20610F 174
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WGSYEYDYWGQGTQVTVSS LG20611D 175
EVQLVESGGGLVQAGGSLRLSCAASERTVIAYTMGWFRRAPGKERDFVAAM
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WGSYEYDYWGQGTQVTVSS LG20611H 176
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WPLVADTRSYHFWGQGTQVTVSS LG20612F 177
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WPLVADTRSYHFWGQGTQVTVSS LG2062A 178
EVQLVESGGGLVQAGGSLRLSCEASGRTFSNYAMGWFRQAPGKEREFVAVV
TRWSGGRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAWYYTWAYDHWGQGTQVTVSS LG2062C 179
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YSNWDRASQYDYWGQGTQVTVSS LG2062E 180
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NRNSGAYYYAWAYDYWGQGTQVTVSS LG2062G 182
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EVQLVESGGGLVQPGGSLRLSCAASGSSFSINAMGWFRQAPGKEREFVAVV
TRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAVYYTWAYDYWGQGTQVTVSS LG2063A 184
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NRNSGAVYYTWAWDYWGQGTQVTVSS LG2063B 185
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NRNSGAYYYTWAYDYWGQGTQVTVSS LG2063D 187
EVQLVESGGGLVQAGGSLRLSCEASGRSFSSVAMGWFRQAPGKEREFVAAL
SRWSGARTVYADSVKGRFTISGDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAVYYTWAYDYWGQGTQVTVSS LG2063E 188
EVQLVESGGGLVQAGGSLRLSCEASGRTFSSYAMGWFRQAPGKEREFVAVV
TRWSGGRTVYABSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAWYYTWAYDHWGQGTQVTVSS LG2063F 189
EVQLVESGGGLVQAGGSLRLSCEASGRTFSRYGMGWFRQAPGKEREFVAAV
SRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELT
NRNSGAYYYTWAYDYWGQGTQVTVSS LG2064D 190
EVQLVESGGGLVQAGGSLRLSCEASGRTFSPIAMGWFRQAPGKEREFVAVV
TRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAIYYTWAYDYWGQGTQVTVSS LG2064G 191
EVQLVESGGGLVQAGGSLRLSCEASGRTFSSVAMGWFRQAPGKEREFVAAV
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NRNSGAVYYPWAYDYWGQGTQVTVSS LG2065A 192
EVQLVESGGGLVQAGGSLRLSCEASRRTFSSYAMVGWFRQAPGKEREFVAA
VTRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADS
TNRNSGAVYYSWAYDYWGQGTQVTVSS LG2065E 193
EVQLVESGGGLVQAGGSLRLSCEASGRTERYQAMGWFRQAPGKEREFVAVV
TRWSGARTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAADST
NRNSGAIYYTWAYDYWGQGTQVTVSS LG2066A 194
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VMPLRSNDYWGQGTQVTVSS LG2067B 196
EVQLVESGGGSVQPGGSARLSCAVLGSIGSLNAMGWYRQTPGKERELVARI
TSLGPIMYAEFVKGRFTISRDNDKNTVYLQMNSLKPEDTAVYYCKTRWYEG
IWREYWGQGTRVTVSS LG2067C 197
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IWYQKDYRAYDAWGRGTQVTVSS LG2067E 198
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NWNGGNTIYADSAKGRFTISRDNAKNTVYLQMNSLKAEDTAVYYCAARPRF
WGSYEYDYWGQGTQVTVSS LG2067G 199

EVQLVESGGGLVQAGGSLRLSCAASERTFIPYPMGWFRQAPGKEREFVGAI
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EVFRTTRLDYDSWGRGTQVTVSS LG2067H 200
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FVSREYDYRGQGTQVTVSS LG20711A 201
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TVFGSLNYADSVKGRFSISKDSAKNTVLLQMNSLKPEDTAVYSCNLRQYES
DRWRDYWGQGTQVTVSS LG20711B 202
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SWGTCNEEYYYGMDYWGKGTLVTVSS LG20711D 203
EVQLVESGGGLVQAGGSLRLSCTASGRTLSSYAMGWFRQTPGKEREFVASI
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GGTTAWBRWGQGTQVTVSS LG20711E 204
EVQLVESGGGLVQAGGSLRLSCTAGGDTFSSYAMGWFRQTPGKEREFVASI
SWIGKFTYYADSVKGRFTISGENAKNTVYLQMNSLKPEDTAVYYCAAKTIV
GGTTAWDRWGQGTQVTVSS LG20711F 205
EVQLVESGGGLVQPGGSLRLSCAASGFVFSHYAMSWVRQAPGKGLEWVSDI
TNGGLSTTYRDSVKGRFTISRDNAKNTLYLQMDSLKPEDTAVYYCSKDLYP
FVSREYDYRGQGTQVTVSS LG20711G 206
EVQLVESGGGLVQAGGSLRLSCAAPGRTFSTWVMGWFRQAPGKEREFVARI
DWGGSSTSYADIVKGRFTISRDNAKNTVYLQMNSLKPEDAAVYYCAADLDG
NGSIDYGYEYWGQGTQVTVSS LG20711H 207
EVQLVESGGGLVQPGGSLRLSCAASGFVFSHYAMSWVRQAPGKGLEWVSBI
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FISKEYDYRGQGTQVTVSS LG2071A 208
EVQMVESGGGLVQPGGSLRLSCVASGSIARLNTMGWYRQAPGKQRELVATL
SIFGVSDYADSVKGRFTISRDNAKNMVYLQMNSLKPEDTALYFCKQRQHDG
GSWYDYWGQGTQVTVSS LG2071B 209
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TTGGSTNYADSVKGRFTISSENAKNTVYLQMNSLKAEDTAVYYCNALGRMA
VAHSVSDFNSWGQGTQVTVSS LG2071C 210
EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATI
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YIYSDSLSERSYDYWGQGTQVTVSS LG207D1 211
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SRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELT
NRNPGAYYYTWAYDYWGQGTQVTVSS LG2071E 212
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SGGIPYYSDSVKGRFTMSRDNAKNTADLQMNSLKPEDTALYYCAGSSRIYI
YSDSLSEGSYDYWGQGTQVTVSS LG2071F 213
EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATI
PWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRI
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TWSSGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAASGY
RSTDRLSTPEWINYWGQGTQVTVSS IV6 3093
QVQLQESGGGLVQTGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV
TWSAGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAATGY
RSTDRLAEPGWVNYWGQGTQVTVSS IV7 3094
QVQLQQSGGGLVQTGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV
TWSAGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAASGY
RSTDRLSEPAWINYWGQGTQVTVSS IV9 3095
QVQLQESGGGLVQTGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV

TWSAGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAATGY
RSTDRLTEPAWVNYWGQGTQVTVSS IV10 3096
QVQLQESGGGLVQAGGSLRLSCATSGRPFGGYAMAWFRQAPGKGREFVAAV
TWSAGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAATGY
RSTDRLSDPNWVNYWGQGTQVTVSS IV11 3097
QVQLQESGGGLVQAGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV
TWSSGTTNYAGSVKDRFTVSRDNANNTMYLRMNSLKPEDTAVYICGAASGY
RSTDRLSDAAWINYWGQGTQVTVSS IV12 3098
QVQLQQSGGGLVQTGGSLRLSCAASGRTFGGYAMAWFREAPGKGREFVAAV
TWSSGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAASGY
RSTDRLSTPEWINYWGQGTQVTVSS IV16 3099
QVQLQESGGGLVQTGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV
TWSSGTTNYAGSVKDRFTVSRDNGNNTMYLQMNSLKPEDTAVYICGVASGY
RSTDRLSEPGWINYWGQGTQVTVSS IV24 3100
QVQLQESGGGLVQTGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAI
TWSAGTTNYADSMKDRFTVSRDTANNTMYLEMNRLKPDDTAVYICGAATGY
RSTDRLSTPAWINYWGQGTQVTVSS IV26 3101
QVQLQESGGGLVRTGDSLRLSCAASGRTFNGYAMAWFRQAPGKGREFVAAV
TWSSGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAASGY
RSTDRLSDPAWTNYWGQGTQVTVSS IV30 3102
QVQLQESGGGLVETGGSLRLSCAASGRTFGGYAMAWFRQAPGKGREFVAAV
TWTSGTTNYAGSVKDRFTVSRDNANNTMYLQMNSLKPEDTAVYICGAASGY
RSPDRLSEPEWINYWGQGTQVTVSS IV34 3103
QVQLQESGGGLVQTGGSLRLSCAASGGTFGGYAMAWFRQAPGKGREFVASV
IWNGGTTNYLDSVKDRFTVSRDMANNTMYLQMNSLKPEDTAVYICGAASGY
RSTDRLSEPGWVNYWGQGTQVTVSS IV14 3104
QVQLQESGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LAYYTSRLRSRYDYWGQGTQVTVSS IV15 3105
QVQLQQSGGGLVQAGGSLRLSCAASGGTLNNYAMGWFRQAPGAEREFVGAI
SAGGDSTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LTYYTSRLRSRYDYWGQGTQVTVSS IV17 3106
QVQLQESGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV18 3107
QVQLQQSGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV29 3108
QVQLQESGGGLVQAGGSLRLSCVASGRTLDNYAMGWFRQAPGAEREFVGAI
SANGEDTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT

LTYYTSRLRSRYEYWGQGTQVTVSS IV31 3109
QVQLQQSGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKSTVVLDMNSLKPEDTAVYYCAADGKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV33 3110
QVQLQQSGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFSISKDLAKSTVYLDMNSLKPEDTAVYYCAADQKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV35 3111
QVQLQESGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTDYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV36 3112
QVQLQESGGGLVQAGGSLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDYAKSTVYLDMNSLKPEDTAVYYCAADQKT
LTYYTSRLRSRYDYWGQGTQVTVSS IV40 3113
QVQLQESGGGLVQAGGSLRLSCAASGHTLNNYAMGWFRQGPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKRTVYLDMNSLKPEDTAVYYCAADGKT
LTYYTSRLRSQYDYWGQGTQVTVSS IV42 3114
QVQLQQSGGGLVQAGESLRLSCAASGRTLNNYAMGWFRQAPGAEREFVGAI
SASGDSTQYTESVQGRFTISKDNAKSTVYLDMNSLKPEDTAVYYCAADRKT
LTFYTSRLRSRYDYWGQGTQVTVSS IV8 3115
QVQLQESGGGLVQAGGFLRLSCAASGRSFNTYAMGWFRQAPGKEREFVAGI
TRSGTATDYADSVKGRFTISRDNARNTVYLQMNRLKSEDSAVYYCAAHASY
DRMIYSEYKYWGQGTQVTVSS IV21 3116
QVQLQQSGGGLVQAGGFLRLSCAASGRSFNTYAMGWFRQAPGKEREFVAGI
TRSGTATDYIDSVKGRFTISRDNARDTVYLQMNRLNPEDSAVYYCAAHANY
DRMINSEYKYWGQGTQVTVSS IV23 3117
QVQLQESGGGLVQAGGFLRLSCAASGRSFNTYAMGWFRQAPGKEREFVAGI
TRSGTATDYIDSVKGRFTISRDNARDTVYLQMNRLNPEDSAVYYCAAHANY
DRMINSEYKYWGQGTQVTVSS IV45 3118
QVQLQQSGGGLVQAGGFLRLSCAASGRSFNTYAVGWFRQAPGKEREFVAGI
TRSGTATDYADSVKGRFTISRDNARNTVYLQMNRLKPEDSAVYYCAAHASY
DRMINSEYKYWGQGTQVTVSS IV47 3119
QVQLQQSGGGLVQAGGFLRLSCAASGRSFNTYAMGWFRQAPGKEREFVAGI
TRSGTATEYADSVKGRFTISRDNARNTVLLQMNRLKPEDSAVYYCAAHANY
DRMINSEYKYWGQGTQVTVSS IV48 3120
QVQLQESGGGLVQAGGFLRLTCAASGRSFNTYAMGWFRQAPGKDRKFVAGI
TRSGTVTDYADSVKGRFTISRDNARNTVYLQMNRLKPEDSAVYYCAGHASY
DRMINSEYKYWGQGTQVTVSS IV50 3121
QVQLQESGGGLVQAGGFLRLSCAASGRSFNTYAMGWFRQAPGKEREFVAGI
TRSGTATDYADSVKGRFTISRDNARNTVYLQMNRLKPEDSAVYYCAAHASY
DRMIYSEYKYWGQGTQVTVSS IV22 3122

QVQLQESGGGLVQAGDSLRLSCAASGPSFNNGAMSWFRQAPGKEREFVAAI
RWSGGGIRYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTAVYYCAIDPRA
DLVATMTSIRYWGQGTQVTVSS IV37 3123
QVQLQESGGGLVQAGDSLRLSCAAPGRSFSGGAMSWFRQVPGKEREFVAAI
RWSGGGIRYADSVKGRFTISRDNAKNTFYLQMNSLKPEDTAVYYCAIDPRA
DLVATMTSIRYWGQGTQVTVSS IV38 3124
QVQLQESGGGLVQAGGSLRLSCAASGPSFNNGAMSWFRQAPGKEREFVAAI
RWSGGGIRYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTAVYYCAIDPRA
DLVATMTSIRYWGQGTQVTVSS IV5 3125
QVQLQQSGGGLVQAGGSLRLSCAASGRTFSTTGMGWFRQAPGKEREFVAAF
WWTGGQTFYADSVKGRFTISGDNAGNTVDLQMNSLKPEDTAVYACAAMSKP
RNLWRTDSYDYWGQGTQVTVSS IV27 3126
QVQLQESGGGLVQAGGSLRLSCAASGSTFSTYAMGWFRQAPGKEREFVAAF
WWTDEQTFYADSVKGRFTISRGNAKNTVDLQMNSLKPEDTAVYACAAMSKP
YNLWRTDSYDYWGQGTQVTVSS IV25 3127
QVQLQQSGGGLVQSGGSLSLSCAASGITLNNRVVGWFRQAPGKEREFVGRI
MWSVGDTFYARSVKGRFTISRDNAKNTMYLQMNALKPEDTAVYYCAAARDP
DLYTGQYEYWGQGTQVTVSS IV28 3128
QVQLQESGGGLVQPGGSLRLSCSASGFAFDDYAMSWVRQAPGKGLEWVSSI
NWNGGSTYYAESMKGRFTISRDSAKNTLYLQMNSLKSEDTAVYYCAKGEGS
ANWGLDFGSWGQGTQVTVSS

In the above Table A-1, SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 refer to amino acid sequences of the invention that are directed to and/or specifically bind to hemagglutinin H5 of influenza; SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 refer to amino acid sequences of the invention that are directed to and/or specifically bind to the F protein of hRSV; and SEQ ID NO's: 237 to 247 and 2684 to 2717 refer to amino acid sequences of the invention that are directed to and/or specifically bind to the G protein of rabies virus.

In particular, the invention in some specific aspects provides:

- amino acid sequences that are directed against (as defined herein) an envelope protein of a virus and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1); these amino acid sequences may further be such that they neutralize binding of the binding partner (such as the viral receptor) to an envelope protein of a virus; and/or compete with the binding partner (such as the viral receptor) for binding to an envelope protein

of a virus; and/or are directed against an interaction site (as defined herein) on an envelope protein of a virus (such as the viral receptor binding site);

- amino acid sequences that cross-block (as defined herein) the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) to an envelope protein of a virus and/or that compete with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) for binding to an envelope protein of a virus. Again, these amino acid sequences may further be such that they neutralize binding of the binding partner (such as the viral receptor) to an envelope protein of a virus; and/or compete with the binding partner (such as the viral receptor) for binding to an envelope protein of a virus; and/or are directed against an interaction site (as defined herein) on an envelope protein of a virus (such as the viral receptor binding site);
  which amino acid sequences may be as further described herein (and may for example be NANOBODIES® (V_{HH} sequences)); as well as polypeptides of the invention that comprise one or more of such amino acid sequences (which may be as further described herein, and may for example be bispecific and/or biparatopic polypeptides as described herein), and nucleic acid sequences that encode such amino acid sequences and polypeptides. Such amino acid sequences and polypeptides do not include any naturally occurring ligands.

Accordingly, some particularly preferred NANOBODIES® (V_{HH} sequences) of the invention are NANOBODIES® (V_{HH} sequences) which can bind (as further defined herein) to and/or are directed against an envelope protein of a virus and which:

- i) have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded. In this respect, reference is also made to Table B-1, which lists the framework 1 sequences (SEQ ID NO's: 408 to 689, 2449 to 2466, 2582 to 2589, 2718 to 2753 and 3129 to 3193), framework 2 sequences (SEQ ID NO's: 972 to 1253, 2485 to 2502, 2598 to 2605, 2790 to 2825 and 3259 to 3323), framework 3 sequences (SEQ ID NO's: 1536 to 1817, 2521 to 2538, 2614 to 2621, 2862 to 2897 and 3389 to 3453) and framework 4 sequences (SEQ ID NO's: 2100 to 2381, 2557 to 2573, 2630 to 2637, 2934 to 2969 and 3519 to 3583) of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) (with respect to the amino acid residues at positions 1 to 4 and 27 to 30 of the framework 1 sequences, reference is also made to the comments made below. Thus, for determining the degree of amino acid identity, these residues are preferably

disregarded);
and in which:

- ii) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2 below.

In these NANOBODIES® (V_{HH} sequences), the CDR sequences are generally as further defined herein.

Again, such NANOBODIES® (V_{HH} sequences) may be derived in any suitable manner and from any suitable source, and may for example be naturally occurring V_{HH} sequences (i.e. from a suitable species of Camelid) or synthetic or semi-synthetic amino acid sequences, including but not limited to "humanized" (as defined herein) NANOBODIES® (V_{HH} sequences), "camelized" (as defined herein) immunoglobulin sequences (and in particular camelized heavy chain variable domain sequences), as well as NANOBODIES® (V_{HH} sequences) that have been obtained by techniques such as affinity maturation (for example, starting from synthetic, random or naturally occurring immunoglobulin sequences), CDR grafting, veneering, combining fragments derived from different immunoglobulin sequences, PCR assembly using overlapping primers, and similar techniques for engineering immunoglobulin sequences well known to the skilled person; or any suitable combination of any of the foregoing as further described herein. Also, when a NANOBODY® (V_{HH} sequence) comprises a V_{HH} sequence, said NANOBODY® (V_{HH} sequence) may be suitably humanized, as further described herein, so as to provide one or more further (partially or fully) humanized NANOBODIES® (V_{HH} sequences) of the invention. Similarly, when a NANOBODY® (V_{HH} sequence) comprises a synthetic or semi-synthetic sequence (such as a partially humanized sequence), said NANOBODY® (V_{HH} sequence) may optionally be further suitably humanized, again as described herein, again so as to provide one or more further (partially or fully) humanized NANOBODIES® (V_{HH} sequences) of the invention.

In particular, humanized NANOBODIES® (V_{HH} sequences) may be amino acid sequences that are as generally defined for NANOBODIES® (V_{HH} sequences) in the previous paragraphs, but in which at least one amino acid residue is present (and in particular, in at least one of the framework residues) that is and/or that corresponds to a humanizing substitution (as defined herein). Some preferred, but non-limiting humanizing substitutions (and suitable combinations thereof) will become clear to the skilled person based on the disclosure herein. In addition, or alternatively, other potentially useful humanizing substitutions can be ascertained by comparing the sequence of the framework regions of a naturally occurring V_{HH} sequence with the corresponding framework sequence of one or more closely related human V_H sequences, after which one or more of the potentially useful humanizing substitutions (or combinations thereof) thus determined can

be introduced into said V_{HH} sequence (in any manner known per se, as further described herein) and the resulting humanized V_{HH} sequences can be tested for affinity for the target, for stability, for ease and level of expression, and/or for other desired properties. In this way, by means of a limited degree of trial and error, other suitable humanizing substitutions (or suitable combinations thereof) can be determined by the skilled person based on the disclosure herein. Also, based on the foregoing, (the framework regions of) a NANOBODY® (V_{HH} sequence) may be partially humanized or fully humanized.

Some particularly preferred humanized NANOBODIES® (V_{HH} sequences) of the invention are humanized variants of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), of which the amino acid sequences of SEQ ID NO's: 2999 to 3015 (see Table A-8) are some especially preferred examples.

Thus, some other preferred NANOBODIES® (V_{HH} sequences) of the invention are NANOBODIES (V_{HH} sequences) which can bind (as further defined herein) to an envelope protein of a virus and which:

- i) are a humanized variant of one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1); and/or
- ii) have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) and/or at least one of the amino acid sequences of SEQ ID NO's: 2999 to 3015 (see Table A-8), in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  and in which:
- iii) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2 below.

According to another specific aspect of the invention, the invention provides a number of stretches of amino acid residues (i.e. small peptides) that are particularly suited for binding to an envelope protein of a virus. These stretches of amino acid residues may be present in, and/or may be corporated into, an amino acid sequence of the invention, in particular in such a way that they form (part of) the antigen binding site of an amino acid sequence of the invention. As these stretches of amino acid residues were first generated as CDR sequences of heavy chain antibodies or V_{HH} sequences that were raised against an envelope protein of a virus (or may be based on and/or derived from such CDR sequences, as further described herein), they will also generally be referred to herein as “CDR sequences” (i.e. as

CDR1 sequences, CDR2 sequences and CDR3 sequences, respectively). It should however be noted that the invention in its broadest sense is not limited to a specific structural role or function that these stretches of amino acid residues may have in an amino acid sequence of the invention, as long as these stretches of amino acid residues allow the amino acid sequence of the invention to bind to an envelope protein of a virus. Thus, generally, the invention in its broadest sense comprises any amino acid sequence that is capable of binding to an envelope protein of a virus and that comprises one or more CDR sequences as described herein, and in particular a suitable combination of two or more such CDR sequences, that are suitably linked to each other via one or more further amino acid sequences, such that the entire amino acid sequence forms a binding domain and/or binding unit that is capable of binding to an envelope protein of a virus. It should however also be noted that the presence of only one such CDR sequence in an amino acid sequence of the invention may by itself already be sufficient to provide an amino acid sequence of the invention that is capable of binding to an envelope protein of a virus; reference is for example again made to the so-called "Expedite fragments" described in WO 03/050531.

Thus, in another specific, but non-limiting aspect, the amino acid sequence of the invention may be an amino acid sequence that comprises at least one amino acid sequence that is chosen from the group consisting of the CDR1 sequences, CDR2 sequences and CDR3 sequences that are described herein (or any suitable combination thereof). In particular, an amino acid sequence of the invention may be an amino acid sequence that comprises at least one antigen binding site, wherein said antigen binding site comprises at least one amino acid sequence that is chosen from the group consisting of the CDR1 sequences, CDR2 sequences and CDR3 sequences that are described herein (or any suitable combination thereof).

Generally, in this aspect of the invention, the amino acid sequence of the invention may be any amino acid sequence that comprises at least one stretch of amino acid residues, in which said stretch of amino acid residues has an amino acid sequence that corresponds to the sequence of at least one of the CDR sequences described herein. Such an amino acid sequence may or may not comprise an immunoglobulin fold. For example, and without limitation, such an amino acid sequence may be a suitable fragment of an immunoglobulin sequence that comprises at least one such CDR sequence, but that is not large enough to form a (complete) immunoglobulin fold (reference is for example again made to the "Expedite fragments" described in WO 03/050531). Alternatively, such an amino acid sequence may be a suitable "protein scaffold" that comprises least one stretch of amino acid residues that corresponds to such a CDR sequence (i.e. as part of its antigen binding site). Suitable scaffolds for presenting amino acid sequences will be clear to the skilled person, and for example comprise, without limitation, to binding scaffolds based on or derived from immunoglobulins (i.e. other than the immunoglobulin sequences already described herein), protein scaffolds derived from protein A domains (such as Affibodies™), tendamistat,

fibronectin, lipocalin, CTLA-4, T-cell receptors, designed ankyrin repeats, avimers and PDZ domains (Binz et al., Nat. Biotech 2005, Vol 23:1257), and binding moieties based on DNA or RNA including but not limited to DNA or RNA aptamers (Ulrich et al., Comb. Chem. High Throughput Screen 2006 9(8): 619-32).

Again, any amino acid sequence of the invention that comprises one or more of these CDR sequences is preferably such that it can specifically bind (as defined herein) to an envelope protein of a virus, and more in particular such that it can bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein), that is as defined herein.

More in particular, the amino acid sequences according to this aspect of the invention may be any amino acid sequence that comprises at least one antigen binding site, wherein said antigen binding site comprises at least two amino acid sequences that are chosen from the group consisting of the CDR1 sequences described herein, the CDR2 sequences described herein and the CDR3 sequences described herein, such that (i) when the first amino acid sequence is chosen from the CDR1 sequences described herein, the second amino acid sequence is chosen from the CDR2 sequences described herein or the CDR3 sequences described herein; (ii) when the first amino acid sequence is chosen from the CDR2 sequences described herein, the second amino acid sequence is chosen from the CDR1 sequences described herein or the CDR3 sequences described herein; or (iii) when the first amino acid sequence is chosen from the CDR3 sequences described herein, the second amino acid sequence is chosen from the CDR1 sequences described herein or the CDR3 sequences described herein.

Even more in particular, the amino acid sequences of the invention may be amino acid sequences that comprise at least one antigen binding site, wherein said antigen binding site comprises at least three amino acid sequences that are chosen from the group consisting of the CDR1 sequences described herein, the CDR2 sequences described herein and the CDR3 sequences described herein, such that the first amino acid sequence is chosen from the CDR1 sequences described herein, the second amino acid sequence is chosen from the CDR2 sequences described herein, and the third amino acid sequence is chosen from the CDR3 sequences described herein. Preferred combinations of CDR1, CDR2 and CDR3 sequences will become clear from the further description herein. As will be clear to the skilled person, such an amino acid sequence is preferably an immunoglobulin sequence (as further described herein), but it may for example also be any other amino acid sequence that comprises a suitable scaffold for presenting said CDR sequences.

Thus, in one specific, but non-limiting aspect, the invention relates to an amino acid sequence directed against an envelope protein of a virus, that comprises one or more

stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  or any suitable combination thereof.

When an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c):

- i) any amino acid substitution in such an amino acid sequence according to b) and/or c) is preferably, and compared to the corresponding amino acid sequence according to a), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to b) and/or c) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to a);
  and/or
- iii) the amino acid sequence according to b) and/or c) may be an amino acid sequence that is derived from an amino acid sequence according to a) by means of

affinity maturation using one or more techniques of affinity maturation known per se.

Similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f):

- i) any amino acid substitution in such an amino acid sequence according to e) and/or f) is preferably, and compared to the corresponding amino acid sequence according to d), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to e) and/or f) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to d);
  and/or
- iii) the amino acid sequence according to e) and/or f) may be an amino acid sequence that is derived from an amino acid sequence according to d) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Also, similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i):

- i) any amino acid substitution in such an amino acid sequence according to h) and/or i) is preferably, and compared to the corresponding amino acid sequence according to g), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to h) and/or i) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to g);
  and/or
- iii) the amino acid sequence according to h) and/or i) may be an amino acid sequence that is derived from an amino acid sequence according to g) by means of affinity maturation using one or more techniques of affinity maturation known per se.

It should be understood that the last preceding paragraphs also generally apply to any amino acid sequences of the invention that comprise one or more amino acid sequences according to b), c), e), f), h) or i), respectively.

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- ii) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to

2613, 2826 to 2861 and 3324 to 3388; and

- iii) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against an envelope protein of a virus.

In a more specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against an envelope protein of a virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the

amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- ii) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388; and
- iii) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388, or of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258 or of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258 or of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388.

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding to an envelope protein of a virus.

In an even more specific, but non-limiting aspect, the invention relates to an amino acid sequence directed against an envelope protein of a virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen

from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

  the second stretch of amino acid residues is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

  and the third stretch of amino acid residues is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

Preferably, in this specific aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding to an envelope protein of a virus.

Preferred combinations of such stretches of amino acid sequences will become clear from

the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to an envelope protein of a virus; and more in particular bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

  and/or

  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of

the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

and/or

- CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258; and/or CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388; and/or CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

and

- CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to

2613, 2826 to 2861 and 3324 to 3388;

- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  and
  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258; and CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388; and CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to an envelope protein of a virus; and more in particular bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128. This degree of amino acid identity

can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128, in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

In a more specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the F-protein of human RSV virus, that comprises one or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  or any suitable combination thereof.

When an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c):

- i) any amino acid substitution in such an amino acid sequence according to b) and/or c) is preferably, and compared to the corresponding amino acid sequence according to a), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to b) and/or c) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to a);
  and/or
- iii) the amino acid sequence according to b) and/or c) may be an amino acid sequence that is derived from an amino acid sequence according to a) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f):

- i) any amino acid substitution in such an amino acid sequence according to e) and/or f) is preferably, and compared to the corresponding amino acid sequence according to d), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to e) and/or f) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to d);
  and/or
- iii) the amino acid sequence according to e) and/or f) may be an amino acid sequence that is derived from an amino acid sequence according to d) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Also, similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i):

- i) any amino acid substitution in such an amino acid sequence according to h) and/or i) is preferably, and compared to the corresponding amino acid sequence according to g), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to h) and/or i) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to g);
  and/or
- iii) the amino acid sequence according to h) and/or i) may be an amino acid sequence that is derived from an amino acid sequence according to g) by means of affinity maturation using one or more techniques of affinity maturation known per se.

It should be understood that the last preceding paragraphs also generally apply to any amino acid sequences of the invention that comprise one or more amino acid sequences according to b), c), e), f), h) or i), respectively.

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- ii) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613; and
- iii) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding the F-protein of human RSV virus.

In a more specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the F-protein of human RSV virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971. 2484 and 2590 to 2597;
- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;

- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- ii) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613; and
- iii) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613 or of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597 or of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556, and 2622 to 2629, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484, and 2590 to 2597 or of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613.

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding to the F-protein of human RSV virus.

In an even more specific, but non-limiting aspect, the invention relates to an amino acid sequence directed against the F-protein of human RSV virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597

the second stretch of amino acid residues is chosen from the group consisting of:

- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

and the third stretch of amino acid residues is chosen from the group consisting of:

- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

Preferably, in this specific aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613; and the third stretch of amino acid residues is chosen from the group

consisting of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues form part of the antigen binding site for binding to the F-protein of human RSV virus.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448, and 2574 to 2581 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the F-protein of human RSV virus; and more in particular bind to the F-protein of human RSV virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;

  and/or
  - CDR2 is chosen from the group consisting of:

- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

  and/or
  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597; and/or CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613; and/or CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;

  and

- CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

and

- CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597; and CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613; and CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to at least one epitope of the F-protein of human RSV virus; and more in particular bind to the F-protein of human RSV virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at

least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581, in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

In another specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the hemagglutinin of influenza virus.

In particular, the invention relates to an amino acid sequence directed against the hemagglutinin H5 protein of influenza virus that comprises one or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;

or any suitable combination thereof.

When an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c):

- i) any amino acid substitution in such an amino acid sequence according to b) and/or c) is preferably, and compared to the corresponding amino acid sequence according to a), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to b) and/or c) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to a);
  and/or
- iii) the amino acid sequence according to b) and/or c) may be an amino acid sequence that is derived from an amino acid sequence according to a) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f):

- i) any amino acid substitution in such an amino acid sequence according to e) and/or f) is preferably, and compared to the corresponding amino acid sequence according to d), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to e) and/or f) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to d);
  and/or
- iii) the amino acid sequence according to e) and/or f) may be an amino acid sequence that is derived from an amino acid sequence according to d) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Also, similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i):

- i) any amino acid substitution in such an amino acid sequence according to h) and/or i) is preferably, and compared to the corresponding amino acid sequence according to g), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to h) and/or i) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to g);

and/or

- iii) the amino acid sequence according to h) and/or i) may be an amino acid sequence that is derived from an amino acid sequence according to g) by means of affinity maturation using one or more techniques of affinity maturation known per se.

It should be understood that the last preceding paragraphs also generally apply to any amino acid sequences of the invention that comprise one or more amino acid sequences according to b), c), e), f), h) or i), respectively.

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- ii) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388; and
- iii) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
  or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding the hemagglutinin H5 protein of influenza virus.

In a more specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the hemagglutinin H5 protein of influenza virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
  such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258
- ii) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388; and
- iii) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
  such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388 or of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258 or of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454

to 3518; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258 or of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388.

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding to the hemagglutinin H5 protein of influenza virus.

In an even more specific, but non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the hemagglutinin H5 protein of influenza virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

the second stretch of amino acid residues is chosen from the group consisting of:

- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

and the third stretch of amino acid residues is chosen from the group consisting of:

- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899

and 3454 to 3518.

Preferably, in this specific aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 721 and 2467 to 2483; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding to the hemagglutinin H5 protein of influenza virus.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the hemagglutinin H5 protein of influenza virus; and more in particular bind to the hemagglutinin H5 protein of influenza virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755

and 3194 to 3258;

- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

  and/or

  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

  and/or

  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258; and/or CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388; and/or CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

  and

  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

  and

  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518; or any suitable fragment of such an amino acid sequence.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258; and CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388; and CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as

defined herein) to the hemagglutinin H5 protein of influenza virus; and more in particular bind to the hemagglutinin H5 protein of influenza virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128, in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

In particular, the invention relates to an amino acid sequence directed against at least one epitope of the G-protein of rabies virus that comprises one or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;

or any suitable combination thereof.

When an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c):

- i) any amino acid substitution in such an amino acid sequence according to b) and/or c) is preferably, and compared to the corresponding amino acid sequence according to a), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to b) and/or c) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to a);
  and/or
- iii) the amino acid sequence according to b) and/or c) may be an amino acid sequence that is derived from an amino acid sequence according to a) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f):

- i) any amino acid substitution in such an amino acid sequence according to e) and/or f) is preferably, and compared to the corresponding amino acid sequence according to d), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to e) and/or f) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to d);
  and/or
- iii) the amino acid sequence according to e) and/or f) may be an amino acid sequence that is derived from an amino acid sequence according to d) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Also, similarly, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i):

- i) any amino acid substitution in such an amino acid sequence according to h) and/or i) is preferably, and compared to the corresponding amino acid sequence according to g), a conservative amino acid substitution, (as defined herein);
  and/or
- ii) the amino acid sequence according to h) and/or i) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding amino acid sequence according to g);
  and/or
- iii) the amino acid sequence according to h) and/or i) may be an amino acid sequence

that is derived from an amino acid sequence according to g) by means of affinity maturation using one or more techniques of affinity maturation known per se.

It should be understood that the last preceding paragraphs also generally apply to any amino acid sequences of the invention that comprise one or more amino acid sequences according to b), c), e), f), h) or i), respectively.

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- ii) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861; and
- iii) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding the G-protein of rabies virus.

In a more specific, but again non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the G-protein of rabies virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the

amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

- i) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- ii) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861; and
- iii) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861 or of SEQ ID NO's: 1929 to 1939 and 2900 to 2933; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789 or of SEQ ID NO's: 1929 to 1939 and 2900 to 2933; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933, the second stretch of amino acid residues corresponds to one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789 or of SEQ ID NO's: 1365 to 1375 and 2828 to 2861.

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding to the G-protein of rabies virus.

In an even more specific, but non-limiting aspect, the invention relates to an amino acid sequence directed against at least one epitope of the G-protein of rabies virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  the second stretch of amino acid residues is chosen from the group consisting of:

- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e)
- f) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- g) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;

and the third stretch of amino acid residues is chosen from the group consisting of:

- h) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- j) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

Preferably, in this specific aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding to the G-protein of rabies virus.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the G-protein of rabies virus; and more in particular bind to the G-protein of rabies virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  and/or
  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  and/or
  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789; and/or CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861; and/or CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;

- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  and
    - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  and
    - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933; or any suitable fragment of such an amino acid sequence.

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789; and CDR2 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861; and CDR3 is chosen from the group consisting of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the G-protein of rabies virus; and more in particular bind to the G-protein of rabies virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and

2684 to 2717. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717, in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

In such an amino acid sequence of the invention, the framework sequences may be any suitable framework sequences, and examples of suitable framework sequences will be clear to the skilled person, for example on the basis the standard handbooks and the further disclosure and prior art mentioned herein.

The framework sequences are preferably (a suitable combination of) immunoglobulin framework sequences or framework sequences that have been derived from immunoglobulin framework sequences (for example, by humanization or camelization). For example, the framework sequences may be framework sequences derived from a light chain variable domain (e.g. a V_L-sequence) and/or from a heavy chain variable domain (e.g. a V_H-sequence). In one particularly preferred aspect, the framework sequences are either framework sequences that have been derived from a V_{HH}-sequence (in which said framework sequences may optionally have been partially or fully humanized) or are conventional V_H sequences that have been camelized (as defined herein).

The framework sequences are preferably such that the amino acid sequence of the invention is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody); is a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody); is a “dAb” (or an amino acid sequence that is suitable for use as a dAb); or is a NANOBODY® (V_{HH} sequence) (including but not limited to V_{HH} sequence). Again, suitable framework sequences will be clear to the skilled person, for example on the basis the standard handbooks and the further disclosure and prior art mentioned herein.

In particular, the framework sequences present in the amino acid sequences of the invention may contain one or more of Hallmark residues (as defined herein), such that the amino acid sequence of the invention is a NANOBODY® (V_{HH} sequence). Some preferred, but non-limiting examples of (suitable combinations of) such framework sequences will become clear from the further disclosure herein.

Again, as generally described herein for the amino acid sequences of the invention, it is also possible to use suitable fragments (or combinations of fragments) of any of the foregoing, such as fragments that contain one or more CDR sequences, suitably flanked by and/or linked via one or more framework sequences (for example, in the same order as these CDR's and framework sequences may occur in the full-sized immunoglobulin sequence

from which the fragment has been derived). Such fragments may also again be such that they comprise or can form an immunoglobulin fold, or alternatively be such that they do not comprise or cannot form an immunoglobulin fold.

In one specific aspect, such a fragment comprises a single CDR sequence as described herein (and in particular a CDR3 sequence), that is flanked on each side by (part of) a framework sequence (and in particular, part of the framework sequence(s) that, in the immunoglobulin sequence from which the fragment is derived, are adjacent to said CDR sequence. For example, a CDR3 sequence may be preceded by (part of) a FR3 sequence and followed by (part of) a FR4 sequence). Such a fragment may also contain a disulphide bridge, and in particular a disulphide bridge that links the two framework regions that precede and follow the CDR sequence, respectively (for the purpose of forming such a disulphide bridge, cysteine residues that naturally occur in said framework regions may be used, or alternatively cysteine residues may be synthetically added to or introduced into said framework regions). For a further description of these "Expedite fragments", reference is again made to WO 03/050531, as well as to WO 08/068280.

In another aspect, the invention relates to a compound or construct, and in particular a protein or polypeptide (also referred to herein as a "compound of the invention" or "polypeptide of the invention", respectively) that comprises or essentially consists of one or more amino acid sequences of the invention (or suitable fragments thereof), and optionally further comprises one or more other groups, residues, moieties or binding units. As will become clear to the skilled person from the further disclosure herein, such further groups, residues, moieties, binding units or amino acid sequences may or may not provide further functionality to the amino acid sequence of the invention (and/or to the compound or construct in which it is present) and may or may not modify the properties of the amino acid sequence of the invention.

For example, such further groups, residues, moieties or binding units may be one or more additional amino acid sequences, such that the compound or construct is a (fusion) protein or (fusion) polypeptide. In a preferred but non-limiting aspect, said one or more other groups, residues, moieties or binding units are immunoglobulin sequences. Even more preferably, said one or more other groups, residues, moieties or binding units are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).

Alternatively, such groups, residues, moieties or binding units may for example be chemical groups, residues, moieties, which may or may not by themselves be biologically and/or pharmacologically active. For example, and without limitation, such groups may be linked

to the one or more amino acid sequences of the invention so as to provide a "derivative" of an amino acid sequence or polypeptide of the invention, as further described herein.

Also within the scope of the present invention are compounds or constructs, that comprises or essentially consists of one or more derivatives as described herein, and optionally further comprises one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers. Preferably, said one or more other groups, residues, moieties or binding units are amino acid sequences.

In the compounds or constructs described above, the one or more amino acid sequences of the invention and the one or more groups, residues, moieties or binding units may be linked directly to each other and/or via one or more suitable linkers or spacers. For example, when the one or more groups, residues, moieties or binding units are amino acid sequences, the linkers may also be amino acid sequences, so that the resulting compound or construct is a fusion (protein) or fusion (polypeptide).

As will be clear from the further description above and herein, this means that the amino acid sequences of the invention can be used as "building blocks" to form polypeptides of the invention, i.e. by suitably combining them with other groups, residues, moieties or binding units, in order to form compounds or constructs as described herein (such as, without limitations, the bi-, tri-, multiparatopic, bi-, tri-, multivalent and bi-, tri-, multispecific polypeptides of the invention described herein) which combine within one molecule one or more desired properties or biological functions.

The compounds or polypeptides of the invention can generally be prepared by a method which comprises at least one step of suitably linking the one or more amino acid sequences of the invention to the one or more further groups, residues, moieties or binding units, optionally via the one or more suitable linkers, so as to provide the compound or polypeptide of the invention. Polypeptides of the invention can also be prepared by a method which generally comprises at least the steps of providing a nucleic acid that encodes a polypeptide of the invention, expressing said nucleic acid in a suitable manner, and recovering the expressed polypeptide of the invention. Such methods can be performed in a manner known per se, which will be clear to the skilled person, for example on the basis of the methods and techniques further described herein.

The process of designing/selecting and/or preparing a compound or polypeptide of the invention, starting from an amino acid sequence of the invention, is also referred to herein as "formatting" said amino acid sequence of the invention; and an amino acid of the invention that is made part of a compound or polypeptide of the invention is said to be "formatted" or to be "in the format of" said compound or polypeptide of the invention. Examples of ways in which an amino acid sequence of the invention can be formatted and examples of such formats will be clear to the skilled person based on the disclosure herein;

and such formatted amino acid sequences form a further aspect of the invention.

In one specific aspect of the invention, a compound of the invention or a polypeptide of the invention may have an increased half-life, compared to the corresponding amino acid sequence of the invention. Some preferred, but non-limiting examples of such compounds and polypeptides will become clear to the skilled person based on the further disclosure herein, and for example comprise amino acid sequences or polypeptides of the invention that have been chemically modified to increase the half-life thereof (for example, by means of pegylation); amino acid sequences of the invention that comprise at least one additional binding site for binding to a serum protein (such as serum albumin); or polypeptides of the invention that comprise at least one amino acid sequence of the invention that is linked to at least one moiety (and in particular at least one amino acid sequence) that increases the half-life of the amino acid sequence of the invention. Examples of polypeptides of the invention that comprise such half-life extending moieties or amino acid sequences will become clear to the skilled person based on the further disclosure herein; and for example include, without limitation, polypeptides in which the one or more amino acid sequences of the invention are suitable linked to one or more serum proteins or fragments thereof (such as (human) serum albumin or suitable fragments thereof) or to one or more binding units that can bind to serum proteins (such as, for example, domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, “dAb”'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences) that can bind to serum proteins such as serum albumin (such as human serum albumin), serum immunoglobulins such as IgG, or transferrin; reference is made to the further description and references mentioned herein); polypeptides in which an amino acid sequence of the invention is linked to an Fc portion (such as a human Fc) or a suitable part or fragment thereof; or polypeptides in which the one or more amino acid sequences of the invention are suitable linked to one or more small proteins or peptides that can bind to serum proteins (such as, without limitation, the proteins and peptides described in WO 91/01743, WO 01/45746, WO 02/076489 and in WO 08/068280.

Generally, the compounds or polypeptides of the invention with increased half-life preferably have a half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding amino acid sequence of the invention per se.

In a preferred, but non-limiting aspect of the invention, such compounds or polypeptides of the invention have a serum half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence of the invention per se.

In another preferred, but non-limiting aspect of the invention, such compounds or polypeptides of the invention exhibit a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more. For example, compounds or polypeptides of the invention may have a half-life of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

In another aspect, the invention relates to a nucleic acid that encodes an amino acid sequence of the invention or a polypeptide of the invention (or a suitable fragment thereof). Such a nucleic acid will also be referred to herein as a "nucleic acid of the invention" and may for example be in the form of a genetic construct, as further described herein.

In another aspect, the invention relates to a host or host cell that expresses (or that under suitable circumstances is capable of expressing) an amino acid sequence of the invention and/or a polypeptide of the invention; and/or that contains a nucleic acid of the invention. Some preferred but non-limiting examples of such hosts or host cells will become clear from the further description herein.

The invention further relates to a product or composition containing or comprising at least one amino acid sequence of the invention, at least one polypeptide of the invention (or a suitable fragment thereof), at least one compound of the invention and/or at least one nucleic acid of the invention, and optionally one or more further components of such compositions known per se, i.e. depending on the intended use of the composition. Such a product or composition may for example be a pharmaceutical composition (as described herein), a veterinary composition or a product or composition for diagnostic use (as also described herein). Some preferred but non-limiting examples of such products or compositions will become clear from the further description herein.

The invention also relates to the use of an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention, or of a composition comprising the same, in (methods or compositions for) modulating viral entry and/or viral replication and/or for modulating the biological pathways that are mediated by an envelope protein of a virus (and/or its viral receptor) either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or in a multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a viral disease).

The invention also relates to methods for modulating viral entry and/or viral replication and/or for modulating the biological pathways that are mediated by an envelope protein of

a virus (and/or its viral receptor) either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a viral disease), which method comprises at least the step of contacting an envelope protein of a virus with at least one amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention, or with a composition comprising the same, in a manner and in an amount suitable to modulate viral entry and/or viral replication and/or to modulate the biological pathways that are mediated by an envelope protein of a virus and/or its viral receptor, with at least one amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention.

The invention also relates to the use of an one amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention in the preparation of a composition (such as, without limitation, a pharmaceutical composition or preparation as further described herein) for modulating viral entry and/or viral replication and/or for modulating the biological pathways that are mediated by an envelope protein of a virus (and/or its viral receptor), either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a viral disease.

In the context of the present invention, "modulating" or "to modulate" generally means either reducing, preventing or inhibiting viral entry and/or viral replication and/or reducing, preventing or inhibiting the biological pathways that are mediated by an envelope protein of a virus and/or its viral receptor, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, "modulating" or "to modulate" may mean either reducing, preventing or inhibiting viral entry and/or viral replication and/or reducing, preventing or inhibiting the biological pathways that are mediated by an envelope protein of a virus and/or its viral receptor as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) viral entry and/or viral replication and/or normal (i.e. naturally occurring) biological pathways that are mediated by an envelope protein of a virus and/or its viral receptor in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention.

As will be clear to the skilled person, "modulating" may also involve effecting a change (which may either be an increase or a decrease) in binding specificity and/or selectivity of an envelope protein of a virus for one or more of its binding partners; and/or effecting a change (which may either be an increase or a decrease) in the sensitivity of an envelope protein of a virus for one or more conditions in the medium or surroundings in which an

envelope protein of a virus is present (such as pH, ion strength, the presence of co-factors, etc.), compared to the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention. As will be clear to the skilled person, this may again be determined in any suitable manner and/or using any suitable assay known per se, such as the assays described herein or in the prior art cited herein.

"Modulating" may also mean effecting a change with respect to one or more biological or physiological mechanisms, effects, responses, functions, pathways or activities in which an envelope protein of a virus (or in which its binding partners or pathway(s) are involved) is involved. Again, as will be clear to the skilled person this may be determined in any suitable manner and/or using any suitable (in vitro and usually cellular or in assay) assay known per se, such as the assays described herein or in the prior art cited herein. In particular, with respect to one or more biological or physiological mechanisms, effects, responses, functions, pathways or activities in which an envelope protein of a virus and/or its viral receptor is involved, effecting a change can mean a change by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to the biological or physiological mechanisms, effects, responses, functions, pathways or activities in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or polypeptide of the invention.

Modulating may for example involve reducing, preventing or inhibiting the binding of an envelope protein of a virus to one of its binding partners and/or competing with a natural binding partner for binding to an envelope protein of a virus. Modulating may be reversible or irreversible, but for pharmaceutical and pharmacological purposes will usually be in a reversible manner.

Accordingly, the present invention also relates to amino acid sequences and polypeptides that can be used to modulate, and in particular to inhibit and/or to prevent the viral-mediated biological pathways in which an envelope protein of a virus and/or a viral receptor are involved. In particular, the amino acid sequences and polypeptides of the present invention can be used to neutralize a virus (as defined herein) and/or to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein).

More specifically, the amino acid sequences and polypeptides according to the present invention may neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place) and/or in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place). Accordingly, the amino acid sequences and polypeptides of the present invention that

neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place), are said herein to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell. Furthermore, the amino acid sequences and polypeptides of the present invention that neutralize a virus (as defined herein) and/or modulate, reduce and/or inhibit the infectivity of a virus (as defined herein) in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place), are said herein to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell.

In a specific aspect, the present invention relates to multivalent (such as bivalent, biparatopic, bispecific, trivalent, triparatopic, trispecific, as further defined herein) amino acid sequences and polypeptides that modulate, and in particular to inhibit and/or to prevent the viral-mediated biological pathways in which an envelope protein of a virus and/or a viral receptor are involved. In particular, the multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides of the present invention can neutralize a virus (as defined herein) and/or to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein). In one aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against hemagglutinint H5 envelope protein of influenza and show increased in vitro and/or in vivo neutralization of influenza virus (as e.g. measured by a pseudotype neutralization assay such as described herein) compared to the corresponding monovalent amino acid sequence. The neutralization may be increased by at least 2 times, preferably at least 3 times, such as at least 5 times or at least 10 times, for example by at least 15 times, at least 20 times, at least 30 times, at least 50 times, or 100 times or more, compared to the neutralization in the same assay under the same conditions by the corresponding monovalent amino acid sequence. In another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against the G envelope protein of rabies and show increased in vitro and/or in vivo neutralization of rabies (as e.g. measured by a RFITT assay such as described herein) compared to the corresponding monovalent amino acid sequence. The neutralization may be increased by at least 2 times, preferably at least 3 times, such as at least 5 times or at least 10 times, for example by at least 15 times, at least 20 times, at least 30 times, at least 50 times, or 100 times or more, compared to the neutralization in the same assay under the same conditions by the corresponding monovalent amino acid sequence. In another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against F-protein of RSV and show increased in vitro and/or in vivo neutralization of RSV compared to the corresponding monovalent amino acid sequence. The neutralization may be increased by at least 2 times, preferably at least 3

times, such as at least 5 times or at least 10 times, for example by at least 15 times, at least 20 times, at least 30 times, at least 50 times, or 100 times or more, compared to the neutralization in the same assay under the same conditions by the corresponding monovalent amino acid sequence. In yet another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against hemagglutinin H5 envelope protein of influenza and show increased competition with sialic acid for binding hemagglutinint H5 envelope protein of influenza compared to the corresponding monovalent amino acid sequence. The competition may be increased by at least 2 times, preferably at least 3 times, such as at least 5 times or at least 10 times, for example by at least 15 times, at least 20 times, at least 30 times, at least 50 times, or 100 times or more, compared to the competition in the same assay under the same conditions by the corresponding monovalent amino acid sequence. In yet another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides show increased cross reactivity and/or neutralization of different genotypes, subtypes, escape mutants and/or strains of a certain virus. In one aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against the G envelope protein of rabies and may show cross reactivity and/or neutralization of different genotypes of rabies (such as e.g. genotype 1 and 5). In another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against hemagglutinin H5 envelope protein of influenza and show cross reactivity and/or neutralization of different subtypes and/or strains of influenza virus (such as e.g. H5N1 and H1N1; H3N2 and H1N1; H5N1 and H3N2; H5N1 and H2N2; H5N1, H1N1 and H3N2; H5N1, H2N2 and H3N2; H5N1, H1N1 and H2N2; H5N1, H1N1, H2N2 and H3N2). In yet another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against F protein of RSV and show cross reactivity and/or neutralization of different strains (such as e.g. Long and A-2, Long and B-1, A-2 and B-1, Long, A-2 and B-1) of RSV. In yet another aspect, these multivalent (preferably bivalent, more preferably trivalent) amino acid sequences and polypeptides are directed against F protein of RSV and show cross reactivity and/or neutralization of different escape mutants of RSV (such as e.g. escape mutants in antigenic site II, escape mutants in antigenic site IV-VI, and/or escape mutants in both antigenic site II and antigenic site IV-VI).

Accordingly, the amino acid sequences and (multivalent) polypeptides of the present invention can modulate and in particular inhibit and/or prevent viral entry and/or viral replication in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway(s); preferably, the amino acid sequences and polypeptides of the present invention can modulate and in particular inhibit and/or prevent viral entry in a target host cell by binding to an envelope protein of a virus, such that virion aggregation is induced and/or virion structure is destabilized and/or virion

attachment to a target host cell is modulated, inhibited and/or prevented (for instance by modulating and/or inhibiting and/or preventing the interaction between the an envelope protein of a virus and a viral receptor on a target host cell and/or the interaction between the an envelope protein of a virus and a target host cell or by competing with said envelope protein for binding to said viral receptor or said target host cell) and/or viral fusion with said target host cell is modulated, inhibited and/or prevented (for instance at the target host cell membrane or within an endosomal and/or lysosomal compartment of said target host cell), for example by preventing said envelope protein of a virus from undergoing a conformational change. Alternatively, the amino acid sequences and polypeptides of the present invention can modulate and in particular inhibit and/or prevent viral replication (as defined herein) in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway; preferably, the amino acid sequences of the present invention can modulate and in particular inhibit and/or prevent viral replication in a target host cell by binding to an envelope protein of a virus, such that transcription and/or translation of the viral genome is affected, inhibited and/or prevented and/or viral packaging and/or the formation of functional virions is affected, inhibited and/or prevented and/or budding of nascent virions from the target host cell membrane is reduced, inhibited and/or prevented.

Also according to this aspect, bi- and multivalent (as defined herein), bi- and multispecific (as defined herein) and bi- and multiparatopic (as defined herein) polypeptides according to the invention may be useful for the prevention and/or treatment of viral diseases by specifically binding to at least one epitope of an envelope protein of a virus and at least one further epitope (which may or may not be different from said at least one epitope) of a target, wherein said target may or may not be different from said envelope protein.

Accordingly, the present invention also relates to biparatopic amino acid sequences and polypeptides according to the invention or compositions comprising the same, that combine two different modes of action, for example reducing, preventing and/or inhibiting viral entry (such for example at the stage of viral attachment, viral fusion, etc.) and/or viral replication (such for example at the stage of transcription, translation, viral packaging, budding, etc.), each mediated by one of the binding units of the biparatopic amino acid sequence and/or polypeptide of the invention, wherein each binding unit binds to a different site of said envelope protein of a virus.

Furthermore, the present invention also relates to triparatopic amino acid sequences and polypeptides according to the invention or compositions comprising the same, that combine two or three different modes of action, such as reducing, preventing and/or inhibiting viral entry (such for example at the stage of viral attachment, viral fusion, etc.) and/or viral replication (such for example at the stage of transcription, translation, viral packaging, budding, etc.), each mediated by one of the binding units of the triparatopic

amino acid sequence and/or polypeptide of the invention, wherein each binding unit binds to a different site of said envelope protein of a virus.

More generally, the present invention relates to multiparatopic amino acid sequences and polypeptides according to the invention or compositions comprising the same, that combine two or more different modes of action, such as reducing, preventing and/or inhibiting viral entry (such for example at the stage of viral attachment, viral fusion, etc.) and/or viral replication (such for example at the stage of transcription, translation, viral packaging, budding, etc.), each mediated by one of the binding units of the multiparatopic amino acid sequence and/or polypeptide of the invention, wherein each binding unit binds to a different site of said envelope protein of a virus.

The invention further relates to methods for preparing or generating the amino acid sequences, polypeptides, nucleic acids, host cells, products and compositions described herein. Some preferred but non-limiting examples of such methods will become clear from the further description herein.

Generally, these methods may comprise the steps of:

- a) providing a set, collection or library of amino acid sequences; and
- b) screening said set, collection or library of amino acid sequences for amino acid sequences that can bind to and/or have affinity for an envelope protein of a virus; and
- c) isolating the amino acid sequence(s) that can bind to and/or have affinity for an envelope protein of a virus.

In such a method, the set, collection or library of amino acid sequences may be any suitable set, collection or library of amino acid sequences. For example, the set, collection or library of amino acid sequences may be a set, collection or library of immunoglobulin sequences (as described herein), such as a naïve set, collection or library of immunoglobulin sequences; a synthetic or semi-synthetic set, collection or library of immunoglobulin sequences; and/or a set, collection or library of immunoglobulin sequences that have been subjected to affinity maturation.

Also, in such a method, the set, collection or library of amino acid sequences may be a set, collection or library of heavy chain variable domains (such as V_H domains or V_{HH} domains) or of light chain variable domains. For example, the set, collection or library of amino acid sequences may be a set, collection or library of domain antibodies or single domain antibodies, or may be a set, collection or library of amino acid sequences that are capable of functioning as a domain antibody or single domain antibody.

In a preferred aspect of this method, the set, collection or library of amino acid sequences

may be an immune set, collection or library of immunoglobulin sequences, for example derived from a mammal that has been suitably immunized with an envelope protein of a virus or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

In the above methods, the set, collection or library of amino acid sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) amino acid sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to the review by Hoogenboom in Nature Biotechnology, 23, 9, 1105-1116 (2005).

In another aspect, the method for generating amino acid sequences comprises at least the steps of:

- a) providing a collection or sample of cells expressing amino acid sequences;
- b) screening said collection or sample of cells for cells that express an amino acid sequence that can bind to and/or have affinity for an envelope protein of a virus; and
- c) either (i) isolating said amino acid sequence; or (ii) isolating from said cell a nucleic acid sequence that encodes said amino acid sequence, followed by expressing said amino acid sequence.

For example, when the desired amino acid sequence is an immunoglobulin sequence, the collection or sample of cells may for example be a collection or sample of B-cells. Also, in this method, the sample of cells may be derived from a mammal that has been suitably immunized with an envelope protein of a virus or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

The above method may be performed in any suitable manner, as will be clear to the skilled person. Reference is for example made to EP 0 542 810, WO 05/19824, WO 04/051268 and WO 04/106377. The screening of step b) is preferably performed using a flow cytometry technique such as FACS. For this, reference is for example made to Lieby et al., Blood, Vol. 97, No. 12, 3820 (2001).

In another aspect, the method for generating an amino acid sequence directed against an envelope protein of a virus may comprise at least the steps of:

- a) providing a set, collection or library of nucleic acid sequences encoding amino acid sequences;
- b) screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for an envelope protein of a virus;
  and
- c) isolating said nucleic acid sequence, followed by expressing said amino acid sequence. In such a method, the set, collection or library of nucleic acid sequences encoding amino acid sequences may for example be a set, collection or library of nucleic acid sequences encoding a naïve set, collection or library of immunoglobulin sequences; a set, collection or library of nucleic acid sequences encoding a synthetic or semi-synthetic set, collection or library of immunoglobulin sequences; and/or a set, collection or library of nucleic acid sequences encoding a set, collection or library of immunoglobulin sequences that have been subjected to affinity maturation.

Also, in such a method, the set, collection or library of nucleic acid sequences may encode a set, collection or library of heavy chain variable domains (such as V_H domains or V_{HH} domains) or of light chain variable domains. For example, the set, collection or library of nucleic acid sequences may encode a set, collection or library of domain antibodies or single domain antibodies, or a set, collection or library of amino acid sequences that are capable of functioning as a domain antibody or single domain antibody.

In a preferred aspect of this method, the set, collection or library of amino acid sequences may be an immune set, collection or library of nucleic acid sequences, for example derived from a mammal that has been suitably immunized with an envelope protein of a virus or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

The set, collection or library of nucleic acid sequences may for example encode an immune set, collection or library of heavy chain variable domains or of light chain variable domains. In one specific aspect, the set, collection or library of nucleotide sequences may encode a set, collection or library of V_{HH} sequences.

In the above methods, the set, collection or library of nucleotide sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) nucleotide sequences encoding amino acid sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to the review by Hoogenboom in Nature

Biotechnology, 23, 9, 1105-1116 (2005).

In another aspect, the method for generating an amino acid sequence directed against an envelope protein of a virus may comprise at least the steps of:

- a) providing a set, collection or library of nucleic acid sequences encoding amino acid sequences;
- b) screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for an envelope protein of a virus and that is cross-blocked or is cross blocking a NANOBODY® (V_{HH} sequence) of the invention, e.g. one of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (Table A-1), or a humanized version of a NANOBODY® (V_{HH} sequence) of the invention, e.g. SEQ ID NO: 2999 to 3015 (see Table A-8), or a polypeptide or construct of the invention comprising at least one NANOBODY® (V_{HH} sequence) of the invention, e.g. one of SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591 (see Table A-2, Table A-4, Table A-5, Table A-6, Table A-9 and Table A-10); and
- c) isolating said nucleic acid sequence, followed by expressing said amino acid sequence.

The invention also relates to amino acid sequences that are obtainable and/or obtained by the above methods, or alternatively by a method that comprises the one of the above methods and in addition at least the steps of determining the nucleotide sequence or amino acid sequence of said immunoglobulin sequence; and of expressing or synthesizing said amino acid sequence in a manner known per se, such as by expression in a suitable host cell or host organism or by chemical synthesis.

Also, following the steps above, one or more amino acid sequences of the invention may be suitably humanized (or alternatively camelized); and/or the amino acid sequence(s) thus obtained may be linked to each other or to one or more other suitable amino acid sequences (optionally via one or more suitable linkers) so as to provide a polypeptide of the invention. Also, a nucleic acid sequence encoding an amino acid sequence of the invention may be suitably humanized (or alternatively camelized) and suitably expressed; and/or one or more nucleic acid sequences encoding an amino acid sequence of the invention may be linked to each other or to one or more nucleic acid sequences that encode other suitable amino acid sequences (optionally via nucleotide sequences that encode one or more suitable linkers), after which the nucleotide sequence thus obtained may be suitably expressed so as to provide a polypeptide of the invention.

Also encompassed within the present invention are methods for preparing and generating multivalent (such as e.g. bivalent, trivalent, etc.), multiparatopic (such as e.g. biparatopic,

triparatopic, etc.) and/or multispecific (such as e.g. bispecific, trispecific, etc.) amino acids of the invention.

A method for preparing multivalent, multiparatopic and/or multispecific amino acids or constructs of the invention may comprise at least the steps of linking two or more monovalent amino acid sequences or monovalent constructs of the invention and for example one or more linkers together in a suitable manner. The monovalent constructs (and linkers) can be coupled by any method known in the art and as further described herein. Preferred techniques include the linking of the nucleic acid sequences that encode the monovalent constructs (and linkers) to prepare a genetic construct that expresses the multivalent, multiparatopic and/or multispecific amino acid or construct. Techniques for linking amino acid sequences or nucleic acid sequences will be clear to the skilled person, and reference is again made to the standard handbooks, such as Sambrook et al. and Ausubel et al., mentioned above, as well as the Examples below.

Accordingly, the present invention also relates to the use of a monovalent construct (which may comprise or essentially consists of an amino acid sequence of the invention such as a domain antibody, an amino acid sequence that is suitable for use as a domain antibody, a single domain antibody, an amino acid sequence that is suitable for use as a single domain antibody, a "dAb", an amino acid sequences that is suitable for use as a dAb, or a NANOBODY® (V_{HH} sequence)) in providing and/or preparing a multivalent (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) compound or construct. The monovalent construct is then used as a binding domain or binding unit in providing and/or preparing the multivalent (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct comprising two (e.g. in a bivalent and/or biparatopic construct), three (e.g. in a trivalent and/or triparatopic construct) or more (e.g. in a multivalent and/or multiparatopic construct) binding units. In this respect, the monovalent construct may be used as a binding domain or binding unit in providing and/or preparing a multivalent and preferably bivalent or trivalent (such as multiparatopic, and preferably biparatopic or triparatopic) construct of the invention comprising two, three or more binding units.

In one aspect, the invention relates to multivalent polypeptides directed against the F-protein of RSV, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein.

In another aspect, the invention relates to multivalent polypeptides directed against the

F-protein of RSV, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In yet another aspect, the invention relates to multivalent polypeptides directed against the F-protein of RSV, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein.

In yet another aspect, the invention relates to multivalent polypeptides directed against the F-protein of RSV, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein; and at least

one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In yet another aspect, the invention relates to multivalent polypeptides directed against the F-protein of RSV, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also

intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, and a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a multiparatopic (such as a biparatopic) construct, wherein the binding domains or binding units are linked via a linker such that the multiparatopic (such as biparatopic) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits

intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the Synagis® binding site on the RSV F protein (and in

particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, and a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent constructs of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that are capable of competing with Synagis® for binding to the RSV F protein. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two Synagis® binding sites on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of two monovalent constructs comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably exhibits

intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent construct of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that are capable of competing with 101F for binding to the RSV F protein. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two 101F binding sites on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of two monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic)

binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the RSV F protein. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to both the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) as well as the other antigenic determinant, epitope, part or domain of the RSV F protein, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent, biparatopic or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein; and at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to both the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) as well as the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, and a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as binding domains or binding units in providing and/or

preparing a trivalent (biparatopic or triparatopic) construct, wherein the binding domains or binding units are linked via a linker such that the trivalent (biparatopic or triparatopic) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that are capable of competing with Synagis® for binding to the RSV F protein. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three Synagis® binding sites on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the Synagis® binding site on the RSV F protein (and in particular against antigenic site II of the RSV F protein, and more in particular against the region aa 250-275 of the RSV F protein) and/or that is capable of competing with Synagis® for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the 101F binding site on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein) and/or that are capable of competing with 101F for binding to the RSV F protein. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three 101F binding sites on the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein, and more in particular against region aa 423-436 of the RSV F protein), again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the 101F binding site on the RSV

F protein (and in particular against antigenic site IV of the RSV F protein, and more in particular against the region aa 423-436 of the RSV F protein) and/or that is capable of competing with 101F for binding to the RSV F protein, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.

In another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to

intermolecular binding.

In yet another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In yet another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is

used that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect, the invention relates to multivalent polypeptides directed against the hemagglutinin H5 envelope protein of influenza virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C1792 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred

biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one

monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent constructs of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two sialic acid binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of two monovalent constructs comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably

exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent construct of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two VN04-2 binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition. Accordingly, also encompassed in the present invention is the use of two monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent construct of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two MAb C179 binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of two monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the VN04-2 binding site on

the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to both the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent, biparatopic or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent (biparatopic or triparatopic) construct of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to both the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus as well as the

other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent, biparatopic or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three sialic acid binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three

VN04-2 binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that are capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three MAb C179 binding sites on the hemagglutinin H5 envelope protein of influenza virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In another aspect, the invention relates to multivalent polypeptides directed against the G envelope protein of rabies virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.

In another aspect, the invention relates to multivalent polypeptides directed against the G

envelope protein of rabies virus, in which at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus. In such a preferred multiparatopic construct of the invention, the linker is most preferably such that the multiparatopic construct of the invention is capable of (simultaneously) binding to both the MAb 8-2 binding site on the G envelope protein of rabies virus as well as the other antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus, as a binding domain or binding unit in providing and/or preparing a multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct, wherein the binding domains or binding units are linked via a linker such that the multivalent or multiparatopic (such as multispecific, multiparatopic, and preferably trivalent, bivalent, triparatopic, biparatopic, trispecific, bispecific, etc.) construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred biparatopic polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus. In such a preferred biparatopic construct of the invention, the linker is most preferably such that the biparatopic construct of the invention is capable of (simultaneously) binding to both the MAb 8-2 binding site on the G envelope protein of rabies virus as well as the other antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent

construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus, as a binding domain or binding unit in providing and/or preparing a biparatopic construct, wherein the binding domains or binding units are linked via a linker such that the biparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred bivalent polypeptides of the invention, at least two monovalent constructs of the invention (and in particular at least two NANOBODIES® (V_{HH} sequences)) are used that are directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that are capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus. In such a preferred bivalent construct of the invention, the linker is most preferably such that the bivalent construct of the invention is capable of (simultaneously) binding to two MAb 8-2 binding sites on the G envelope protein of rabies virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of two monovalent constructs comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus, as binding domains or binding units in providing and/or preparing a bivalent construct, wherein the binding domains or binding units are linked via a linker such that the bivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.

In some of the most preferred trivalent (biparatopic or triparatopic) polypeptides of the invention, at least one monovalent construct of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus; and at least one amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) is used that is directed against another antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus. In such a preferred trivalent (biparatopic or triparatopic) construct

of the invention, the linker is most preferably such that the trivalent (biparatopic or triparatopic) construct of the invention is capable of (simultaneously) binding to the MAb 8-2 binding sites on the G envelope protein of rabies virus as well as the other antigenic determinant, epitope, part or domain of the G envelope protein of rabies virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of a monovalent construct comprising an amino acid of the invention (and in particular a NANOBODY® (V_{HH} sequence)) that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus, as a binding domain or binding unit in providing and/or preparing a trivalent, biparatopic or triparatopic construct, wherein the binding domains or binding units are linked via a linker such that the trivalent or triparatopic construct preferably exhibits intramolecular binding compared to intermolecular binding.

In some of the most preferred trivalent polypeptides of the invention, at least three monovalent constructs of the invention (and in particular at least three NANOBODIES® (V_{HH} sequences)) are used that are directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that are capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus. In such a preferred trivalent construct of the invention, the linker is most preferably such that the trivalent construct of the invention is capable of (simultaneously) binding to three MAb 8-2 binding sites on the G envelope protein of rabies virus, again most preferably so as to allow binding with increased avidity and also intramolecular binding and/or recognition.

Accordingly, also encompassed in the present invention is the use of three monovalent construct comprising an amino acid sequence of the invention (and in particular at least one NANOBODY® (V_{HH} sequence)) that is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus, as binding domains or binding units in providing and/or preparing a trivalent construct, wherein the binding domains or binding units are linked via a linker such that the trivalent construct preferably exhibits intramolecular binding compared to intermolecular binding.

The invention further relates to applications and uses of the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein, as well as to methods for the prevention and/or treatment for diseases and disorders associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor. Some preferred but non-limiting applications and uses will become clear from the further description herein.

The invention also relates to the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein for use in therapy.

In particular, the invention also relates to the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein for use in therapy of a disease or disorder that can be prevented or treated by administering, to a subject in need thereof, of (a pharmaceutically effective amount of) an amino acid sequence, compound, construct or polypeptide as described herein.

More in particular, the invention relates to the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein for use in therapy of viral diseases.

Other aspects, embodiments, advantages and applications of the invention will also become clear from the further description herein, in which the invention will be described and discussed in more detail with reference to the NANOBODIES® (V_{HH} sequences) of the invention and polypeptides of the invention comprising the same, which form some of the preferred aspects of the invention.

As will become clear from the further description herein, NANOBODIES® (V_{HH} sequences) generally offer certain advantages (outlined herein) compared to "dAb's" or similar (single) domain antibodies or immunoglobulin sequences, which advantages are also provided by the NANOBODIES® (V_{HH} sequences) of the invention. However, it will be clear to the skilled person that the more general aspects of the teaching below can also be applied (either directly or analogously) to other amino acid sequences of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In the present description, examples and claims:

- a) Unless indicated or defined otherwise, all terms used have their usual meaning in the art, which will be clear to the skilled person. Reference is for example made to the standard handbooks mentioned in paragraph a) on page 46 of WO 08/020079.
- b) Unless indicated otherwise, the terms "immunoglobulin sequence", "sequence", "nucleotide sequence" and "nucleic acid" are as described in paragraph b) on page 46 of WO 08/020079,
- c) Unless indicated otherwise, all methods, steps, techniques and manipulations that are not specifically described in detail can be performed and have been performed in a manner known per se, as will be clear to the skilled person. Reference is for example again made to the standard handbooks and the general background art mentioned herein and to the further references cited therein; as well as to for

example the following reviews Presta, Adv. Drug Deliv. Rev. 2006, 58 (5-6): 640-56; Levin and Weiss, Mol. Biosyst. 2006, 2(1): 49-57; Irving et al., J. Immunol. Methods, 2001, 248(1-2), 31-45; Schmitz et al., Placenta, 2000, 21 Suppl. A, S106-12, Gonzales et al., Tumour Biol., 2005, 26(1), 31-43, which describe techniques for protein engineering, such as affinity maturation and other techniques for improving the specificity and other desired properties of proteins such as immunoglobulins.

- d) Amino acid residues will be indicated according to the standard three-letter or one-letter amino acid code. Reference is made to Table A-2 on page 48 of the International application WO 08/020079 of Ablynx N.V. entitled "Amino acid sequences directed against IL-6R and polypeptides comprising the same for the treatment of diseases and disorders associated with 11-6 mediated signalling".
- e) For the purposes of comparing two or more nucleotide sequences, the percentage of "sequence identity" between a first nucleotide sequence and a second nucleotide sequence may be calculated or determined as described in paragraph c) on page 49 of WO 08/020079 (incorporated herein by reference), such as by dividing [the number of nucleotides in the first nucleotide sequence that are identical to the nucleotides at the corresponding positions in the second nucleotide sequence] by [the total number of nucleotides in the first nucleotide sequence] and multiplying by [100%], in which each deletion, insertion, substitution or addition of a nucleotide in the second nucleotide sequence—compared to the first nucleotide sequence—is considered as a difference at a single nucleotide (position); or using a suitable computer algorithm or technique, again as described in paragraph c) on pages 49 of WO 08/020079 (incorporated herein by reference).
- f) For the purposes of comparing two or more amino acid sequences, the percentage of "sequence identity" between a first amino acid sequence and a second amino acid sequence (also referred to herein as "amino acid identity") may be calculated or determined as described in paragraph f) on pages 49 and 50 of WO 08/020079 (incorporated herein by reference), such as by dividing [the number of amino acid residues in the first amino acid sequence that are identical to the amino acid residues at the corresponding positions in the second amino acid sequence] by [the total number of amino acid residues in the first amino acid sequence] and multiplying by [100%], in which each deletion, insertion, substitution or addition of an amino acid residue in the second amino acid sequence—compared to the first amino acid sequence—is considered as a difference at a single amino acid residue (position), i.e. as an "amino acid difference" as defined herein; or using a suitable computer algorithm or technique, again as described in paragraph f) on pages 49 and 50 of WO 08/020079 (incorporated herein by reference).
    - Also, in determining the degree of sequence identity between two amino acid sequences, the skilled person may take into account so-called "conservative" amino acid substitutions, as described on page 50 of WO 08/020079.

- Any amino acid substitutions applied to the polypeptides described herein may also be based on the analysis of the frequencies of amino acid variations between homologous proteins of different species developed by Schulz et al., Principles of Protein Structure, Springer-Verlag, 1978, on the analyses of structure forming potentials developed by Chou and Fasman, Biochemistry 13: 211, 1974 and Adv. Enzymol., 47: 45-149, 1978, and on the analysis of hydrophobicity patterns in proteins developed by Eisenberg et al., Proc. Natl. Acad Sci. USA 81: 140-144, 1984; Kyte & Doolittle; J Molec. Biol. 157: 105-132, 198 1, and Goldman et al., Ann. Rev. Biophys. Chem. 15: 321-353, 1986, all incorporated herein in their entirety by reference. Information on the primary, secondary and tertiary structure of NANOBODIES® (V_{HH} sequences) is given in the description herein and in the general background art cited above. Also, for this purpose, the crystal structure of a V_{HH} domain from a llama is for example given by Desmyter et al., Nature Structural Biology, Vol. 3, 9, 803 (1996); Spinelli et al., Natural Structural Biology (1996); 3, 752-757; and Decanniere et al., Structure, Vol. 7, 4, 361 (1999). Further information about some of the amino acid residues that in conventional V_H domains form the V_H/V_L interface and potential camelizing substitutions on these positions can be found in the prior art cited above.

- g) Amino acid sequences and nucleic acid sequences are said to be "exactly the same" if they have 100% sequence identity (as defined herein) over their entire length;
- h) When comparing two amino acid sequences, the term "amino acid difference" refers to an insertion, deletion or substitution of a single amino acid residue on a position of the first sequence, compared to the second sequence; it being understood that two amino acid sequences can contain one, two or more such amino acid differences;
- i) When a nucleotide sequence or amino acid sequence is said to "comprise" another nucleotide sequence or amino acid sequence, respectively, or to "essentially consist of" another nucleotide sequence or amino acid sequence, this has the meaning given in paragraph i) on pages 51-52 of WO 08/020079.
- j) The term "in essentially isolated form" has the meaning given to it in paragraph j) on pages 52 and 53 of WO 08/020079.
- k) The terms "domain" and "binding domain" have the meanings given to it in paragraph k) on page 53 of WO 08/020079.
- l) The terms "antigenic determinant" and "epitope", which may also be used interchangeably herein. have the meanings given to it in paragraph l) on page 53 of WO 08/020079.
- m) As further described in paragraph m) on page 53 of WO 08/020079, an amino acid sequence (such as a NANOBODY® (V_{HH} sequence), an antibody, a polypeptide of the invention, or generally an antigen binding protein or polypeptide or a fragment

thereof) that can (specifically) bind to, that has affinity for and/or that has specificity for a specific antigenic determinant, epitope, antigen or protein (or for at least one part, fragment or epitope thereof) is said to be "against" or "directed against" said antigenic determinant, epitope, antigen or protein.

- n) The term "specificity" has the meaning given to it in paragraph n) on pages 53-56 of WO 08/020079; and as mentioned therein refers to the number of different types of antigens or antigenic determinants to which a particular antigen-binding molecule or antigen-binding protein (such as a NANOBODY® (V_{HH} sequence) or a polypeptide of the invention) molecule can bind. The specificity of an antigen-binding protein can be determined based on affinity and/or avidity, as described on pages 53-56 of WO 08/020079 (incorporated herein by reference), which also describes some preferred techniques for measuring binding between an antigen-binding molecule (such as a NANOBODY® (V_{HH} sequence) or polypeptide of the invention) and the pertinent antigen. Typically, antigen-binding proteins (such as the amino acid sequences, NANOBODIES® (V_{HH} sequences) and/or polypeptides of the invention) will bind to their antigen with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles). Any K_D value greater than 10^4 mol/liter (or any K_A value lower than 10^4 M^{-1}) liters/mol is generally considered to indicate non-specific binding. Preferably, a monovalent immunoglobulin sequence of the invention will bind to the desired antigen with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. Specific binding of an antigen-binding protein to an antigen or antigenic determinant can be determined in any suitable manner known per se, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition assays, and the different variants thereof known per se in the art; as well as the other techniques mentioned herein. As will be clear to the skilled person, and as described on pages 53-56 of WO 08/020079, the dissociation constant may be the actual or apparent dissociation constant. Methods for determining the dissociation constant will be clear to the skilled person, and for example include the techniques mentioned on pages 53-56 of WO 08/020079.
- o) The half-life of an amino acid sequence, compound or polypeptide of the invention can generally be defined as described in paragraph o) on page 57 of WO 08/020079 and as mentioned therein refers to the time taken for the serum concentration of the amino acid sequence, compound or polypeptide to be reduced by 50%, in vivo, for example due to degradation of the sequence or compound and/or clearance or sequestration of the sequence or compound by natural mechanisms. The in vivo half-

life of an amino acid sequence, compound or polypeptide of the invention can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art, and may for example generally be as described in paragraph o) on page 57 of WO 08/020079. As also mentioned in paragraph o) on page 57 of WO 08/020079, the half-life can be expressed using parameters such as the t1/2-alpha, t1/2-beta and the area under the curve (AUC). Reference is for example made to the Experimental Part below, as well as to the standard handbooks, such as Kenneth, A et al: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and Peters et al, Pharmacokinetic analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd Rev. edition (1982). The terms "increase in half-life" or "increased half-life" as also as defined in paragraph o) on page 57 of WO 08/020079 and in particular refer to an increase in the t1/2-beta, either with or without an increase in the t1/2-alpha and/or the AUC or both.

- p) In the context of the present invention, "modulating" or "to modulate" generally means either reducing or inhibiting the activity of, or alternatively increasing the activity of, a target or antigen, as measured using a suitable in vitro, cellular or in vivo assay. In particular, "modulating" or "to modulate" may mean either reducing or inhibiting the activity of, or alternatively increasing a (relevant or intended) biological activity of, a target or antigen, as measured using a suitable in vitro, cellular or in vivo assay (which will usually depend on the target or antigen involved), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to activity of the target or antigen in the same assay under the same conditions but without the presence of the construct of the invention.
    - As will be clear to the skilled person, "modulating" may also involve effecting a change (which may either be an increase or a decrease) in affinity, avidity, specificity and/or selectivity of a target or antigen for one or more of its binding partners, partners for association into a homomultimeric or heteromultimeric form; and/or effecting a change (which may either be an increase or a decrease) in the sensitivity of the target or antigen for one or more conditions in the medium or surroundings in which the target or antigen is present (such as pH, ion strength, the presence of co-factors, etc.), compared to the same conditions but without the presence of the construct of the invention. As will be clear to the skilled person, this may again be determined in any suitable manner and/or using any suitable assay known per se, depending on the target or antigen involved. "Modulating" may also mean effecting a change (i.e. an activity as an agonist, as an antagonist or as a reverse agonist, respectively, depending on the target or antigen and the desired biological or physiological effect) with respect to one or more biological or physiological mechanisms,

effects, responses, functions, pathways or activities in which the target or antigen (or in which its binding partners or pathway(s) are involved, such as its signalling pathway or metabolic pathway and their associated biological or physiological effects) is involved. Again, as will be clear to the skilled person, such an action as an agonist or an antagonist may be determined in any suitable manner and/or using any suitable (in vitro and usually cellular or in assay) assay known per se, depending on the target or antigen involved. In particular, an action as an agonist or antagonist may be such that an intended biological or physiological activity is increased or decreased, respectively, by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to the biological or physiological activity in the same assay under the same conditions but without the presence of the construct of the invention. Modulating may for example also involve allosteric modulation of the target or antigen; and/or reducing or inhibiting the binding of the target or antigen to one of its binding partners and/or competing with a natural binding partner for binding to the target or antigen. Modulating may also involve activating the target or antigen or the mechanism or pathway in which it is involved. Modulating may for example also involve effecting a change in respect of the folding or conformation of the target or antigen, or in respect of the ability of the target or antigen to fold, to change its conformation (for example, upon binding of a binding partner), to associate with other (sub)units, or to disassociate. Modulating may for example also involve effecting a change in the ability of the target or antigen to transport other compounds or to serve as a channel for other compounds (such as ions).

- Modulating may be reversible or irreversible, but for pharmaceutical and pharmacological purposes will usually be in a reversible manner.

- q) In respect of a target or antigen, the term “interaction site” on the target or antigen means a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen that is a site for binding to a receptor or other binding partner, a catalytic site, a cleavage site, a site for allosteric interaction, a site involved in multimerisation (such as homomerization or heterodimerization) of the target or antigen; or any other site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen that is involved in a biological action or mechanism of the target or antigen. More generally, an “interaction site” can be any site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen to which an amino acid sequence or polypeptide of the invention can bind such that the target or antigen (and/or any pathway, interaction, signalling, biological mechanism or biological effect in which the target or antigen is involved) is modulated (as defined herein).

- r) An amino acid sequence or polypeptide is said to be "specific for" a first target or antigen compared to a second target or antigen when is binds to the first antigen with an affinity (as described above, and suitably expressed as a K_D value, K_A value, K_{off} rate and/or K_{on} rate) that is at least 10 times, such as at least 100 times, and preferably at least 1000 times, and up to 10.000 times or more better than the affinity with which said amino acid sequence or polypeptide binds to the second target or polypeptide. For example, the first antigen may bind to the target or antigen with a K_D value that is at least 10 times less, such as at least 100 times less, and preferably at least 1000 times less, such as 10.000 times less or even less than that, than the K_D with which said amino acid sequence or polypeptide binds to the second target or polypeptide. Preferably, when an amino acid sequence or polypeptide is "specific for" a first target or antigen compared to a second target or antigen, it is directed against (as defined herein) said first target or antigen, but not directed against said second target or antigen.
- s) The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an amino acid sequence or other binding agent (such as a polypeptide of the invention) to interfere with the binding of other amino acid sequences or binding agents of the invention to a given target. The extend to which an amino acid sequence or other binding agents of the invention is able to interfere with the binding of another to the target, and therefore whether it can be said to cross-block according to the invention, can be determined using competition binding assays. One particularly suitable quantitative cross-blocking assay uses a Biacore machine which can measure the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between amino acid sequences or other binding agents in terms of their binding to the target.
    - The following generally describes a suitable Biacore assay for determining whether an amino acid sequence or other binding agent cross-blocks or is capable of cross-blocking according to the invention. It will be appreciated that the assay can be used with any of the amino acid sequences or other binding agents described herein. The Biacore machine (for example the Biacore 3000) is operated in line with the manufacturer's recommendations. Thus in one cross-blocking assay, the target protein is coupled to a CM5 Biacore chip using standard amine coupling chemistry to generate a surface that is coated with the target. Typically 200-800 resonance units of the target would be coupled to the chip (an amount that gives easily measurable levels of binding but that is readily saturable by the concentrations of test reagent being used). Two test amino acid sequences (termed A* and B*) to be assessed for their ability to cross-block each other are mixed at a one to one molar ratio of binding sites in a suitable buffer to create the test mixture. When calculating the concentrations

on a binding site basis the molecular weight of an amino acid sequence is assumed to be the total molecular weight of the amino acid sequence divided by the number of target binding sites on that amino acid sequence. The concentration of each amino acid sequence in the test mix should be high enough to readily saturate the binding sites for that amino acid sequence on the target molecules captured on the Biacore chip. The amino acid sequences in the mixture are at the same molar concentration (on a binding basis) and that concentration would typically be between 1.00 and 1.5 micromolar (on a binding site basis). Separate solutions containing A* alone and B* alone are also prepared. A* and B* in these solutions should be in the same buffer and at the same concentration as in the test mix. The test mixture is passed over the target-coated Biacore chip and the total amount of binding recorded. The chip is then treated in such a way as to remove the bound amino acid sequences without damaging the chip-bound target. Typically this is done by treating the chip with 30 mM HCl for 60 seconds. The solution of A* alone is then passed over the target-coated surface and the amount of binding recorded. The chip is again treated to remove all of the bound amino acid sequences without damaging the chip-bound target. The solution of B* alone is then passed over the target-coated surface and the amount of binding recorded. The maximum theoretical binding of the mixture of A* and B* is next calculated, and is the sum of the binding of each amino acid sequence when passed over the target surface alone. If the actual recorded binding of the mixture is less than this theoretical maximum then the two amino acid sequences are cross-blocking each other. Thus, in general, a cross-blocking amino acid sequence or other binding agent according to the invention is one which will bind to the target in the above Biacore cross-blocking assay such that during the assay and in the presence of a second amino acid sequence or other binding agent of the invention the recorded binding is between 80% and 0.1% (e.g. 80% to 4%) of the maximum theoretical binding, specifically between 75% and 0.1% (e.g. 75% to 4%) of the maximum theoretical binding, and more specifically between 70% and 0.1% (e.g. 70% to 4%) of maximum theoretical binding (as just defined above) of the two amino acid sequences or binding agents in combination. The Biacore assay described above is a primary assay used to determine if amino acid sequences or other binding agents cross-block each other according to the invention. On rare occasions particular amino acid sequences or other binding agents may not bind to a target coupled via amine chemistry to a CM5 Biacore chip (this usually occurs when the relevant binding site on the target is masked or destroyed by the coupling to the chip). In such cases cross-blocking can be determined using a tagged version of the target, for example a N-terminal His-tagged version. In this particular format, an anti-His amino acid sequence

would be coupled to the Biacore chip and then the His-tagged target would be passed over the surface of the chip and captured by the anti-His amino acid sequence. The cross blocking analysis would be carried out essentially as described above, except that after each chip regeneration cycle, new His-tagged target would be loaded back onto the anti-His amino acid sequence coated surface. In addition to the example given using N-terminal His-tagged target, C-terminal His-tagged target could alternatively be used. Furthermore, various other tags and tag binding protein combinations that are known in the art could be used for such a cross-blocking analysis (e.g. HA tag with anti-HA antibodies; FLAG tag with anti-FLAG antibodies; biotin tag with streptavidin).

- The following generally describes an ELISA assay for determining whether an amino acid sequence or other binding agent directed against a target cross-blocks or is capable of cross-blocking as defined herein. It will be appreciated that the assay can be used with any of the amino acid sequences (or other binding agents such as polypeptides of the invention) described herein. The general principal of the assay is to have an amino acid sequence or binding agent that is directed against the target coated onto the wells of an ELISA plate. An excess amount of a second, potentially cross-blocking, anti-target amino acid sequence is added in solution (i.e. not bound to the ELISA plate). A limited amount of the target is then added to the wells. The coated amino acid sequence and the amino acid sequence in solution compete for binding of the limited number of target molecules. The plate is washed to remove excess target that has not been bound by the coated amino acid sequence and to also remove the second, solution phase amino acid sequence as well as any complexes formed between the second, solution phase amino acid sequence and target. The amount of bound target is then measured using a reagent that is appropriate to detect the target. An amino acid sequence in solution that is able to cross-block the coated amino acid sequence will be able to cause a decrease in the number of target molecules that the coated amino acid sequence can bind relative to the number of target molecules that the coated amino acid sequence can bind in the absence of the second, solution phase, amino acid sequence. In the instance where the first amino acid sequence, e.g. an Ab-X, is chosen to be the immobilized amino acid sequence, it is coated onto the wells of the ELISA plate, after which the plates are blocked with a suitable blocking solution to minimize non-specific binding of reagents that are subsequently added. An excess amount of the second amino acid sequence, i.e. Ab-Y, is then added to the ELISA plate such that the moles of Ab-Y target binding sites per well are at least 10 fold higher than the moles of Ab-X target binding sites that were used, per well, during the coating of the ELISA plate. Target is then added such that the moles of target added per well are at least 25-fold lower than the moles of Ab-X

target binding sites that were used for coating each well. Following a suitable incubation period the ELISA plate is washed and a reagent for detecting the target is added to measure the amount of target specifically bound by the coated anti-target amino acid sequence (in this case Ab-X). The background signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence (in this case Ab-X), second solution phase amino acid sequence (in this case Ab-Y), target buffer only (i.e. without target) and target detection reagents. The positive control signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence (in this case Ab-X), second solution phase amino acid sequence buffer only (i.e. without second solution phase amino acid sequence), target and target detection reagents. The ELISA assay may be run in such a manner so as to have the positive control signal be at least 6 times the background signal. To avoid any artefacts (e.g. significantly different affinities between Ab-X and Ab-Y for the target) resulting from the choice of which amino acid sequence to use as the coating amino acid sequence and which to use as the second (competitor) amino acid sequence, the cross-blocking assay may to be run in two formats: 1) format 1 is where Ab-X is the amino acid sequence that is coated onto the ELISA plate and Ab-Y is the competitor amino acid sequence that is in solution and 2) format 2 is where Ab-Y is the amino acid sequence that is coated onto the ELISA plate and Ab-X is the competitor amino acid sequence that is in solution. Ab-X and Ab-Y are defined as cross-blocking if, either in format 1 or in format 2, the solution phase anti-target amino acid sequence is able to cause a reduction of between 60% and 100%, specifically between 70% and 100%, and more specifically between 80% and 100%, of the target detection signal {i.e. the amount of target bound by the coated amino acid sequence) as compared to the target detection signal obtained in the absence of the solution phase anti-target amino acid sequence (i.e. the positive control wells).

- t) An amino acid sequence is said to be “cross-reactive” for two different antigens or antigenic determinants (such as e.g. serum albumin from two different species of mammal, such as e.g. human serum albumin and cyno serum albumin, such as e.g. the same envelop proteins of different strains of a virus, such as e.g. the same envelope proteins of different genotypes of a virus) if it is specific for (as defined herein) both these different antigens or antigenic determinants.
- u) By binding that is “essentially independent of the pH” is generally meant herein that the association constant (K_A) of the amino acid sequence with respect to the serum protein (such as serum albumin) at the pH value(s) that occur in a cell of an animal or human body (as further described herein) is at least 5%, such as at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 60%, such as even more preferably at least 70%, such as at least 80% or 90% or

more (or even more than 100%, such as more than 110%, more than 120% or even 130% or more, or even more than 150%, or even more than 200%) of the association constant (K_A) of the amino acid sequence with respect to the same serum protein at the pH value(s) that occur outside said cell. Alternatively, by binding that is "essentially independent of the pH" is generally meant herein that the k_{off} rate (measured by Biacore) of the amino acid sequence with respect to the serum protein (such as serum albumin) at the pH value(s) that occur in a cell of an animal or human body (as e.g. further described herein, e.g. pH around 5.5, e.g. 5.3 to 5.7) is at least 5%, such as at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 60%, such as even more preferably at least 70%, such as at least 80% or 90% or more (or even more than 100%, such as more than 110%, more than 120% or even 130% or more, or even more than 150%, or even more than 200%) of the k_{off} rate of the amino acid sequence with respect to the same serum protein at the pH value(s) that occur outside said cell, e.g. pH 7.2 to 7.4. By "the pH value(s) that occur in a cell of an animal or human body" is meant the pH value(s) that may occur inside a cell, and in particular inside a cell that is involved in the recycling of the serum protein. In particular, by "the pH value(s) that occur in a cell of an animal or human body" is meant the pH value(s) that may occur inside a (sub)cellular compartment or vesicle that is involved in recycling of the serum protein (e.g. as a result of pinocytosis, endocytosis, transcytosis, exocytosis and phagocytosis or a similar mechanism of uptake or internalization into said cell), such as an endosome, lysosome or pinosome.

- v) As further described herein, the total number of amino acid residues in a NANOBODY® (V_{HH} sequence) can be in the region of 110-120, is preferably 112-115, and is most preferably 113. It should however be noted that parts, fragments, analogs or derivatives (as further described herein) of a NANOBODY® (V_{HH} sequence) are not particularly limited as to their length and/or size, as long as such parts, fragments, analogs or derivatives meet the further requirements outlined herein and are also preferably suitable for the purposes described herein;
- w) As further described in paragraph q) on pages 58 and 59 of WO 08/020079 (incorporated herein by reference), the amino acid residues of a NANOBODY® (V_{HH} sequence) are numbered according to the general numbering for V_H domains given by Kabat et al. ("Sequence of proteins of immunological interest", US Public Health Services, NIH Bethesda, Md., Publication No. 91), as applied to V_{HH} domains from Camelids in the article of Riechmann and Muyldermans, J. Immunol. Methods 2000 Jun. 23; 240 (1-2): 185-195 (see for example FIG. 2 of this publication), and accordingly FR1 of a NANOBODY® (V_{HH} sequence) comprises the amino acid residues at positions 1-30, CDR1 of a NANOBODY® (V_{HH} sequence) comprises the amino acid residues at positions 31-35, FR2 of a NANOBODY® (V_{HH} sequence) comprises the amino acids at positions 36-49, CDR2 of a NANOBODY® (V_{HH}

sequence) comprises the amino acid residues at positions 50-65, FR3 of a NANOBODY® (V_{HH} sequence) comprises the amino acid residues at positions 66-94, CDR3 of a NANOBODY® (V_{HH} sequence) comprises the amino acid residues at positions 95-102, and FR4 of a NANOBODY® (V_{HH} sequence) comprises the amino acid residues at positions 103-113.

- x) In the context of the present invention "target host cell (of a virus)" generally refers to a particular cell, which is or is derived from a living subject, being susceptible to infection with said virus.
- y) The term "infectivity of a virus", as used herein, refers to the proportion of living subjects that, when exposed to said virus, actually become infected by said virus.
- z) The term "neutralization of a virus", as used herein, refers to the modulation and/or reduction and/or prevention and/or inhibition of the infectivity (as defined herein) of a virus by binding of a neutralizing compound to the virion, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, "neutralizing (a virus)" or "to neutralize (a virus)" may mean either modulating, reducing, preventing or inhibiting the infectivity (as defined herein) of a virus, which can be mediated by an envelope protein of a virus and/or its viral receptor as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) infectivity (as defined herein) of a virus, which is mediated by an envelope protein of a virus and/or its viral receptor in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention.
- aa) The term "viral attachment protein", as used herein, is any protein that is present on the virion surface and that is able to directly (for example by interacting with a viral receptor) or indirectly (for example by mediating the interaction of one or more other proteins or molecules to a viral receptor) mediate viral attachment to a target host cell.
- bb) The term "viral fusion protein", as used herein, is any protein that is present on the virion surface and that is able to directly (for example by interacting with membrane compounds of the target host cell) or indirectly (for example by mediating the interaction of one or more other proteins or molecules with membrane compounds of the target host cell) mediate viral fusion to a target host cell.
- cc) The term "viral attachment and viral fusion protein", as used herein is any protein that is present on the virion surface and that is able to directly (for example by interacting with a viral receptor and/or membrane compounds of the target host cell) or indirectly (for example by mediating the interaction of one or more other proteins or molecules to a viral receptor and/or one or more other proteins or molecules with membrane compounds of the target host cell) mediate viral attachment and viral

fusion to a target host cell.

- dd) The term "pre-fusion conformational state (of a viral (attachment, fusion, or both attachment and fusion) protein)", as used herein, refers to the primary and/or secondary and/or tertiary and/or quaternary conformational state of a viral (attachment, fusion, or both attachment and fusion) protein before and/or during the fusion process of a virion with its target host cell, wherein said virion has said viral (attachment, fusion, or both attachment and fusion) protein exposed on its surface.
- ee) The term "intermediate fusion conformational state (of a viral (attachment, fusion, or both attachment and fusion) protein)", as used herein, refers to the primary and/or secondary and/or tertiary and/or quaternary conformational state of a viral (attachment, fusion, or both attachment and fusion) protein during the fusion process of a virion with its target host cell, wherein said virion has said viral (attachment, fusion, or both attachment and fusion) protein exposed on its surface.
- ff) The term "post-fusion conformational state (of a viral (attachment, fusion, or both attachment and fusion) protein)", as used herein, refers to the primary and/or secondary and/or tertiary and/or quaternary conformational state of a viral (attachment, fusion, or both attachment and fusion) protein during and/or after the fusion process of a virion with its target host cell, wherein said virion has said viral (attachment, fusion, or both attachment and fusion) protein exposed on its surface.
- gg) The term "viral receptor", as used herein, refers to a specific molecular component of the cell, which is capable of recognizing and interacting with a virus, and which, after binding to said virus, is capable of generating a signal that initiates a chain of events leading to a biological response.
- hh) The term "viral entry" used herein encompasses any viral-mediated biological pathway that is needed to accomplish virion attachment to a target host cell and/or viral fusion with a target host cell. It is encompassed in the present invention that viral entry, which may be any viral-mediated biological pathway that is needed to accomplish virion attachment to a target host cell and/or viral fusion with a target host cell, can be modulated and/or reduced and/or prevented and/or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, viral entry, which can be mediated by an envelope protein of a virus and/or its viral receptor, can be modulated, reduced, prevented or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) viral entry (as defined herein), which

can be mediated by an envelope protein of a virus and/or its viral receptor in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), polypeptide and/or compound of the invention. Thus, it is also encompassed that that viral attachment and/or viral fusion can be modulated and/or reduced and/or prevented and/or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, viral attachment and/or viral fusion, which can be mediated by an envelope protein of a virus and/or its viral receptor, can be modulated, reduced, prevented or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) viral attachment and/or viral fusion, which can be mediated by an envelope protein of a virus and/or its viral receptor in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), polypeptide and/or compound of the invention.

- ii) The term "viral replication" used herein encompasses any viral-mediated biological pathway that is needed to accomplish transcription and/or translation of the viral genome and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane. It is encompassed in the present invention that viral replication, which may be any viral-mediated biological pathway that is needed to accomplish transcription and/or translation of the viral genome and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane, can be modulated and/or reduced and/or prevented and/or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, viral replication, which can be mediated by an envelope protein of a virus and/or its viral receptor, can be modulated, reduced, prevented or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) viral replication (as defined herein),

which can be mediated by an envelope protein of a virus and/or its viral receptor, in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), polypeptide and/or compound of the invention. Thus, it is also encompassed that transcription and/or translation of the viral genome and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane can be modulated and/or reduced and/or prevented and/or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein). In particular, transcription and/or translation of the viral genome and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane, which can be mediated by an envelope protein of a virus and/or its viral receptor, can be modulated, reduced, prevented or inhibited by specific binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and/or compounds of the invention to an envelope protein of a virus, as measured using a suitable in vitro, cellular or in vivo assay (such as those mentioned herein), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to normal (i.e. naturally occurring) transcription and/or translation of the viral genome and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane, which can be mediated by an envelope protein of a virus and/or its viral receptor in the same assay under the same conditions but without the presence of the amino acid sequence, NANOBODY® (V_{HH} sequence), polypeptide and/or compound of the invention.

- jj) In the context of the present invention "a virus" may be any virus that is generally known in the art. In particular, said virus may be chosen from the group consisting of a DNA virus (such as but not limited to a dsDNA virus or a ssDNA virus), an RNA virus (such as but not limited to a dsRNA virus, a positive-sense ssRNA virus or a negative-sense ssRNA virus) and a Reverse Transcriptase (RT) virus (such as but not limited to dsDNA-RT virus and a ssRNA-RT virus. For example, said virus may belong to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae; and said virus may for instance belong to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses. Accordingly, amino acid sequences, polypeptides and compositions according to the invention may be directed against at least one epitope of an envelope protein of any of the foregoing viruses, chosen from the group consisting of a DNA virus (such as but not limited to a ds DNA virus or a

ssDNA virus), an RNA virus (such as but not limited to a dsRNA virus, a positive-sense ssRNA virus or a negative-sense ssRNA virus) and a Reverse Transcriptase (RT) virus (such as but not limited to dsDNA-RT virus and a ssRNA-RT virus. For example, said virus may belong to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae; and in particular said virus may for instance belong to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses.

- kk) The Figures, Sequence Listing and the Experimental Part/Examples are only given to further illustrate the invention and should not be interpreted or construed as limiting the scope of the invention and/or of the appended claims in any way, unless explicitly indicated otherwise herein.

For a general description of heavy chain antibodies and the variable domains thereof, reference is inter alia made to the prior art cited herein, as well as to the prior art mentioned on page 59 of WO 08/020079 and to the list of references mentioned on pages 41-43 of the International application WO 06/040153, which prior art and references are incorporated herein by reference.

In accordance with the terminology used in the art (see the above references), the variable domains present in naturally occurring heavy chain antibodies will also be referred to as "V_{HH} domains", in order to distinguish them from the heavy chain variable domains that are present in conventional 4-chain antibodies (which will be referred to hereinbelow as "V_H domains") and from the light chain variable domains that are present in conventional 4-chain antibodies (which will be referred to hereinbelow as "V_L domains").

As mentioned in the prior art referred to above, V_{HH} domains have a number of unique structural characteristics and functional properties which make isolated V_{HH} domains (as well as NANOBODIES® (V_{HH} sequences) based thereon, which share these structural characteristics and functional properties with the naturally occurring V_{HH} domains) and proteins containing the same highly advantageous for use as functional antigen-binding domains or proteins. In particular, and without being limited thereto, V_{HH} domains (which have been "designed" by nature to functionally bind to an antigen without the presence of, and without any interaction with, a light chain variable domain) and NANOBODIES® (V_{HH} sequences) can function as a single, relatively small, functional antigen-binding structural unit, domain or protein. This distinguishes the V_{HH} domains from the V_H and V_L domains of conventional 4-chain antibodies, which by themselves are generally not suited for practical application as single antigen-binding proteins or domains, but need to be combined in some form or another to provide a functional antigen-binding unit (as in for example conventional antibody fragments such as Fab fragments; in ScFv's fragments, which consist

of a V_H domain covalently linked to a V_L domain).

Because of these unique properties, the use of V_{HH} domains and NANOBODIES® (V_{HH} sequences) as single antigen-binding proteins or as antigen-binding domains (i.e. as part of a larger protein or polypeptide) offers a number of significant advantages over the use of conventional V_H and V_L domains, scFv's or conventional antibody fragments (such as Fab- or F(ab')$_2$-fragments), including the advantages that are listed on pages 60 and 61 of WO 08/020079.

In a specific and preferred aspect, the invention provides NANOBODIES® (V_{HH} sequences) against an envelope protein of a virus, and in particular NANOBODIES® (V_{HH} sequences) against an envelope protein of a virus that is able to infect a warm-blooded animal, and more in particular NANOBODIES® (V_{HH} sequences) against an envelope protein of a virus that is able to infect a mammal, and especially NANOBODIES® (V_{HH} sequences) against an envelope protein of a human virus; as well as proteins and/or polypeptides comprising at least one such NANOBODY® (V_{HH} sequence).

In particular, the invention provides NANOBODIES® (V_{HH} sequences) against an envelope protein of a virus, and proteins and/or polypeptides comprising the same, that have improved therapeutic and/or pharmacological properties and/or other advantageous properties (such as, for example, improved ease of preparation and/or reduced costs of goods), compared to conventional antibodies against an envelope protein of a virus or fragments thereof, compared to constructs that could be based on such conventional antibodies or antibody fragments (such as Fab' fragments, F(ab')$_2$ fragments, ScFv constructs, "diabodies" and other multispecific constructs (see for example the review by Holliger and Hudson, Nat. Biotechnol. 2005 September; 23(9):1126-36)), and also compared to the so-called "dAb's" or similar (single) domain antibodies that may be derived from variable domains of conventional antibodies. These improved and advantageous properties will become clear from the further description herein, and for example include, without limitation, one or more of:

- increased affinity and/or avidity for an envelope protein of a virus, either in a monovalent format, in a multivalent format (for example in a bivalent or trivalent format) and/or in a multispecific format (for example one of the multispecific formats described herein);
- better suitability for formatting in a multivalent format (for example in a bivalent or trivalent format);
- better suitability for formatting in a multispecific format (for example one of the multispecific formats described herein);
- improved suitability or susceptibility for "humanizing" substitutions (as defined herein);

- less immunogenicity, either in a monovalent format, in a multivalent format (for example in a bivalent or trivalent format) and/or in a multispecific format (for example one of the multispecific formats described herein);
- increased stability, either in a monovalent format, in a multivalent format (for example in a bivalent or trivalent format) and/or in a multispecific format (for example one of the multispecific formats described herein);
- increased specificity towards an envelope protein of a virus, either in a monovalent format, in a multivalent format (for example in a bivalent or trivalent format) and/or in a multispecific format (for example one of the multispecific formats described herein);
- decreased or where desired increased cross-reactivity with an envelope protein of a virus from different species;
  and/or
- one or more other improved properties desirable for pharmaceutical use (including prophylactic use and/or therapeutic use) and/or for diagnostic use (including but not limited to use for imaging purposes), either in a monovalent format, in a multivalent format (for example in a bivalent or trivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow).

As generally described herein for the amino acid sequences of the invention, the NANOBODIES® (V_{HH} sequences) of the invention are preferably in essentially isolated form (as defined herein), or form part of a protein or polypeptide of the invention (as defined herein), which may comprise or essentially consist of one or more NANOBODIES® (V_{HH} sequences) of the invention and which may optionally further comprise one or more further amino acid sequences (all optionally linked via one or more suitable linkers). For example, and without limitation, the one or more amino acid sequences of the invention may be used as a binding unit in such a protein or polypeptide, which may optionally contain one or more further amino acid sequences that can serve as a binding unit (i.e. against one or more other targets than an envelope protein of a virus), so as to provide a monovalent, multivalent or multispecific polypeptide of the invention, respectively, all as described herein. In particular, such a protein or polypeptide may comprise or essentially consist of one or more NANOBODIES® (V_{HH} sequences) of the invention and optionally one or more (other) NANOBODIES® (V_{HH} sequences) (i.e. directed against other targets than an envelope protein of a virus), all optionally linked via one or more suitable linkers, so as to provide a monovalent, multivalent or multispecific NANOBODY® (V_{HH} sequence) construct, respectively, as further described herein. Such proteins or polypeptides may also be in essentially isolated form (as defined herein).

In a NANOBODY® (V_{HH} sequence) of the invention, the binding site for binding against an envelope protein of a virus is preferably formed by the CDR sequences. Optionally, a

NANOBODY® (V_{HH} sequence) of the invention may also, and in addition to the at least one binding site for binding to an envelope protein of a virus, contain one or more further binding sites for binding against other antigens, proteins or targets. For methods and positions for introducing such second binding sites, reference is for example made to Keck and Huston, Biophysical Journal, 71, October 1996, 2002-2011; EP 0 640 130; and WO 06/07260.

As generally described herein for the amino acid sequences of the invention, when a NANOBODY® (V_{HH} sequence) of the invention (or a polypeptide of the invention comprising the same) is intended for administration to a subject (for example for prophylactic, therapeutic and/or diagnostic purposes as described herein), it is preferably directed against an envelope protein of a virus that is able to infect humans; whereas for veterinary purposes, it is preferably directed against an envelope protein of a virus that is able to infect the species to be treated. Also, as with the amino acid sequences of the invention, a NANOBODY® (V_{HH} sequence) of the invention may or may not be cross-reactive (i.e. directed against two or more homologous envelope proteins of a virus that is able to infect two or more species of mammal, such as against two or more homologous envelope proteins of a virus that is both able to infect humans and at least one of the species of mammal mentioned herein).

A NANOBODY® (V_{HH} sequence) of the invention may or may not be cross-reactive for two or more different genotypes, subtypes, viral escape mutants and/or strains of a certain virus. In this respect, the present invention provides multivalent NANOBODIES® (V_{HH} sequences) or polypeptides which show increased cross-reactivity for different genotypes, subtypes, viral escape mutants and/or strains of a certain virus compared to the corresponding monovalent NANOBODY® (V_{HH} sequence). In one aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H1N1. In another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H3N2. In another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H1N1 as well as influenza subtype H3N2. In another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H2N2. Yet in another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H3N2. Yet in another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H2N2 as well as influenza subtype H3N2. Yet in another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H2N2. Yet in another aspect, the

(multivalent) NANOBODIES® (V_{HH} sequences) are directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1, influenza subtype H2N2 as well as influenza subtype H3N2. In another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against rabies virus and may bind rabies genotype 1 as well as genotype 5. In yet another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against RSV and may bind different strains of RSV (such as e.g. Long, A-2 and/or B-1). In yet another aspect, the (multivalent) NANOBODIES® (V_{HH} sequences) are directed against RSV and may bind different escape mutants of RSV (such as e.g. described in Lopez et al. 1998, J. Virol. 72: 6922-6928) and/or escape mutants specific for antigen site II, antigen site IV-VI or the combination of both antigenic sites.

Also, again as generally described herein for the amino acid sequences of the invention, the NANOBODIES® (V_{HH} sequences) of the invention may generally be directed against any antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus.

However, it is generally assumed and preferred that the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are preferably directed against an interaction site (as defined herein), and in particular against at least one epitope of an envelope protein of a virus, such that at least one viral-mediated biological pathway in which an envelope protein of a virus and/or a viral receptor are involved is inhibited, prevented and/or modulated.

In particular, it is assumed and preferred that the NANOBODIES® (V_{HH} sequences), polypeptides and compositions of the present invention are directed against at least one epitope of an envelope protein of a virus, such that viral entry in a target host cell (such as for instance virion attachment to a target host cell and/or viral fusion with a target host cell) and/or viral replication in a target host cell (such as for instance viral transcription and/or viral translation and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane) is inhibited, prevented and/or modulated.

The NANOBODIES® (V_{HH} sequences) and polypeptides may be directed against at least one epitope of an envelope protein of a virus that is surface-exposed or that is located in a cavity or cleft formed by an envelope protein of a virus. Preferably, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against an interaction site (as defined herein), and in particular against an epitope that is located in a cavity or cleft formed by a trimer of fusion proteins (such as a fusion protein trimer that is a trimer of hairpins or a six-helix bundle) or a dimer of fusion proteins, wherein said fusion proteins can be in their pre-, intermediate, or post-fusion conformational state.

Furthermore, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may also be directed against an epitope that is located in the stem region and/or in the neck

region and/or in the globular head region of a fusion protein. Preferably, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against an epitope that is located in the stem region of a fusion protein, such as for instance against an epitope that is located in the region comprising one or more of the amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA; against an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA; against an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA; against an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA; or against an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA. Alternatively, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may be directed against an epitope that is located in the globular head of a fusion protein (wherein said globular head may for example comprise a β-barrel-type structure or an immunoglobulin-type β-sandwich domain and a β-sheet domain).

Also, in particular, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may preferably be directed against an interaction site, which is chosen from the group consisting of the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus, the Fla site and/or the region comprising amino acid 389 of the F-protein of RSV virus, amino acids 422 to 438 of the F-protein of RSV virus, sialic acid binding site of the H5 HA envelope protein of influenza virus, the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus (Thoulouze et al. 1998, J. Virol. 72: 7181-7190).

Finally, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may be directed against any epitope that is located in the C-terminal region of a fusion protein and/or in the N-terminal domain of a fusion protein and/or in or comprising the fusion peptide of a fusion protein and/or in the transmembrane domain of a fusion protein and/or in a α-helical coiled-coil of a fusion protein and/or in a β-structure of a fusion protein and/or in Domain I of a fusion protein and/or in Domain II of a fusion protein, such as for example in the fusion peptide of Domain II of a fusion protein, and/or in Domain III of a fusion protein, such as for example in the stem region at the C-terminus of Domain III of a fusion protein or in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.

In one aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein. In particular, they may be directed against antigenic site II (also referred to as site A) of the RSV F protein and more

preferably against region aa 250-275 of the RSV F protein.

In another aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. In particular, they may be directed against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein.

In yet another aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

In yet another aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are directed against the MAb 8-2 binding site on G envelope protein of rabies virus and/or capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.

Also, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may be directed against any other epitope of an envelope protein of a virus (for instance any other epitope that is close to one of the aforementioned epitopes).

Thus, in one preferred, but non-limiting aspect, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention are generally directed against any epitope or in particular against one of the above-mentioned epitopes of an envelope protein of a virus, and are as further defined herein. For example, said epitope may be present on an envelope protein of a virus that is chosen from the group consisting of the F protein of RSV virus, the G protein of RSV virus, the SH protein of RSV virus, the M protein of RSV virus, the M2 protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2, σ1 of Reovirus 1, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein

of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

Accordingly, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may be directed against any epitope that is present on an envelope protein of a virus, which is chosen from the group consisting of the F protein of RSV virus, the G protein of RSV virus, the SH protein of RSV virus, the M protein of RSV virus, the M2 protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2, σ1 of Reovirus 1, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

As already described herein, the amino acid sequence and structure of a NANOBODY® (V_{HH} sequence) can be considered—without however being limited thereto—to be comprised of four framework regions or “FR's” (or sometimes also referred to as “FW's”), which are referred to in the art and herein as “Framework region 1” or “FR1”; as “Framework region 2” or “FR2”; as “Framework region 3” or “FR3”; and as “Framework region 4” or “FR4”, respectively; which framework regions are interrupted by three complementary determining regions or “CDR's”, which are referred to in the art as “Complementarity Determining Region 1” or “CDR1”; as “Complementarity Determining Region 2” or “CDR2”; and as “Complementarity Determining Region 3” or “CDR3”, respectively. Some preferred framework sequences and CDR's (and combinations thereof) that are present in the NANOBODIES® (V_{HH} sequences) of the invention are as described herein. Other suitable CDR sequences can be obtained by the methods described herein.

According to a non-limiting but preferred aspect of the invention, (the CDR sequences

present in) the NANOBODIES® (V_{HH} sequences) of the invention are such that:

- the NANOBODIES® (V_{HH} sequences) can bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles);
  and/or such that:
- the NANOBODIES® (V_{HH} sequences) can bind to an envelope protein of a virus with a k_{on}-rate of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$;
  and/or such that they:
- the NANOBODIES® (V_{HH} sequences) can bind to an envelope protein of a virus with a k_{off} rate between 1 s^{-1} ($t_{1/2}$=0.69 s) and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, (the CDR sequences present in) the NANOBODIES® (V_{HH} sequences) of the invention are such that: a monovalent NANOBODY® (V_{HH} sequence) of the invention (or a polypeptide that contains only one NANOBODY® (V_{HH} sequence) of the invention) is preferably such that it will bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

The affinity of the NANOBODY® (V_{HH} sequence) of the invention against an envelope protein of a virus can be determined in a manner known per se, for example using the general techniques for measuring K_D. K_A, k_{off} or k_{on} mentioned herein, as well as some of the specific assays described herein.

Some preferred IC50 values for binding of the NANOBODIES® (V_{HH} sequences) of the invention (and of polypeptides comprising the same) to an envelope protein of a virus will become clear from the further description and examples herein.

In a preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against an envelope protein of a virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- CDR1 is chosen from the group consisting of:

- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

  and/or
  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

  and/or
  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;

  or any suitable fragment of such an amino acid sequence.

In particular, according to this preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against an envelope protein of a virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  and
    - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  and
    - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  or any suitable fragment of such an amino acid sequences.

In a more specifically preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against the F-protein of human RSV virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597; and/or
    - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and

2606 to 2613;

- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

and/or

- CDR3 is chosen from the group consisting of:

- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;

or any suitable fragment of such an amino acid sequence.

In particular, according to this preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against the F-protein of human RSV virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;

and

- CDR2 is chosen from the group consisting of:

- d) the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of

the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

and

- CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;

or any suitable fragment of such an amino acid sequences.

Yet, in another specifically preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against hemagglutinin of influenza virus, and more specifically hemagglutinin H5 of influenza virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- - CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

and/or

- CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

and/or

- CDR3 is chosen from the group consisting of:

- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;

or any suitable fragment of such an amino acid sequence.

In particular, according to this preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against hemagglutinin of influenza virus, and more specifically hemagglutinin H5 of influenza virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

and

- CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

and

- CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to

2899 and 3454 to 3518;

- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;

or any suitable fragment of such an amino acid sequences.

Finally, in yet another specifically preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against the G-protein of rabies virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;

and/or

- CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;

and/or

- CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;

or any suitable fragment of such an amino acid sequence.

In particular, according to this preferred but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) (as defined herein) against the G-protein of rabies virus, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- CDR1 is chosen from the group consisting of:
- a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b) amino acid sequences that have at least 80% amino acid identity with at least one

of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;

- c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  and
  - CDR2 is chosen from the group consisting of:
- d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  and
  - CDR3 is chosen from the group consisting of:
- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  or any suitable fragment of such an amino acid sequences.

As generally mentioned herein for the amino acid sequences of the invention, when a NANOBODY® (V_{HH} sequence) of the invention contains one or more CDR1 sequences according to b) and/or c):

- i) any amino acid substitution in such a CDR according to b) and/or c) is preferably, and compared to the corresponding CDR according to a), a conservative amino acid substitution (as defined herein);
  and/or
- ii) the CDR according to b) and/or c) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding CDR according to a);
  and/or
- iii) the CDR according to b) and/or c) may be a CDR that is derived from a CDR according to a) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Similarly, when a NANOBODY® (V_{HH} sequence) of the invention contains one or more CDR2 sequences according to e) and/or f):

- i) any amino acid substitution in such a CDR according to e) and/or f) is preferably, and compared to the corresponding CDR according to d), a conservative amino acid substitution (as defined herein);

and/or

- ii) the CDR according to e) and/or f) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding CDR according to d);
  and/or
- iii) the CDR according to e) and/or f) may be a CDR that is derived from a CDR according to d) by means of affinity maturation using one or more techniques of affinity maturation known per se.

Also, similarly, when a NANOBODY® (V_{HH} sequence) of the invention contains one or more CDR3 sequences according to h) and/or i):

- i) any amino acid substitution in such a CDR according to h) and/or i) is preferably, and compared to the corresponding CDR according to g), a conservative amino acid substitution (as defined herein);
  and/or
- ii) the CDR according to h) and/or i) preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding CDR according to g);
  and/or
- iii) the CDR according to h) and/or i) may be a CDR that is derived from a CDR according to g) by means of affinity maturation using one or more techniques of affinity maturation known per se.

It should be understood that the last three paragraphs generally apply to any NANOBODY® (V_{HH} sequence) of the invention that comprises one or more CDR1 sequences, CDR2 sequences and/or CDR3 sequences according to b), c), e), f), h) or i), respectively.

Of the NANOBODIES® (V_{HH} sequences) of the invention, NANOBODIES® (V_{HH} sequences) comprising one or more of the CDR's explicitly listed above are particularly preferred; NANOBODIES® (V_{HH} sequences) comprising two or more of the CDR's explicitly listed above are more particularly preferred; and NANOBODIES® (V_{HH} sequences) comprising three of the CDR's explicitly listed above are most particularly preferred.

Some particularly preferred, but non-limiting combinations of CDR sequences, as well as preferred combinations of CDR sequences and framework sequences, are mentioned in Table B-1 below, which lists the CDR sequences and framework sequences that are present in a number of preferred (but non-limiting) NANOBODIES® (V_{HH} sequences) of the invention. As will be clear to the skilled person, a combination of CDR1, CDR2 and CDR3 sequences that occur in the same clone (i.e. CDR1, CDR2 and CDR3 sequences that are mentioned on the same line in Table B-1) will usually be preferred (although the invention in its broadest sense is not limited thereto, and also comprises other suitable combinations

of the CDR sequences mentioned in Table B-1). Also, a combination of CDR sequences and framework sequences that occur in the same clone (i.e. CDR sequences and framework sequences that are mentioned on the same line in Table B-1) will usually be preferred (although the invention in its broadest sense is not limited thereto, and also comprises other suitable combinations of the CDR sequences and framework sequences mentioned in Table B-1, as well as combinations of such CDR sequences and other suitable framework sequences, e.g. as further described herein).

Also, in the NANOBODIES® (V_{HH} sequences) of the invention that comprise the combinations of CDR's mentioned in Table B-1, each CDR can be replaced by a CDR chosen from the group consisting of amino acid sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with the mentioned CDR's; in which:

- i) any amino acid substitution in such a CDR is preferably, and compared to the corresponding CDR sequence mentioned in Table B-1, a conservative amino acid substitution (as defined herein);
  and/or
- ii) any such CDR sequence preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the corresponding CDR sequence mentioned in Table B-1;
  and/or
- iii) any such CDR sequence is a CDR that is derived by means of a technique for affinity maturation known per se, and in particular starting from the corresponding CDR sequence mentioned in Table B-1.

However, as will be clear to the skilled person, the (combinations of) CDR sequences, as well as (the combinations of) CDR sequences and framework sequences mentioned in Table B-1 will generally be preferred.

TABLE B-1 Preferred combinations of CDR sequences, preferred combinations of framework sequences, and preferred combinations of framework and CDR sequences. Clone ID FR1 ID CDR1 ID FR2 ID CDR2 LG202A10 126 EVQLVESGG 408 DYPIG 690 WFRQAP 972 AIYAIGG GLVQAGDSLR GKEREF DVYYAD LSCIDSGRTFS VA SVKG LG202A12 127 EVQLVESGG 409 SYAMG 691 WFRQAP 973 AITWSG GLVQAGGSL GKERDF GSTYYA RLSCAASGGT VS DSVKG LG202A5 128 EVQLVESGG 410 GYWMT 692 WVRQAP 974 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG LG202A9 129 EVQLVESGG 411 GYWMS 693 WVRQAP 975 AINNVG GSVQPGGSL GKGLEW GDTYYA RLSCAASGFT VS DSVKG FR LG202B10 130 EVQLVESGG 412 GYWMS 694 WVRQAP 976 AINNVG GLVQPGGSL GKGLEW DEVYYA RLSCAASGFT VS DSVKG FR LG202B7 131 EVQLVESGG 413 GYWMS 695 WVRQAP 977 AINNVG GLVQPGGSL GKGLEW DEVYYA

RLSCAASGFT VS DSVKG FR LG202B8 132 EVQLVESGG 414 GYWMS 696 WVRQAP 978 AISNSG GLVQPGGSL GKGLEW GETYYA RLSCAASGFT VS DSVKG FS LG202B9 133 EVQLVESGG 415 GYWMS 697 WVRQAP 979 AINNLGG GSVQPGGSL GKGLEW DTYYAD RLSCAASGFT VS SVKG FR LG202C1 134 KVQLVESGG 416 GYWMT 698 WVRQAP 980 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG LG202C11 135 EVQLVESGG 417 GYWMS 699 WVRQAP 981 AINNVG GSVQPGGSL GKGLEW GDTYYA RLSCAASGFT VS DSVKG FR LG202C2 136 EVQLVESGG 418 GYWMT 700 WVRQAP 982 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG LG202C7 137 EVQLVESGG 419 GYWMS 701 WVRQAP 983 AINNVG GLVQPGGSL GKGLEW DETYYA RLSCAASGFT VS NSVKG FS LG202C8 138 EVQLVESGG 420 SYWMD 702 WVRQTP 984 GISPSGS GLVQPGGSL GKDLEY NTDYAD RLSCTGSGFT VS SVKG FS LG202C9 139 EVQLVESGG 421 GYWMS 703 WVRQAP 985 AINNVG GLVQPGGSL GKGLEW GETYYA RLSCAASGFT VS DSVKG FR LG202D5 140 EVQLVESGG 422 STAMG 704 WSRQAP 986 SISSAGT GLVQAGGSL GKQRE IRYVDSV RLSCAASGST WVA KG GS LG202D7 141 EVQLVESGG 423 GYWMS 705 WVRQAP 987 AINNLGG GSVQPGGSL GKGLEW DTYYAD RLSCAASGFT VS SVKG FR LG202D8 142 EVQLVESGG 424 GYWMS 706 WVRQAP 988 AINNVG GLVQPGGSL GKGLEW DEVYYA RLSCAASGFT VS DSVKG FR LG202E11 143 EVQLVESGG 425 GYWMS 707 WVRQAP 989 AINNVG GLVQPGGSL GKGLEW DEVYYA RLSCAASGFT VS DSVKG FR LG202E2 144 EVQLVESGG 426 GYWMT 708 WVRQAP 990 SIANDGK GLVQPGGSL GKGLEW STYYVD RLSCAASGFT VS SVKG FG LG202E5 145 EVQLVESGG 427 GYWMT 709 WVRQAP 991 SINNIGE DLVQPGGSLR GKGLEW ETYYVD LSCAASGFTFR VS SVKG LG202E6 146 EVQLVESGG 428 SYAMG 710 WFRQAP 992 AISWSG GLVQAGGSL GKEREF RTTYYA RLSCAASGRT VA DFVKG FS LG202E7 147 EVQLVESGG 429 GYWMS 711 WVRQAP 993 AINNVG GLVQPGGSL GKGLEW GETYYA RLSCAASGFT VS DSVKG FR LG202F10 148 EVQLVESGG 430 GYWMS 712 WVRQAP 994 AINNLGG GSVQPGGSL GKGLEW DTYYAD RLSCAASGFT VS SVKG FR LG202F12 149 EVQLVESGG 431 GYWMS 713 WVRQAP 995 AINNVG GLVQPGGSL GKGLEW GDTYYA RLSCAASGFT VS DSVKG FS LG202F3 150 EVQLVESGG 432 GYWMT 714 WVRQAP 996 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG LG202F4 151 EVQLVESGG 433 GYWMT 715 WVRQAP 997 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG LG202F8 152 EVQLVESGG 434 SYDMG 716 WFRQAP 998 AISRSGD GLVQPGGSL GEERAF VRYVDP RLSCAASGLIFS VG VKG LG202G11 153 EVQLVESGG 435 GYWMS 717 WVRQAP 999 AINNVG GLVQPGGSL GKGLEW GETYYA RLSCAASGFT VS DSVKG FR LG202G3 154 EVQLMESGG 436 GYTMG 718 WFRQAP 1000 GISWSG GLVQAGGSL GKGRE DSTYYA RLSCAASGRT WVA DSVKG FS LG202G8 155 EVQLVESGG 437 GYWMS 719 WVRQAP 1001 AINNLGG GSVQPGGSL GKGLEW DTYYAD RLSCAASGFT VS SVKG FR LG202H2 156 EVQLVESGG 438 GYWMT 720 WVRQAP 1002 SINNIGE DLVQPGGSLR GKGLEW EVYYVD LSCAASGFTFS VS SVKG LG202H8 157 EVQLVESGG 439 GYWMS 721 WVRQAP 1003 AINNVG GSVQPGGSL GKGLEW GDTYYA RLSCAASGFT VS DSVKG FR LG191B9 158 EVQLVESGG 440 SSFMA 722 WFRQVL 1004 GISPGG GLVQAGGSL GSDREF RFTYYA RLSCAASGRT VG DSRKG FS LG191D3 159

EVQLVESGG 441 RYGMG 723 WFRQAP 1005 AVSRLS GLVQAGGSL GKEREF GPRTVY RLSCEASGRT VA ADSVKG YS LG192A8 160 EVQLVESGG 442 AYTMG 724 WFRRAP 1006 AMNWN GLVQAGGSL GKERDF GGNTIYA RLSCAASERT VA DSAKG VI LG192B1 161 EVQLVESGG 443 NYAIG 725 WFRQAP 1007 CINSGG GLVQPGGSL GKEREG SITDYLD RLSCAASGLT VS SVKG FR LG192C10 162 EVQLVESGG 444 NYMVG 726 WFRQAP 1008 AISDTAY GLVQAGGSL GGERMF YADSVKG RLSCAASEGY VA FR LG192C4 163 EVQLVESGG 445 SYAMVG 727 WFRQAP 1009 AVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG FS LG192C6 164 EVQLVESGG 446 YQAMG 728 WFRQAP 1010 VVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG ER LG192D3 165 EVQLVESGG 447 RYTMG 729 WFRQAP 1011 AISWSD GLVQAGGSL GKEREF DSTYYR RLSCATSGRT VA DSVKG RS LG191E4 166 EVQLVESGG 448 ADTMG 730 WFRQAP 1012 TIPWSG GLVQAGGSL GKEREF GIAYYSD RLSCAASGPT VA SVKG FS LG192F2 167 EVQLVESGG 449 PIAMG 731 WFRQAP 1013 VVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG FS LG192H1 168 EVQLVESGG 450 TNHMG 732 WYRRAP 1014 TINRGDS GLVQAGGSL GKQREL PYYADS RLSCAASGIIFS VG VKG LG192H2 169 EVQLVESGG 451 NYAMG 733 WFRQAP 1015 VVTRWS GLVQAGGSL GKEREF GGRTVY RLSCEASGRT VA ADSVKG FS LG20610B 170 EVQLVESGG 452 SYAMG 734 WFRQTP 1016 SISWIGK GLVQAGGSL GKEREF FTYYAD RLSCTASGRT VA SVKG FS LG20610C 171 EVQLVESGG 453 SSFMA 735 WFRQAL 1017 GISPGG GLVQTGGSLR GSDREF RITYYAD LSCAASGRTFS VG SRKG LG20610D 172 EVQLVESGG 454 SSFMA 736 WFRQAL 1018 GISPGG GLVQTGGSLR GSDREF RITYYAD LSCAASGRTFS VG SRKG LG20610E 173 EVQLVESGG 455 NGAMG 737 WFRQAP 1019 SISWSG GLVQAGGSL GKEREF GSTYYA RLSCAASVRT VA DSVKG FS LG20610F 174 EVQLVESGG 456 AYTMG 738 WFRRAP 1020 AMNWN GLVQAGGSL GKERDF GGNTIYA RLSCAASERT VA DSAKG VI LG20611D 175 EVQLVESGG 457 AYTMG 739 WFRRAP 1021 AMNWN GLVQAGGSL GKERDF GGNTIYA RLSCAASERT VA DSAKG VI LG20611H 176 EVQLVESGG 458 NYMVG 740 WFRQAP 1022 AISDTAY GLVQAGGSL GGERMF YADSVKG RLSCAASEGY VA FR LG20612F 177 EVQLVESGG 459 NYMVG 741 WFRQAP 1023 AISDTAY GLVQAGGSL GGERMF YADSVKG RLSCAASEGY VA FR LG2062A 178 EVQLVESGG 460 NYAMG 742 WFRQAP 1024 VVTRWS GLVQAGGSL GKEREF GGRTVY RLSCEASGRT VA ADSVKG FS LG2062C 179 EVQLVESGGE 461 VYTMG 743 WFRQAP 1025 AISGGSI LVQAGDSLTV MKEREF RYADSV SCAASGRTFS VA KG LG2062E 180 EVQLVESGG 462 SYWMY 744 WVRQAP 1026 AISTGG GLVQPGGSL GKGLEW GDTHYA RLSCAASGFT VS DSVKG FS LG2062F 181 EVQLVESGG 463 RYGMG 745 WFRQAP 1027 AVSRLS GLVQAGGSL GKEREF GPRTVY RLSCEASGRT VA ADSVKG YS LG2062G 182 EVQLVESGG 464 INAMG 746 WFRQAP 1028 VVTRWS GLVQPGGSL GKEREF GARTVY RLSCAASGSS VA ADSVKG FS LG2062H 183 EVQLVESGG 465 INAMG 747 WFRQAP 1029 VVTRWS GLVQPGGSL GKEREF GARTVY RLSCAASGSS VA ADSVKG FS LG2063A 184 EMQLVESGG 466 SYAMG 748 WFRQAP 1030 AVSRWS GLVQAGGSL GKEREF GPRTVY RLSCEASGRS VA ADSVKG FS LG2063B 185 EVQLVESGG 467 DYAIG 749 WFRQAP 1031 CIRCSD GLVQAGGSL GKEREG GSTYYA RLSCAASGFT VS DSVKG FD LG2063C 186 EVQLVESGG 468 SYAMG 750 WFRQAP 1032

AVSGWI GLVQAGGSL GKEREF GPRPVY RLSCEASGGS VA ADSVKG FS LG2063D 187 EVQLVESGG 469 SVAMG 751 WFRQAP 1033 ALSRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRS VA ADSVKG FS LG2063E 188 EVQLVESGG 470 SYAMG 752 WFRQAP 1034 VVTRWS GLVQAGGSL GKEREF GGRTVY RLSCEASGRT VA ABSVKG FS LG2063F 189 EVQLVESGG 471 RYGMG 753 WFRQAP 1035 AVSRLS GLVQAGGSL GKEREF GPRTVY RLSCEASGRT VA ADSVKG FS LG2064D 190 EVQLVESGG 472 PIAMG 754 WFRQAP 1036 VVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG FS LG2064G 191 EVQLVESGG 473 SVAMG 755 WFRQAP 1037 AVSRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG FS LG2065A 192 EVQLVESGG 474 SYAMVG 756 WFRQAP 1038 AVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASRRT VA ADSVKG FS LG2065E 193 EVQLVESGG 475 YQAMG 757 WFRQAP 1039 VVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG ER LG2066A 194 EVQLVESGG 476 SYAMVG 758 WFRQAP 1040 AVTRWS GLVQAGGSL GKEREF GARTVY RLSCEASGRT VA ADSVKG FS LG2066D 195 EVQLVESGG 477 ITGMG 759 WYRQAP 1041 QISHYDS GLVQPGGSL GNQREL TMYADS GLSCAASGNI VA VKG FS LG2067B 196 EVQLVESGG 478 LNAMG 760 WYRQTP 1042 RITSLGP GSVQPGGSA GKEREL IMYAEFV RLSCAVLGSI VA KG GS LG2067C 197 EVQLVESGG 479 DYAMG 761 WFRQAP 1043 GISWAG GLAQPGGSL GKEREF HNTVYA RLSCAASGFT VA GSMKG FN LG2067E 198 EVQLVESGG 480 AYTMG 762 WFRRAP 1044 AMNWN GLVQAGGSL GKERDF GGNTIYA RLSCAASERT VA DSAKG VI LG2067G 199 EVQLVESGG 481 PYPMG 763 WFRQAP 1045 AISGGG GLVQAGGSL GKEREF FPTFYA RLSCAASERT VG DSVKG FI LG2067H 200 EVQLVESGG 482 HYAMS 764 WVRQAP 1046 DITHGGL GLVQPGGSL GKGLEW STTYRD RLSCAASGFV VS SVKG FS LG20711A 201 EVQLVESGG 483 VNAMG 765 WHRQA 1047 QLTVFG GLVQPGGSLT PGKERE SLNYAD LSCAASGSVFS LVA SVKG LG20711B 202 EVQLVESGG 484 YYAIG 766 WFRQAP 1048 CISSSDS GLVQPGGSL GKEREG STYYAD RLSCAASGFT VS SVKG FD LG20711D 203 EVQLVESGG 485 SYAMG 767 WFRQTP 1049 SISWIGK GLVQAGGSL GKEREF FTYYAD RLSCTASGRT VA SVKG LS LG20711E 204 EVQLVESGG 486 SYAMG 768 WFRQTP 1050 SISWIGK GLVQAGGSL GKEREF FTYYAD RLSCTAGGDT VA SVKG FS LG20711F 205 EVQLVESGG 487 HYAMS 769 WVRQAP 1051 DITNGGL GLVQPGGSL GKGLEW STTYRD RLSCAASGFV VS SVKG FS LG20711G 206 EVQLVESGG 488 TWVMG 770 WFRQAP 1052 RIDWGG GLVQAGGSL GKEREF SSTSYA RLSCAAPGRT VA DIVKG FS LG20711H 207 EVQLVESGG 489 HYAMS 771 WVRQAP 1053 BITHGGL GLVQPGGSL GKGLEW TTTYRD RLSCAASGFV VS SVKG FS LG2071A 208 EVQMVESGG 490 LNTMG 772 WYRQAP 1054 TLSIFGV GLVQPGGSL GKQREL SDYADS RLSCVASGSI VA VKG AR LG2071B 209 EVQLVESGG 491 IFTMG 773 WYRQAP 1055 DITTGGS GLVQAGGSL GKQREL TNYADS RLSCAASGSL VA VKG FR LG2071C 210 EVQLVESGG 492 ADTMG 774 WFRQAP 1056 TIPWSG GLVQAGGSL GKEREF GIAYYSD RLSCAASGPT VA SVKG FS LG207D1 211 EVQLVESGG 493 SYGMG 775 WFRQAP 1057 AVSRLS GLVQAGGSL GKEREF GPRTVY RLSCEASGRT VA ADSVKG FS LG2071E 212 EVQLVESGG 494 TMG 776 WFRQAP 1058 TIPWSG GLVQAGGSL GKEREF GIPYYSD RLSCAASGPT VA SVKG FS LG2071F 213 EVQLVESGG 495 ADTMG 777 WFRQAP 1059 TIPWSG GLVQAGGSL GKEREF GIAYYSD

RLSCAASGPT VA SVKG FS LG2074A 214 EVQLVESGG 496 INAMG 778 WYRQAP 1060 HITFGGS GLVQPGGSL GKQRDL SYYADS RLSCAASGSI VA VKG FS LG2074B 215 EVQLVESGG 497 INAMG 779 WYRQAP 1061 HITFGGN GLVQPGGSL GKQRDL SYYADS RLSCAASGSI VA VKG FS LG2074D 216 EVQLVESGG 498 NLAMG 780 WFRQAR 1062 TISWSH GLVQAGGSL GKEREF PNTYYT RLSCVASGRT VA DSVKG FN LG2074H 217 EVQLVESGG 499 INAMA 781 WHRQA 1063 HISSGG GLVQAGGSL PGKERE STYYGD RLSCAASGSS LVA FVKG GV LG2075A 218 EVQLVESGG 500 IFTMG 782 WYRQAP 1064 DITTGGS GLVQAGGSL GKQREL TNYADS RLSCAASGSL VA VKG FR LG2075B 219 EVQLVESGG 501 INAMG 783 WYRQAP 1065 HISSGG GLVQPGGSL GKQREL STYYGD RLSCAASGSI VA SVKG FS LG2075C 220 EVQLVESGG 502 ADTMG 784 WFRQAP 1066 TIPWSG GLVQAGGSL GKEREF GIAYYSD RLSCAASGPT VA SVKG FS LG2075D 221 EVQLVESGG 503 NYAMG 785 WFRQAP 1067 VVTRWS GLVQAGGSL GKEREF GGRTVY RLSCEASGRT VA ADSVKG FS LG2075E 222 EVQLVESGG 504 INAMG 786 WYRQAL 1068 TIGNGG GSVQPGGSL GKQREL NTNYAD RLSCAASGSI VA SAKG VG LG2076A 223 EVQLVESGG 505 INAMG 787 WYRQAP 1069 HITSGGS GLVQPGGSL GKQREL TNYADS RLSCAASGSI VA VKG FS LG2076B 224 EVQLVESGG 506 RYGMG 788 WFRQAP 1070 AVSRLS GLVQAGGSL GKEREF GPRTVY RLSCEASGRT VA ADSVKG YS LG2076C 225 EVQLVESGG 507 IDAMG 789 WYRQAP 1071 AITSGGN GLVQPGGSLK GKQREL TNYADS LSCAASGGFFS VA VKG LG2076D 226 EVQLVESGG 508 LNAMG 790 WYRQVP 1072 SISSGGS GLVQPGGSL GKEREL TTYADS RLSCAASGSI VV VKGRG FG LG2076E 227 EVQLVESGG 509 INAMG 791 WYRQAP 1073 TIGNGG GLVQPGGSL GKQREL NTNYAD RLSCAASGSI VA SAKG VG LG2076F 228 EVQLVESGG 510 TNSVD 792 WYRQIP 1074 TITPSPY GLVQAGGSLK GKQRD TYYADS LSCAVSARIFS WVA VKG LG2079A 229 EVQLVESGG 511 SSFMA 793 WFRQVL 1075 GISPGG GLVQAGGSL GSDREF RFTYYA RLSCAASGRT VG DSRKG FS LG2079B 230 EVQLVESGG 512 SSFMA 794 WFRQVL 1076 GISPGG GLVQAGGSL GSDREF RFTYYA RLSCAASGRT VG DSRKG FS LG2079C 231 EVQLVESGG 513 TITMA 795 WFRQAP 1077 VISWGGI GLVQAGGSL GKEREF TTSYAD RLSCAASGRT VA SVKG GG LG2079D 232 EVQLVESGAG 514 SYAMG 796 WFRQTP 1078 SISWIGE LVQAGGSLRL GKEREF FIYYADS SCTASGRTFS VA VKG LG2079E 233 EVQLVKSGG 515 SYTMG 797 WFRQAP 1079 SISRDG GLVQAGGSLK GKEREF GTPYYA LSCAASGRAFS VA YSVKG LG2079F 234 EVQLVESGG 516 HYAMS 798 WVRQAP 1080 DITNGGL GLVQPGGSL GKGLEW STTYRD RLSCAASGFV VS SVKG FS LG2079G 235 EVQLVESGG 517 AYTMG 799 WFRRAP 1081 AMNWN GLVQAGGSL GKERDF GGNTIYA RLSCAASERT VA DSAKG VI LG2079H 236 EVQLVESGG 518 SSFMA 800 WFRQAL 1082 GISPGS GLVQAGGSL GSDREF RFTYYA RLSCAASGRT LG DSGKG FS LG213B7 237 EVQLVESGG 519 NSAAG 801 WYRATS 1083 RIRSSGS GLVQAGGSL ETQREL TNYADS RLSCTVSGDT VA VKG FD LG213D6 238 EVQLVESGG 520 DSDMS 802 WVRQAP 1084 GINSGG GLVQPGGSL GEGPE GSTVYA RLSCAASGFT WVA DSVKG FG LG213D7 239 EVQLVESGG 521 NSAAG 803 WYRATS 1085 RIRSSGS GLVQAGGSL ETQREL TNYADS RLSCTVSGDT VA VKG FD LG213E6 240 EVQLVESGG 522 RYGVG 804 WFRQAP 1086 SVDWSG GLVQAGASLR GKEREL SRTYYA LSCAASGSTLS VA DSVKG LG213H7 241 EVQLVESGG 523 SYRMG 805 WFRQAP 1087 TISWNG GLVQAGGSL GKEREFIS RSTYYA

RLSCAASGRT DSVKG LS LG214A8 242 EVQLVKSGG 524 PYVMA 806 WFRQAP 1088
RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG214C10 243
EVQLVESGG 525 SYDMS 807 WVRQAP 1089 GINSGG GLVQPGGSL GKGPE GSTGYA
RLSCAASGFI WVS DSVKG FG LG214D10 244 EVQLVESGG 526 SRVVAG 808 WFRQAP 1090
AISWDG GLVQAGGSL GKEREF VQTYYT RLSCAASGG VA DSVEG RTF LG214E8 245
EVQLVESGG 527 PYVMA 809 WFRQAP 1091 RIRWSG GSVQAGGSL GNEREF GDAYYD
RLSCAASGGT VA DSVKG FN LG214F8 246 EVQLVESGG 528 INAMG 810 WYRQAP 1092
AFRTGG DLVQAGGSLR GKLREL STDYAD LSCVASGSTYS VA SVKG LG214H10 247
EVQLVESGG 529 PYVMA 811 WFRQAP 1093 RIRWSG GSVQAGGSL GNEREF GDAYYD
RLSCAASGGT VA DSVKG FN RSVPMP5C1 248 EVQLVESGG 530 SYIMG 812 WFRQAP 1094
AISGTGT GLAQAGGSL GKERMF IKYYGDL RLSCAASGRT VA VKG LT RSVPMP8A1 249
EVQLVESGG 531 DYIMG 813 WFRQAP 1095 AISGTGT GLVQPGGSL GKERMF IKYYGDL
RVSCAASGFT IA VRG FN RSVPMP8G1 250 EVQLVESGG 532 SYIMG 814 WFRQAP 1096
AISGTGT GLVQPGGSL GKERMF IKYYGDL RVSCAASGFT IA VGG FN RSVPMP25B3 251
EVQLVESGG 533 SYIMG 815 WFRQAP 1097 AISGTGT GLVQPGGSL GKERMF IKYYGDL
RLSCAASGFT IA VGG FN RSVPMP8C8 252 EVQLVESGG 534 TYGMG 816 WFRQAA 1098
AISRSGA GLVQAGGSL GKEREF NIYYGTS RLSCVASGGT AV TQG FS RSVPMP5A6 253
EVQLVESGG 535 RSRMF 817 WARQAP 1099 SILTAGD GLVQPGGSL GKGFEW TWYSDS
RLSCTAYGFIFD LS VKG RSVPMP8E11 254 EVQLVESGG 536 RSRMF 818 WARQAP 1100
SILTAGD GLVQPGGSL GKGFEW TWYSDS RLSCTAYGFIFD LS VKG RSVPMP8F11 255
EVQLVESGG 537 RSRMF 819 WARQAP 1101 SILTAGD GLVQPGGSL GKGFEW TWYSDS
RLSCTAYGFIFD LS VKG RSVPMP13F11 256 EVQLVESGG 538 QARMF 820 WARQAP 1102
SILTAGD DLVQPGGSLR GKGFEW TWYSDS LSCTAYGFIFD LS VKG RSVPMP15B8 257
EVQLVESGG 539 QSRMF 821 WARQAP 1103 SILTAGD GLVQPGGSL GKGFEW TWYSDS
RLSCTAYGFIFD LS VKG RSVPMP15G11 258 EVQLVESGG 540 QSRMF 822 WARQAP 1104
SILTAGD GLVQPGGSL GKGFEW TWHSDS RLSCTAYGFIFD LS VKG RSVPMP17C10 259
EVQMVESGG 541 QARMF 823 WARQAP 1105 SILTAGD DLVQPGGSLR GKGFEW TWYSDS
LSCTAYGFIFD LS VKG RSVPMP21E7 260 EVQLVESGG 542 QARMF 824 WARQAP 1106
SILTAGD DLVQPGGSLR GKGFEW TWYSDS LSCTAYGFIFD LS VKG RSVPMP21F8 261
EVQLVESGG 543 QSRMF 825 WARQAP 1107 SILTAGD GLVQPGGSL GKGFEW TWYSDS
RLSCTAYGFV LS VKG FD RSVPMP5A2 262 EVQLVESGG 544 YYVIG 826 WFRQAP 1108
CISSDGS GLVQPGGSL GKEREG TTYADS RLSCEASGFT LS VKG WD RSVPMP5B2 263
EVQLVESGG 545 YYALG 827 WFRQAP 1109 CISSVDH GLVQPGGSL GKEREG STTYAD
RLSCAASGLT VS SVKG LD RSVPMP5C3 264 EVQPVESGG 546 YYVIG 828 WFRQAP 1110
CISSSDG GLVQPGGSL GKEREG STTYAD RLSCEASGFT LS SVKG WD RSVPMP5D2 265
EVQLVESGG 547 YYVIG 829 WFRQAP 1111 CISSSDG GLVQPGGSL GKEREG STTYAD
RLSCEASGFT LS SVKG WD RSVPMP5E2 266 EVQLVESGG 548 YYAIG 830 WFRQAP 1112
CISSSDH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VS SVKG LD RSVPMP5F3 267
EVQLVESGG 549 YYALG 831 WFRQAP 1113 CISSSDH GLVQPGGSL GKEREG STTYTD
RLSCAASGLT VS SVKG LD RSVPMP5G3 268 EVQLVESGG 550 YYVIG 832 WFRQAP 1114

CISSDGS GLVQPGGSL GKEREG TTYADS RLSCEASGFT LS VKG WD RSVPMP5H2 269
EVQLVESGG 551 YYAIG 833 WFRQAP 1115 CISSVDH GLVQPGGSL GKEREG STTYAD
RLSCAASGLT VS SVKG LD RSVPMP5H3 270 EVQLVESGG 552 YYAIG 834 WFRQAP 1116
CISSSDG GLVQPGGSL GKEREG STTYADL RLSCAASGFT VS VKG SD RSVPMP8C1 271
EVQLVESGG 553 YYVIG 835 WFRQAP 1117 CISSDGT GLVQPGGSL GKEREG TTYPDS
RLSCAASGFT VS VKG WD RSVPMP8F2 272 EVQLVESGG 554 YYAIG 836 WFRQAP 1118
CISSSDG GLVQPGGSL GKEREG STTYAD RLSCAASGFT VS SVKG WD RSVPMP8G4 273
EVQLEESGG 555 YYVIG 837 WFRQAP 1119 CISSDGL GLVQPGGSL GKEREG TTYADS
RLSCEASGFT LS VKG WD RSVPMP13A1 274 EVQLVESGG 556 YYALG 838 WFRQAP 1120
CISSADH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VS SVKG LD RSVPMP13A4 275
EVQLVESGG 557 YYALG 839 WFRQAP 1121 CISSADH GLVQPGGSL GKEREG STTYAD
RLSCAASGLT VS SVKG LD RSVPMP13B1 276 EVQLVESGG 558 YYVIG 840 WFRQAP 1122
CISSSDG GLVQPGGSL GKEREG STTYAD RLSCAASGFT VS FVKG WD RSVPMP13B2 277
EVQLVESGG 559 YYVIG 841 WFRQAP 1123 CISSDGS GLVQPGGSV GKEREG TTYADS
RLSCAASGFT LS VKG WD RSVPMP13C1 278 EVQLVESGG 560 YYVIG 842 WFRQAP 1124
CISSDGS GLVQPGGSL GKEREG TTYADS RLSCEASGFT LS VKG WD RSVPMP13C3 279
EVQLVESGG 561 YYALG 843 WFRQAP 1125 CISSVDH GLVQPGGSL GKEREG STTYAD
RLSCAASGLT VS SVKG LD RSVPMP13D6 280 EVQLVESGG 562 YYALG 844 WFRQAP 1126
CISSSDH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VS SVKG LD RSVPMP13E2 281
EVQLVESGG 563 YYAIG 845 WFRQAP 1127 CISSTDH GLVQPGGSL GKEREG STTYAD
RLSCAASGLT VS SVKG LD RSVPMP13E3 282 EVQLVESGG 564 YYALG 846 WFRQAP 1128
CISSSDH GLVQPGGSL GKEREG TTTYAD RLSCAASGLT VS SVKG LD RSVPMP15A5 283
EVQLVESGG 565 YYAIG 847 WFRQAP 1129 CISSSDG GLVQPGGSL GKEREG STTYAD
RLSCAASGFT VS SVKG WD RSVPMP15A6 284 EVQLVESGG 566 YYALG 848 WFRQAP 1130
CIDSSDH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VA SVKG LD RSVPMP15B2 285
EVQLVESGG 567 YYVIG 849 WFRQAP 1131 CISSDGS GLVQPGGSL GKEREG TTYADS
RLSCEASGFT LS VKG WD RSVPMP15B3 286 EVQLVESGG 568 YYALG 850 WFRQAP 1132
CISSSDH GLVQPGGSL GKEREG STTYTD RLSCAASGLT VS SVKG LD RSVPMP15E5 287
EVQLVESGG 569 YYVIG 851 WFRQAP 1133 CISSSDG GLVQPGGSL GKEREG STTYAD
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CISSSDG GLVQPGGSL GKEREG STTYAD RLSCAASGFT VS FVKG WD RSVPMP17D4 289
EVQLVESGG 571 YYALG 853 WFRQAP 1135 CISSVDH GLVQPGGSL GKEREG STTYAD
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CISSVDH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VS PVKG LD RSVPMP19B2 291
EVQLVESGG 573 YYAIG 855 WFRQAP 1137 CISSSDH GLVQPGGSL GKEREG STTYAD
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CISSVDH GLVQPGGSL GKEREG STTYAD RLSCAASGLT VS SVKG LD RSVPMP25A9 293
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CISSSDH GLVQPGGSL GKEREG TTTYAD RLSCAASGLT VS SVKG LD RSVPMP13B5 299
EVQLVESGG 581 YYALG 863 WFRQAP 1145 CISSSDH GLVQPGGSL GKGREG TTTYAD
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CISSSDH GLVQPGGSL GKEREG TTTYAD RLSCAASGLT VS SVKG LD RSVPMP5A1 303
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EVQLVESGG 657 SYGMG 939 WFRQAP 1221 AITWSG GLVQAGASLR GKEREF GYTYYL LSCAASGRMFS VA DSVKG RSVPMP17E1 376 EVQLVESGG 658 RYDMG 940 WFRQAP 1222 GINWSG GLVQPGGSL GEERKF GRTYYA RLSCVASGLT VA DSVKG FS RSVPMP21A4 377 EVQLVESGG 659 RYDMG 941 WFRQAP 1223 GINWSG GLVQAGGSL GEERQF GRTYYA RLSCAASGLT VA DSVKG FS RSVPMP25A11 378 EVQLVESGG 660 RYDMG 942 WFRQAP 1224 GINWSG GLVQAGGSL GEERKF GRTYYA RLSCAASGLT VA DSVKG FS RSVPMP25C8 379 EVQLVESGG 661 RYDMG 943 WFRQAP 1225 GINWSG GLVQPGGSL GKEREF GRTYYA RLSCAASGLT VA DSVKG FS RSVNC23 380 EVQLVESGG 662 SIAMG 944 WFRQAP 1226 AISWSR GLVQPGGSL GKEREF GRTFYA RLSCAASGRT VA DSVKG FS RSVPMP20A11 381 EVQLVESGG 663 SYTMG 945 WFRQAP 1227 CVSRDG GLVQAGGSLK GKEREF GTTYYA LSCAASGRAFS VA YSVKG RSVPMP20A9 382 EVQLVESGG 664 SSFMA 946 WFRQVL 1228 GISPGG GLVQAGGSL GSDREF RFTYYA RLSCAASGRT VG DSRKG FS RSVPMP1F7 383 EVQLVESGG 665 NYAIG 947 WFRQVP 1229 CINSGG GLVQPGGSL GKEREG GRIDYA RLSCAASGFT VS DSVKG FR RSVPMP20D6 384 EVQLVESGG 666 DYAIG 948 WFRQAP 1230 CIRCND GLVQAGGSL GKEREG GSTYYA RLSCAASGFT VS DSVKG FD RSVPMP1F1 385 EVQLVESGG 667 SYTMG 949 WFRQAP 1231 TIPWSG GLVQAGGSL GKEREF GIPYYSD RLSCAASGPT VA SVKG FS RSVPMP3D3 386 EVQLVESGG 668 NLAMG 950 WFRQAR 1232 TISWSH GLVQAGGSL GKEREF PNTYYT RLSCVASGRT VA DSVKG FN RSVPMP3E6 387 EVQLVESGG 669 SYWMY 951 WVRQVP 1233 AISTGG GLVQPGGSL GKGLEW GDTHYQ RLSCEASGFT VS DSVKG FS RSVPMP1C8 388 EVQLVESGG 670 TYVMA 952 WFRQAP 1234 AINWSG GLVQAGDSLR GKEREC ENIYYAD LSCAASGLTFS VA SVKG RSVPMP1A2 389 EVQLVESGG 671 YYAMG 953 WFRQAP 1235 TISRSGE GLVQAGGSL GKEREF WIYYKD RLSCAASERT VA AMKG FS RSVPMP1C5 390 EVQLVESGG 672 YYAIG 954 WFRQAP 1236 CFPSRY GLVQPGGSL GKEREG SSDGST RLSCAASGFT VS YYADSV LD KG RSVPMP20G5 391 EVQLVESGG 673 FYDTAG 955 WYRQAP 1237 LITDISG GLVQPGGSLK GKQREL GYIKYAD LSCAGSGSIFR VA SVKG RSVPMP4D8 392 EVQLVESGG 674 SYGMG 956 WFRQAP 1238 AISWSD GLVQAGGSP GKEREF SSTYYA RLSCAASGGT VA DSVKG FS RSVPMP20B6 393 EVQLVESGG 675 INFMN 957 WYRQAP 1239 SITSGGY GLVQAGGSL GKQREL TNYADS RLSCASSGSI VA VKG YS RSVPMP1D11 394 EVQLVESGG 676 IATMA 958 WYRQAP 1240 SISSSGY GLVQPGGSL GKQREL RIYADSV RLSCAASGNI VA KG FS RSVPMP20A8 395 EVQLVESGG 677 GYEMG 959 WFRQAP 1241 AISQSG GLVQAGDSLR GRERAF GTTSYA LSCAASGLTFS VA VSVKG RSVPMP20E7 396 EVQLVESGG 678 GYEMG 960 WFRQAP 1242 AISQSG GLVQVGDSLR GKERAF GTTSYA LSCAASGLTFS VA VSVKG RSVPMP20G8 397 EVQLVESGG 679 GYEMG 961 WFRQAP 1243 AISQSG GLVQAGDSLR GKERAF GTTSYA LSCAASGLTFS VA VSVKG RSVPMP2D3 398 EVQLVESGG 680 GYEMG 962 WFRQAP 1244 AISQSG GLVQAGDSLR GKERAF GTTSYA LSCAASGLTFS VA VSVKG RSVPMP2G5 399 EVQLVESGG 681 GYEMG 963 WFRQAP 1245 AISQSG GLVQAGDSLR GKERAF GTTSYA LSCAASGLTFS VA VSVKG RSVPMP2A6 400 EVQLVESGG 682 TYAMG 964 WVRQAP 1246 CISNGGL GLVQPGGSL GKGLEW RTMYAD RLSCAASGFA VS SVKG FS RSVPMP3A2 401 EVQLVESGG 683 SNAMG 965 WFRQAP 1247 AVTRWS GLVQAGGSL GKEREF GARTVY

RLSCEASGRT VA ADSVKG FS RSVPMP4A8 402 EVQLVESGG 684 SYDMG 966 WFRQAP 1248 AVTRWS GLVQAGGSL GKEREF GARGVY RLSCEASGRT VA ADSVKG FS RSVPMP4F9 403 EVQLVESGG 685 NYAMG 967 WFRQAP 1249 VVSRWS GLVQAGGSL GKEREF GGRTLY RLSCEASGRT VA ADSVKG FS RSVPMP1A6 404 EVQLVESGG 686 SYAMG 968 WFRQAP 1250 AIWWSG GLVQAGGSL GKEREF GSTYYA RLSCAASGRT VA DSVKG FS RSVPMP3C2 405 EVQLVESGG 687 PYAMG 969 WFRQAP 1251 AISWSG GLVQAGGSL GKEREF GTTYYA RLSCAASGRT VA DSVKG FS RSVPMP4H9 406 EVQLVESGG 688 SYAMG 970 WFRQAP 1252 AISWSG GLVQAGGSL GKERDF GSTYYA RLSCTASGRT VA DSVKG FS RSVPMP4B10 407 KVQLVESGG 689 SYAMG 971 WFRQAP 1253 AISGWIG GLVQAGGSL GKEREF PRPVYA RLSCEASGGS VA DSVKG FS 203B1 2431 EVQLVESGG 2449 GYWMT 2467 WVRQAP 2485 SINNVGE DLVQPGGSLR GKGLEW ETYYVD LSCAASGFTFR VS SVKG 203B2 2432 EVQLVESGG 2450 GYWMT 2468 WVRQAP 2486 SINNIGE DLVQPGGSLR GKGLEW EAYYVD LSCAASGFTFR VS SVKG 203G1 2433 EVQLVESGG 2451 GYWMT 2469 WVRQAP 2487 SINNIGE DLVQPGGSLR GKGLEW ETYYVD LSCAASGFTFS VT SVKG 203H1 2434 EVQLVESGG 2452 IYSMG 2470 WFRQQ 2488 SIGRSG GVVQAGGSL PGKERE NSTNYA RLSCAASGLT FVA SSVKD FD 203E12 2435 EVQLVESGG 2453 GYWMS 2471 WVRQAP 2489 AINNVG GLVQPGGSL GKGLEW DEVYYA RLSCAASGFT VS DSVKG FR 203E1 2436 EVQLMESGG 2454 SYTMG 2472 WFRQAP 2490 AISTVGS GLVQAGGSL GKERDF TYYSDS RLSCVAPGRI VA VKG FS 203A12 2437 EVQLVESGG 2455 DYPIG 2473 WFRQAP 2491 AIYAIGG GLVQAGDSLT GKEREF DVYYAD LSCIDSGRTFS VA SVKG 203A9 2438 EVQLVESGG 2456 DYPIG 2474 WFRQAP 2492 AIYPTDD GLVQAGDSLR GKEREF NPTGPN LSCIDSGRTFS VA AYYADS VKG 203B12 2439 EVQLVESGG 2457 SYAMG 2475 WVRRAP 2493 SISSGGA GLVQPGGSL GEGLEW LPTYAD RLSCAASGFT VS SVKG FS 203D2 2440 EVQLVESGG 2458 STAMG 2476 WSRQAP 2494 SISSAGT GLVQAGGSL GKQRE IRYVDSV RLSCAASGST WVA KG GS 203D9 2441 EVQLVESGG 2459 SYAMA 2477 WFRQAP 2495 GITWNG GWVQAGDSL GKERDF GSTYYA RLSCAASGRT VT DSVKG LS 203G3 2442 EVQLVESGG 2460 GYWMT 2478 WVRQAP 2496 SINNIGD DLVQPGGSLR GKGLEW EPYYVD LSCAASGFTFR VS SVKG 203G9 2443 EVQLVESGG 2461 SYWMD 2479 WVRQTP 2497 GISPSG GLVQPGGSL GKGLEY GNTDYA RLSCTASGFT VS DSVKG FS 203G10 2444 EVQLVESGG 2462 SYAMA 2480 WFRQAP 2498 GITWNG GWVQAGDSL GKERDF GSTYYA RLSCAASGRT VT DSVKG LS 203H9 2445 EVQLVESGG 2463 SYWMD 2481 WVRQTP 2499 GISPSG GLVQPGGSL GKDLEY GNTDYA RLSCTGSGFT VS DSVKG FS 203H10 2446 EVQLVESGG 2464 DYPIG 2482 WFRQAP 2500 AIYAIGG GLVQAGDSLR GKEREF DVYYAD LSCIDSGRTFS VA SVKG 202E4 2447 EVQLVESGG 2465 EYAMG 2483 WYRQAP 2501 TINSLGG GLVQAGGSL GKQREF TSYADS RLSCAASVSA VA VKG FS 189E2 2448 KVQLVESGG 2466 INAMG 2484 WYRQAP 2502 HIASSGS GLVQPGGSL GKQREL TIYADSV RLSCAASGSI VA KG FS PRSVPMP20C3 2574 EVQLVESGG 2582 FNTMG 2590 WYRQAP 2598 DITSGGS GLVQAGGSL GKQREL TVYADS RLSCAASRSI VA VKG FS PRSVPMP20C5 2575 EVQLVESGG 2583 INAMG 2591 WHRQAL 2599 QSSSGG GLVQPGGSL GKQREL STYYAD RLSCAASGSI VA SAKG FS PRSVPMP20B2 2576 EVQLVESGG 2584 SYDMG 2592 WFRQAP 2600 AVTRWS GLVQAGGSL GKEREF GARGVY RLSCEASGRT VA ADSVKG FS

PRSVPMP20C1 2577 EVQLVESGG 2585 SFAMG 2593 WFRQAP 2601 AISWSG GLVQAGGSL GKEREF GSTYYA RLSCAASGRT VA DSVKG FS PRSVPMP1G8 2578 EVQLVESGG 2586 RFGMG 2594 WFRRAP 2602 AINLSGD GSVQAGGSL GKERDF TTYYVD RLSCAASGGS VA SVQG FN PRSVNMP1A4 2579 EVQLVESGG 2587 NYVLG 2595 WFRQAP 2603 AINWRG GLVQAGGSLS GKEREF DITIGPP ISCAASGGSLS VA NVEG PRSVPMP13E12 2580 EVQLVESGG 2588 RYIMG 2596 WFRQAP 2604 AISRSGD GLVQAGGSL GKEREF ITSFADF RLSCAASGRT VG VKG FS PRSVPMP5C6 2581 EVQLVESGG 2589 RYAMG 2597 WFRQAP 2605 AISSSGD GLVQAGASLR GKERES NIYYADS LSCAASGLAFS VA VKG LG203E7 2682 EVQLVESGG 2718 FYDMG 2754 WYRQAP 2790 NIASGG GLVQPGESLR GMQREL STNLAD LSCAFSGIVFE VA AVKG LG203G8 2683 EVQLVESGG 2719 FYDMG 2755 WYRQAP 2791 NIASRGS GLVQPGESLR GKQREL TDLADS LSCAFSGIVFE VA VKG LG211A10 2684 EVQLVESGG 2720 SSATG 2756 WYRAVS 2792 RIRSGG GLAQAGGSL ATEREL STDYAD RLSCAVSGEA VA SVKG VG LG211A8 2685 EVQLVESGG 2721 SYRLG 2757 WFRQAP 2793 TISWNG GLVQAGGSL GKEREFIS RSTYYA RLSCAASGRT DSVKG LS LG211B10 2686 EVQLVESGG 2722 INAMG 2758 WYRQAP 2794 AFRTGG DLVQAGGSLR GKLREL STDYAD LSCVASGSTYS VA SVKG LG211B8 2687 EVQLVESGG 2723 SYRLG 2759 WFRQAP 2795 TISWNG GLVQAGGSL GKEREFIS RSTYYA RLSCAASGRT DSVKG LS LG211C12 2688 EVQLVESGG 2724 NSAAG 2760 WYRATS 2796 RIRSSGS GLVQAGGSL ETQREL TNYADS RLSCTVSGDT VA VKG FD LG211C8 2689 EVQLVESGG 2725 PYVMA 2761 WFRQAP 2797 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG211D10 2690 EVQLVESGG 2726 SYYMG 2762 WFRQAP 2798 AFSWSS GLVQAGGSL GNEREF SKPYYA RLSCAASGRT VA DSVKG VS LG211D8 2691 EVQLVESGG 2727 RYYMG 2763 WFRQAP 2799 AFSWSG GLVQAGGSL GKEREV GMTYYA RLSCAASGRA VA DSVKG FS LG211E10 2692 EVQLVESGG 2728 SYYMG 2764 WFRQAP 2800 AFSWSG GLVQAGGSL GNEREF SKPYYA RLSCAASGRT VA DSVKG VS LG211E12 2693 EVQLVESGG 2729 SYRLS 2765 WFRQAP 2801 THSWDG GLVQAGGSL GKEREF RRTYYA RLSCAASGRT VA DSVKG LS LG211E8 2694 EVQLVESGG 2730 RYYMG 2766 WFRQAP 2802 AFSWSG GLVQAGGSL GKEREV GMTYYA RLSCAASGRA VA DSVKG FS LG211H8 2695 EVQLVESGG 2731 SYRLG 2767 WFRQAP 2803 TISWNG GLVQAGGSL GKEREFIS RSTYYA RLSCAASGRT DSVKG LS LG212A10 2696 EVQLVESGG 2732 NSAAG 2768 WYRATS 2804 RIRSSGS GLVQAGGSL ETQREL TNYADS RLSCTVSGDT VA VKG FD LG212A12 2697 EVQLVESGG 2733 NSAAG 2769 WYRATS 2805 RIRSSGS GLVQAGGSL ETQREL TNYADS RLSCAVSGDT VA VKG FD LG212A2 2698 EVQLVESGG 2734 TYFVG 2770 WFRQAP 2806 AISWSG GLVQAGGSL GKERDF DRTFYA RLSCAASGRT VA DSVKG FD LG212A8 2699 EVQLVESGG 2735 PYVMA 2771 WFRQAP 2807 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG212B12 2700 EVQLVESGG 2736 NYDMS 2772 WVRQAP 2808 GINTGG GLVQPGGSL GKGPE STLYAD RLSCAASGFT WVS SVKG FG LG212B2 2701 EMQLVESGG 2737 WYVMA 2773 WFRQAP 2809 WINRSG GLVQAGDSLR GKEREF ASTYYA LSCAASGDTFS VT DSVKG LG212C12 2702 EVQLVESGG 2738 SSDMS 2774 WVRQAP 2810 GINSGG GLVQPGGSL GKGPE GRTLYA RLSCAASGFT WVS DSVKG FG LG212D10 2703 EVQLVESGG 2739 PYVMA 2775 WFRQAP 2811 RIRWSG GSVQAGGSL GNEREF GDAYYD

RLSCAASGGT VA DSVKG FN LG212D12 2704 EVQLVESGG 2740 PYVMA 2776 WFRQAP 2812 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG212D2 2705 EVQLVESGG 2741 SSDMS 2777 WVRQAP 2813 GINSGG GLVQPGGSL GKGPE GITDYAN RLSCAASGFT WVS SVKG FG LG212E10 2706 EVQLVESGG 2742 INAMG 2778 WYRQAP 2814 AFRTGG DLVQAGGSLR GKLREL STDYAD LSCVASGSTYS VA SVKG LG212E12 2707 EVQLVESGG 2743 PYVMA 2779 WFRQAP 2815 RIRWSSI GLVQAGGSL GNEREF NTAYDD RLSCAASGGT VA SVKG FS LG212E6 2708 EVQLVESGG 2744 SRDMH 2780 WVRQAP 2816 SGINSG GLVQPGGSL GKGGPE ASNTHY RLSCEASGFT WV ADSVKG FG LG212F10 2709 EVQLVESGG 2745 PYVMA 2781 WFRQAP 2817 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG212F12 2710 EVQLVESGG 2746 SSATG 2782 WYRAVS 2818 RIRSGG GLAQAGGSL ATEREL STDYAD RLSCAVSGEA VA SVKG VG LG212F6 2711 EVQLVESGG 2747 SYDMS 2783 WVRQAP 2819 HINTGG GLVQPGGSL GKGSE GSTTYA RLSCAASGFT WVS DSVKG FG LG212F8 2712 EVQLVESGG 2748 INAMG 2784 WYRQAP 2820 AFRTGG DLVQAGGSLR GKLREL STDYAD LSCVASGSTYS VA SVKG LG212G10 2713 EVQLVESGG 2749 PYVMA 2785 WFRQAP 2821 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG212G2 2714 EVQLVESGG 2750 SHDMS 2786 WVRQAP 2822 GIKSGG GLVQPGGSL GKGSE GSTLYA RLSCAASGFT WVS DSVKG FG LG212H10 2715 EVQLVESGG 2751 PYVMA 2787 WFRQAP 2823 RIRWSG GSVQAGGSL GNEREF GDAYYD RLSCAASGGT VA DSVKG FN LG212H2 2716 EVQLVESGG 2752 TYFVG 2788 WFRQAP 2824 AISWSG GLVQAGGSL GKERDF DRTFYA RLSCAASGRT VA DSVKG FD LG212H8 2717 EVQLVESGG 2753 FIMG 2789 WYRQAP 2825 DITRGDE GLVQAGGSL GKQREL RNYLDA RLSCTSSGSI VA VKG FN IV121 3064 QVQLQESGG 3129 FNPMA 3194 WYRQAP 3259 SITSGGT GLVQPGGSL GQQREL TNYANS RLSCTASRTD VA VKG IS IV122 3065 QVQLQQSGG 3130 FNPMG 3195 WYRQAP 3260 VLTTGG GLVQPGGSL GKQREL TTNYAD RLSCAASRSD VA SVKG FA IV123 3066 QVQLQESGG 3131 FNPMG 3196 WYRQAP 3261 TITSGGT GLVQPGGSL GKQREL TNYADS RLSCAASRSG VA VKG FS IV126 3067 QVQLQESGG 3132 FNPMG 3197 WYRQAP 3262 TMTSGG GLVQPGGSL GKQREL TTGYAD RLSCAASRTD VA SVKG IS IV127 3068 QVQLQESGG 3133 FNPMG 3198 WYRQAP 3263 VITASLT GLVQPGGSL GKQREL TNYADS RLSCAASRSG VA VKG FV IV131 3069 QVQLQQSGG 3134 FNPMG 3199 WYRQAP 3264 SITSGGT GLVQAGGSL GKQREL TNYVDS RLSCAASGSG VA VKG FS IV132 3070 QVQLQESGG 3135 FNPMG 3200 WYRQA 3265 VLTTGG GLVQPGGSL RGKQRE TTKYAD RLSCAASVSG EVA SVKD FI IV133 3071 QVQLQQSGG 3136 FNPMG 3201 WYRQAP 3266 TMTSGG GLVQPGGSL GKQREL TTNYAD RLSCAASSSG VA SVKG FS IV134 3072 QVQLQESGG 3137 FNPMG 3202 WYRQAP 3267 SITSGGT GLVQAGGSL GKQREL TNYVDS RLSCAASGSG VA VKG FS IV135 3073 QVQLQQSGG 3138 FNPMG 3203 WYRQAP 3268 TITNGGT GLVQPGGSL GKQREL TNYADS RLSCAASRGD VA VKG IS IV136 3074 QVQLQESGG 3139 FNPMG 3204 WYRQAP 3269 TITSGGT GLVQPGGSL GKQREL TNYADS RLSCAASRSG VA VKG FS IV140 3075 QVQLQESGG 3140 FNPMG 3205 WYRQAP 3270 VLTTGG GLVQPGGSL GKQREL TTNYAD RLSCAASRSD VA SVKG FA IV144 3076 QVQLQQSGG 3141 FNPMG 3206 WHRQA 3271 SITSGGS GLVQAGGSL PGKQRE ISYVDSV RLSCAASGNIIS LVA KG IV156 3077

QVQLQQSGG 3142 FNPMG 3207 WYRQAP 3272 TITSGGT GLVQPGGSL GKQREL TNYADS RLSCAASRSG VA VKG FS IV157 3078 QVQLQQSGG 3143 FNPMG 3208 WYRQAP 3273 TISNGGT GLVQPGGSL GKQREL TNYADS RLSCAASRSD VA VKG IS IV160 3079 QVQLQESGG 3144 FNPMG 3209 WYRQAP 3274 TISNGGT GLVQPGGSL GKQREL TNYADS RLSCAASRSD VA VKG IS IV124 3080 QVQLQESGG 3145 INRMG 3210 WYRQAP 3275 AITYGGS GLVQPGGSL GKQREL TNYADS RLSCAASGSI VA VKG FS IV125 3081 QVQLQQSGG 3146 INTMG 3211 WYRQAP 3276 VISSGSG GLVQAGGSL GKQREL GSTNYA RLSCAASGSA VA DSVKG FS IV145 3082 QVQLQQSGG 3147 INAMG 3212 WYRQAP 3277 AISSGGS GLVQPGGSL GKQREL TNYADS RLSCAASGST VA VKG FS IV146 3083 QVQLQQSGG 3148 INAMG 3213 WYRQAP 3278 AISSGGS GLVQAGGSL GKQREL ANYADS RLSCAASGSS VA VKG FS IV147 3084 QVQLQESGG 3149 INAMG 3214 WYRQAP 3279 AISSGGS GLVQAGGSL GKQREL TNYADS RLSCAASGST VA VKG FS IV151 3085 QVQLQESGG 3150 SLTMA 3215 WFRQAP 3280 VVNWDG GLVQAGDSLR GKDRDF DRTNYA LSCAASGRTFN VS DSVKG IV153 3086 QVQLQESGG 3151 FYTLG 3216 WFRQAP 3281 ATSNIGG GLVQAGGSL GKEREF YIYYGDS RLSCAFSGDT VA VKG FS IV154 3087 QVQLQESGG 3152 SAAMG 3217 WFRQAP 3282 AISYTGD GLVQAGGSL GKEREF VTRYAD RLSCAASGRP VS SVKG FS IV155 3088 QVQLQESGG 3153 RYAMG 3218 WFRQAP 3283 TKTSGG GLVQAGGSL GKEREF VTYYGA RLSCAASGRS VA SVKG LS IV1 3089 QVQLQESGG 3154 GYALA 3219 WFRQAP 3284 AVTWTS GLVETGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV2 3090 QVQLQESGG 3155 GYAMA 3220 WFRQAP 3285 SVTWNG GLVQTGGSLR RKGREF GATDYA LSCAASGRTFG VA GSVKD IV3 3091 QVQLQESGG 3156 GYAMA 3221 WFRQVP 3286 AVTWSS GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA RSVKD IV4 3092 QVQLQESGG 3157 GYAMA 3222 WFRQAP 3287 AVTWSS GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV6 3093 QVQLQESGG 3158 GYAMA 3223 WFRQAP 3288 AVTWSA GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV7 3094 QVQLQQSGG 3159 GYAMA 3224 WFRQAP 3289 AVTWSA GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV9 3095 QVQLQESGG 3160 GYAMA 3225 WFRQAP 3290 AVTWSA GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV10 3096 QVQLQESGG 3161 GYAMA 3226 WFRQAP 3291 AVTWSA GLVQAGGSL GKGREF GTTNYA RLSCATSGRP VA GSVKD FG IV11 3097 QVQLQESGG 3162 GYAMA 3227 WFRQAP 3292 AVTWSS GLVQAGGSL GKGREF GTTNYA RLSCAASGRT VA GSVKD FG IV12 3098 QVQLQQSGG 3163 GYAMA 3228 WFREAP 3293 AVTWSS GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV16 3099 QVQLQESGG 3164 GYAMA 3229 WFRQAP 3294 AVTWSS GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV24 3100 QVQLQESGG 3165 GYAMA 3230 WFRQAP 3295 AITWSA GLVQTGGSLR GKGREF GTTNYA LSCAASGRTFG VA DSMKD IV26 3101 QVQLQESGG 3166 GYAMA 3231 WFRQAP 3296 AVTWSS GLVRTGDSLR GKGREF GTTNYA LSCAASGRTFN VA GSVKD IV30 3102 QVQLQESGG 3167 GYAMA 3232 WFRQAP 3297 AVTWTS GLVETGGSLR GKGREF GTTNYA LSCAASGRTFG VA GSVKD IV34 3103 QVQLQESGG 3168 GYAMA 3233 WFRQAP 3298 SVIWNG GLVQTGGSLR GKGREF GTTNYL LSCAASGGTFG VA DSVKD IV14 3104 QVQLQESGG 3169 NYAMG 3234 WFRQAP 3299 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG

LN IV15 3105 QVQLQQSGG 3170 NYAMG 3235 WFRQAP 3300 AISAGG GLVQAGGSL GAEREF DSTQYT RLSCAASGGT VG ESVQG LN IV17 3106 QVQLQESGG 3171 NYAMG 3236 WFRQAP 3301 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG LN IV18 3107 QVQLQQSGG 3172 NYAMG 3237 WFRQAP 3302 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG LN IV29 3108 QVQLQESGG 3173 NYAMG 3238 WFRQAP 3303 AISANGE GLVQAGGSL GAEREF DTQYTE RLSCVASGRT VG SVQG LD IV31 3109 QVQLQQSGG 3174 NYAMG 3239 WFRQAP 3304 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG LN IV33 3110 QVQLQQSGG 3175 NYAMG 3240 WFRQAP 3305 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG LN IV35 3111 QVQLQESGG 3176 NYAMG 3241 WFRQAP 3306 AISASGD GLVQAGGSL GAEREF STDYTE RLSCAASGRT VG SVQG LN IV36 3112 QVQLQESGG 3177 NYAMG 3242 WFRQAP 3307 AISASGD GLVQAGGSL GAEREF STQYTE RLSCAASGRT VG SVQG LN IV40 3113 QVQLQESGG 3178 NYAMG 3243 WFRQG 3308 AISASGD GLVQAGGSL PGAERE STQYTE RLSCAASGHT FVG SVQG LN IV42 3114 QVQLQQSGG 3179 NYAMG 3244 WFRQAP 3309 AISASGD GLVQAGESLR GAEREF STQYTE LSCAASGRTLN VG SVQG IV8 3115 QVQLQESGG 3180 TYAMG 3245 WFRQAP 3310 GITRSGT GLVQAGGFLR GKEREF ATDYAD LSCAASGRSFN VA SVKG IV21 3116 QVQLQQSGG 3181 TYAMG 3246 WFRQAP 3311 GITRSGT GLVQAGGFLR GKEREF ATDYIDS LSCAASGRSFN VA VKG IV23 3117 QVQLQESGG 3182 TYAMG 3247 WFRQAP 3312 GITRSGT GLVQAGGFLR GKEREF ATDYIDS LSCAASGRSFN VA VKG IV45 3118 QVQLQQSGG 3183 TYAVG 3248 WFRQAP 3313 GITRSGT GLVQAGGFLR GKEREF ATDYAD LSCAASGRSFN VA SVKG IV47 3119 QVQLQQSGG 3184 TYAMG 3249 WFRQAP 3314 GITRSGT GLVQAGGFLR GKEREF ATEYAD LSCAASGRSFN VA SVKG IV48 3120 QVQLQESGG 3185 TYAMG 3250 WFRQAP 3315 GITRSGT GLVQAGGFLR GKDRKF VTDYAD LTCAASGRSFN VA SVKG IV50 3121 QVQLQESGG 3186 TYAMG 3251 WFRQAP 3316 GITRSGT GLVQAGGFLR GKEREF ATDYAD LSCAASGRSFN VA SVKG IV22 3122 QVQLQESGG 3187 NGAMS 3252 WFRQAP 3317 AIRWSG GLVQAGDSLR GKEREF GGIRYA LSCAASGPSFN VA DSVKG IV37 3123 QVQLQESGG 3188 GGAMS 3253 WFRQVP 3318 AIRWSG GLVQAGDSLR GKEREF GGIRYA LSCAAPGRSFS VA DSVKG IV38 3124 QVQLQESGG 3189 NGAMS 3254 WFRQAP 3319 AIRWSG GLVQAGGSL GKEREF GGIRYA RLSCAASGPS VA DSVKG FN IV5 3125 QVQLQQSGG 3190 TTGMG 3255 WFRQAP 3320 AFWWT GLVQAGGSL GKEREF GGQTFY RLSCAASGRT VA ADSVKG FS IV27 3126 QVQLQESGG 3191 TYAMG 3256 WFRQAP 3321 AFWWTD GLVQAGGSL GKEREF EQTFYA RLSCAASGST VA DSVKG FS IV25 3127 QVQLQQSGG 3192 NRVVG 3257 WFRQAP 3322 RIMWSV GLVQSGGSLS GKEREF GDTFYA LSCAASGITLN VG RSVKG IV28 3128 QVQLQESGG 3193 DYAMS 3258 WVRQAP 3323 SINWNG GLVQPGGSL GKGLEW GSTYYA RLSCSASGFA VS ESMKG FD Clone ID FR3 ID CDR3 ID FR4 ID LG202A10 1254 RFTISRDNA 1536 ASGGGS 1818 WGRGT 2100 KNTVYLQMS IRSARR QVTVSS SLKPEDTAIY YDY SCAV LG202A12 1255 RFTISRDNA 1537 DDQKYD 1819 WGQGT 2101 KNTVYLQMN YIAYAEY QVTVSS SLKPEDTAV EYDY YYCAA LG202A5 1256 RFTISRDNA 1538 DWASD 1820 NSQGT 2102 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202A9 1257 RFTISRDNA 1539 DWHND 1821 KGQGT 2103 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG202B10 1258

RFTISRDNA 1540 DWYND 1822 KGQGT 2104 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCTR LG202B7 1259 RFTISRDNA 1541 DWFDD 1823 KGQGT 2105 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCTR LG202B8 1260 RFTISRDNA 1542 DWHSD 1824 RGQGT 2106 KNTLYLQMN PNKHEY QVTVSS SLRSEDTAV YYCTR LG202B9 1261 RFTISRDNA 1543 DWYDD 1825 KGQGT 2107 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA YYCTR LG202C1 1262 RFTISRDNA 1544 DWASD 1826 NSQGT 2108 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202C11 1263 RFTISRDNA 1545 DWHND 1827 KGQGT 2109 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG202C2 1264 RFTISRDNA 1546 DWASD 1828 NSQGT 2110 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202C7 1265 RFTIARDNT 1547 DWHSE 1829 KGQGT 2111 KRTLYLQMN PNKYEY QVTVSS SLKSEDTAV YYCTR LG202C8 1266 RFTISRDNA 1548 SLTLTD 1830 RSQGT 2112 KNTLYLQMN SPDL QVTVSS SLKPEDTAL YYCRR LG202C9 1267 RFTISRDNA 1549 DWYND 1831 KGQGT 2113 KNALYLQMN PNKNEY QVTVSS SLKSEDTAV YYCAR LG202D5 1268 RFTISRDNA 1550 VGNFTTY 1832 WGRGT 2114 KNTGYLQM QVTVSS NSLKPEDTA VYYCYV LG202D7 1269 RFTISRDNA 1551 DWYDD 1833 KGQGT 2115 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG202D8 1270 RFTISRDNA 1552 DWYND 1834 KGQGT 2116 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCTR LG202E11 1271 RFTISRDNA 1553 DWYND 1835 KGQGT 2117 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCTR LG202E2 1272 RFSISRDNA 1554 DWASD 1836 NSQGT 2118 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVR LG202E5 1273 RFTISRDNA 1555 DWASD 1837 NSQGT 2119 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202E6 1274 RFTISRDNA 1556 DLSPGN 1838 WGEGT 2120 KNTVYLQMN EYGEM QVTVSS SLKPEDTAV MEYEYDY S YYCAA LG202E7 1275 RFTISRDNA 1557 DWYND 1839 KGQGT 2121 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAA YYCAR LG202F10 1276 RFTISRDNA 1558 DWYDD 1840 KGQGT 2122 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG202F12 1277 RFTISRDNA 1559 DWYND 1841 KGQGT 2123 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCAR LG202F3 1278 RFTISRDNA 1560 DWASD 1842 NSQGT 2124 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202F4 1279 RFTISRDNA 1561 DWASD 1843 NSQGT 2125 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202F8 1280 RFTITRDNA 1562 DADGW 1844 WGQGT 2126 KNTVYLQMN WHRGQ QVTVSS SLKPEDTAV AYHW YYCAA LG202G11 1281 RFTISRDNA 1563 DWYND 1845 KGQGT 2127 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAA YYCAR LG202G3 1282 RFTISREDA 1564 ECAMYG 1846 WGQGT 2128 KNTVYLQMN SSWPPP QVTVSS SLKPGDTAD CMD YYCAA LG202G8 1283 RFTISRDNA 1565 DWYDD 1847 KGQGT 2129 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG202H2 1284 RFTISRDNA 1566 DWASD 1848 NSQGT 2130 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK LG202H8 1285 RFTISRDNA 1567 DWHND 1849 KGQGT 2131 KNMLYLQM PNKNEY QVTVSS NSLKAEDTA VYYCAR LG191B9 1286 RFTISGDNA 1568 DTQFSG 1850 WGQGT 2132 NNTVYLQMH YVPKET QVTVSS SVKPEDTAT NEYDY YYCAA LG191D3 1287 RFTISRDNA 1569 ELTNRN 1851 WGQGT 2133 ENTVYLQMN SGAYYY QVTVSS SLKPEDTAV AWAYDY YTCAA LG192A8 1288 RFTISRDNA 1570 RPRFW 1852

WGQGT 2134 KNTVYLQMN GSYEYDY QVTVSS SLKAEDTAV YYCAA LG192B1 1289 RFAISRDNA 1571 DLTSSC 1853 WGKGT 2135 KNTVYLQMN PIYSGT LVTVSS SLKPEDTAV DY YYCAT LG192C10 1290 RFTISRDNA 1572 APKSW 1854 WGQGT 2136 KNTVYLPMN GTWPLV QVTVSS SLKPEDTAV ADTRSY YYCAA HF LG192C4 1291 RFTISRDNA 1573 DSTNRN 1855 WGQGT 2137 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV SWAYDY YTCAA LG192C6 1292 RFTISRDNA 1574 DSTNRN 1856 WGQGT 2138 ENTVYLQMN RGAIYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG192D3 1293 RFTISRDNA 1575 DSAFGT 1857 WGQGT 2139 KKTVYLQMN GYSDNY QVTVSS TLKPEDTAV YSTSEE YYCAA YDY LG191E4 1294 RFTMSRDNA 1576 SSRIYIY 1858 WGQGT 2140 KNTVDLQMN SDSLSE QVTVSS SLKPEDTAL RSYDY YYCAG LG192F2 1295 RFTISRDNA 1577 DSTNRN 1859 WGQGT 2141 ENTVYLQMN SGAIYYT QVTVSS SLKPEDTAV WAYDY YTCAA LG192H1 1296 RFTISRDNA 1578 GYIY 1860 WGQGT 2142 KNMVYLQM QVTVSS NSLKPEDTA VYYCNA LG192H2 1297 RFTISRDNA 1579 DSTNRN 1861 WGQGT 2143 ENTVYLQMN SGAWY QVTVSS SLKPEDTAV YTWAYDH YTCAA LG20610B 1298 RFTISGENA 1580 KTLVGV 1862 WGQGT 2144 KNTVYLQMN TTAFDR QVTVSS SLKPEDTAV YYCAA LG20610C 1299 RFTISRDNA 1581 DTQYSG 1863 WGQGT 2145 NNTVYLQMD VVLKES QVTVSS SLKPEDTAT TDYDY YYCAA LG20610D 1300 RFTISRDNA 1582 DTQYSG 1864 WGQGT 2146 NNTVYLQMD VVLKES QVTVSS SLKPEDTAT TDYDY YYCAA LG20610E 1301 RFTISGDNA 1583 RGVAVT 1865 WGQGT 2147 KSTVYLQMN TILWNY QVTVSS SLKPEDTAV YYCAV LG20610F 1302 RFTISRDNA 1584 RPRFW 1866 WGQGT 2148 KNTVYLQMN GSYEYDY QVTVSS SLKAEDTAV YYCAA LG20611D 1303 RFTISRDNA 1585 RPRFW 1867 WGQGT 2149 KNTVYLQMN GSYEYDY QVTVSS SLKAEDTAV YYCAA LG20611H 1304 RFTISRDNA 1586 APKSW 1868 WGQGT 2150 KNTVYLPMN GTWPLV QVTVSS SLKPEDTAV ADTRSY YYCAA HF LG20612F 1305 RFTISRDNA 1587 APKSW 1869 WGQGT 2151 KNTVYLPMN GTWPLV QVTVSS SLKPEDTAV ADTRSY YYCAA HF LG2062A 1306 RFTISRDNA 1588 DSTNRN 1870 WGQGT 2152 ENTVYLQMN SGAWY QVTVSS SLKPEDTAV YTWAYDH YTCAA LG2062C 1307 RFAISSDNA 1589 QGSIVF 1871 WGQGT 2153 GNTVYLQM YSNWD QVTVSS NNLQPEDTA RASQYDY VYYCAA LG2062E 1308 RFTISRDNP 1590 NRDSGS 1872 WGQGT 2154 KNTLYLQMN SYITFSL QVTVSS SLKPEDTAL ADFGS YYCAR LG2062F 1309 RFTISRDNA 1591 ELTNRN 1873 WGQGT 2155 ENTVYLQMN SGAYYY QVTVSS SLKPEDTAV AWAYDY YTCAA LG2062G 1310 RFTISRDNA 1592 DSTNRN 1874 WGQGT 2156 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG2062H 1311 RFTISRDNA 1593 DSTNRN 1875 WGQGT 2157 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG2063A 1312 RFTISRDNA 1594 DSTNRN 1876 WGQGT 2158 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV TWAWDY YTCAA LG2063B 1313 RFTISSDNA 1595 DFSLAQ 1877 WGKGT 2159 KNTVYLQMN YKTIHR LVTVSS SLKPEDTAV MPPYG YYCAA MDY LG2063C 1314 RFTISRDNA 1596 DATNRN 1878 WGQGT 2160 ENTVYLQMN SGAYYY QVTVSS SLQPEDTAV TWAYDY YTCAA LG2063D 1315 RFTISGDNA 1597 DSTNRN 1879 WGQGT 2161 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG2063E 1316 RFTISRDNA 1598 DSTNRN 1880 WGQGT 2162 ENTVYLQMN SGAWY QVTVSS SLKPEDTAV YTWAYDH YTCAA LG2063F

1317 RFTISRDNA 1599 ELTNRN 1881 WGQGT 2163 ENTVYLQMN SGAYYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG2064D 1318 RFTISRDNA 1600 DSTNRN 1882 WGQGT 2164 ENTVYLQMN SGAIYYT QVTVSS SLKPEDTAV WAYDY YTCAA LG2064G 1319 RFTISGDNA 1601 DSTNRN 1883 WGQGT 2165 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV PWAYDY YTCAA LG2065A 1320 RFTISRDNA 1602 DSTNRN 1884 WGQGT 2166 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV SWAYDY YTCAA LG2065E 1321 RFTISRDNA 1603 DSTNRN 1885 WGQGT 2167 ENTVYLQMN SGAIYYT QVTVSS SLKPEDTAV WAYDY YTCAA LG2066A 1322 RFTISRDNA 1604 DSTNRN 1886 WGQGT 2168 ENTVYLQMN SGAVYY QVTVSS SLKPEDTAV SWAYDY YTCAA LG2066D 1323 RFTISRDNA 1605 QIIPRVM 1887 WGQGT 2169 KNTVYLQMN PLRSNDY QVTVSS SLKPEDTAV YYCNA LG2067B 1324 RFTISRDND 1606 RWYEGI 1888 WGQGT 2170 KNTVYLQMN WREY RVTVSS SLKPEDTAV YYCKT LG2067C 1325 RFTVSRDNA 1607 SLGTIW 1889 WGRGT 2171 ENTLYLQMN YQKDYR QVTVSS SLESEDTAV AYDA YYCAK LG2067E 1326 RFTISRDNA 1608 RPRFW 1890 WGQGT 2172 KNTVYLQMN GSYEYDY QVTVSS SLKAEDTAV YYCAA LG2067G 1327 RFTISRDNA 1609 NRQGEV 1891 WGRGT 2173 ENTVYLQMN FRTTRL QVTVSS SLKPEDTAV DYDS YFCAR LG2067H 1328 RFTISRDNA 1610 DRYPFV 1892 RGQGT 2174 KNTLYLQMD SREYDY QVTVSS SLKPEDTAV YYCSK LG20711A 1329 RFSISKDSA 1611 RQYESD 1893 WGQGT 2175 KNTVLLQMN RWRDY QVTVSS SLKPEDTAV YSCNL LG20711B 1330 RFTISRDNA 1612 DFSRSW 1894 WGKGT 2176 KNTVYLQMN GTCNEE LVTVSS SLKPEDTAV YYYGMDY YYCAA LG20711D 1331 RFTISGENA 1613 KTIVGG 1895 WGQGT 2177 KNTVYLQMN TTAWBR QVTVSS SLKPEDTAV YYCAA LG20711E 1332 RFTISGENA 1614 KTIVGG 1896 WGQGT 2178 KNTVYLQMN TTAWDR QVTVSS SLKPEDTAV YYCAA LG20711F 1333 RFTISRDNA 1615 DLYPFV 1897 RGQGT 2179 KNTLYLQMD SREYDY QVTVSS SLKPEDTAV YYCSK LG20711G 1334 RFTISRDNA 1616 DLDGNG 1898 WGQGT 2180 KNTVYLQMN SIDYGY QVTVSS SLKPEDAAV EY YYCAA LG20711H 1335 RFTISRDNA 1617 DRYPFIS 1899 RGQGT 2181 KNTLYLQMD KEYDY QVTVSS SLKPEDTAV YYCSK LG2071A 1336 RFTISRDNA 1618 RQHDG 1900 WGQGT 2182 KNMVYLQM GSWYDY QVTVSS NSLKPEDTA LYFCKQ LG2071B 1337 RFTISSENAK 1619 LGRMAV 1901 WGQGT 2183 NTVYLQMNS AHSVSD QVTVSS LKAEDTAVY FNS YCNA LG2071C 1338 RFTMSRDNA 1620 SSRIYIY 1902 WGQGT 2184 KNTVDLQMN SDSLSE QVTVSS SLKPEDTAL RSYDY YYCAG LG207D1 1339 RFTISRDNA 1621 ELTNRN 1903 WGQGT 2185 ENTVYLQMN PGAYYY QVTVSS SLKPEDTAV TWAYDY YTCAA LG2071E 1340 RFTMSRDNA 1622 SSRIYIY 1904 WGQGT 2186 KNTADLQMN SDSLSE QVTVSS SLKPEDTAL GSYDY YYCAG LG2071F 1341 RFTMSRDNA 1623 SSRIYIY 1905 WGQGT 2187 KNTVDLQMN SDSLSE QVTVSS SLKPEDTAL RSYDY YYCAG LG2074A 1342 RFTISRDNA 1624 RGLGSH 1906 WGQGT 2188 KNTVYLQMN RVSDY QVTVSS SLKPEDTAV YYCNA LG2074B 1343 RFTISRDNA 1625 RGLGSH 1907 WGQGT 2189 KNTVYLQMN RVSDY QVTVSS SLKPEDTAV YYCNA LG2074D 1344 RFTISRDDA 1626 NPSYVY 1908 WGQGT 2190 KNAVYLQMN SDYLSL QVTVSS SLKPEDTAV AGYTY YYCAA LG2074H 1345 RFTISRDNA 1627 PWMDY 1909 WGQGT 2191 KDTVYLQMN NRRDY QVTVSS SLKPEDTAV YYCHV LG2075A 1346 RFTISSENAK 1628 LGRMAV 1910

WGQGT 2192 NTVYLQMNS AHSVSD QVTVSS LKAEDTAVY FNS YCNA LG2075B 1347 RFTISRDNA 1629 RTLGAH 1911 WGQGT 2193 KNTADLQMN GIDDY QVTVSS SLKPEDTAV YYCNA LG2075C 1348 RFTMSRDNA 1630 SSRIYIY 1912 WGQGT 2194 KNTVDLQMN SDSLSE QVTVSS SLKPEDTAL RSYDY YYCAG LG2075D 1349 RFTISRDNA 1631 DSTNRN 1913 WGQGT 2195 ENTVYLQMN SGAWY QVTVSS SLKPEDTAV YTWAYDH YTCAA LG2075E 1350 RFSISRHNA 1632 KQPENH 1914 WGQGT 2196 KNSVYLQMN AITNY QVTVSS SLKPEDTAV YFCNL LG2076A 1351 RFTISRDNA 1633 RGAGAH 1915 WGQGT 2197 KNTVYLQMN RVDDY QVTVSS SLKPEDTAV YYCNH LG2076B 1352 RFTISRDNA 1634 ELTNRN 1916 WGQGT 2198 ENTVYLQMN SGAYYY QVTVSS SLKPEDTAV AWAYDY YTCAA LG2076C 1353 RFTISRDNA 1635 EGREAR 1917 WGQGT 2199 KNTVYLQMN NHGLYE QVTVSS SLKPEDTAV YHS YYCNT LG2076D 1354 RFTISRDDA 1636 RVPGAH 1918 WGKGT 2200 KNTVYLQMN YIMDY LVTVSS SLKPEDTGV YYCNA LG2076E 1355 RFSISRHNA 1637 KQPENH 1919 WGQGT 2201 KNSVYLQMN AITNY QVTVSS SLKPEDTAV YFCNL LG2076F 1356 RFTISRDDA 1638 LDN 1920 WGQGT 2202 KNTVYLHMN QVTVSS SLKPEDTAV YYCKT LG2079A 1357 RFTISGDNA 1639 DTQFSG 1921 WGQGT 2203 NNTVYLQMH YVPKET QVTVSS SVKPEDTAT NEYDY YYCAA LG2079B 1358 RFTISGDNA 1640 DTQFSG 1922 WGQGT 2204 NNTVYLQMH YVPKET QVTVSS SVKPEDTAT NEYDY YYCAA LG2079C 1359 RFTISRDHA 1641 RAGSGL 1923 WGQGT 2205 KNEQYLEMN RTTINDY QVTVSS SLKPEDTAV TY YFCTA LG2079D 1360 RFTISGENA 1642 KTLVGD 1924 WGQGT 2206 KNTVYLQMN TTAFDR QVTVSS RLKPEDTAV YYCAA LG2079E 1361 RFTISRDNA 1643 KENGMF 1925 WGQGT 2207 KNTVYLQMN ITATQE QVTVSS SLGPEDTAIY QSYDY TCAA LG2079F 1362 RFTISRDNA 1644 DLYPFV 1926 RGQGT 2208 KNTLYLQMD SREYDY QVTVSS SLKPEDTAV YYCSK LG2079G 1363 RFTISRDNA 1645 RPRFW 1927 WGQGT 2209 KNTVYLQMN GSYEYDY QVTVSS SLKAEDTAV YYCAA LG2079H 1364 RFTISRDNA 1646 DTEFSG 1928 WGQGI 2210 NNTVYLQMH YVQKES QVTVSS SLKPEDTAT NDYDY YYCAA LG213B7 1365 RFTVSRDNA 1647 VSYGEYF 1929 WGKGT 2211 KNTVYLQMN LVTVSS SLKPEDTAV YYCNV LG213D6 1366 RFTISRDNA 1648 GLMAEV 1930 WGQGT 2212 KNMLYLQM TAGY QVTVSS NSLKPEDTA VYLCAQ LG213D7 1367 RFTVSRDNA 1649 VSYGEYF 1931 WGKGT 2213 KNTVYLQMN LVTVSS SLKPEDTAV YYCNV LG213E6 1368 RFTISRDNA 1650 DSSVVP 1932 WGLGT 2214 KNTGYLQM GIEKYDD QVTVSS NSLKPDDTA VYYCAA LG213H7 1369 RFIFSEDNA 1651 ALIGGY 1933 WGPGT 2215 KNTVYLQMN YSDVDA QVTVSS SLKPEDTAV WSY YYCAA LG214A8 1370 RFAITRDAA 1652 ATYGYG 1934 WGQGT 2216 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG214C10 1371 RFTISRDNA 1653 NLYPTT 1935 WGQGT 2217 KNTLYLQMN DDV QVTVSS SLKPEDTAV YYCST LG214D10 1372 RFTVSRDSA 1654 DKGVYT 1936 WGQGT 2218 KITVFLQMD TVSRSM QVTVSS NLKPEDTAV ADYGA YYCAA LG214E8 1373 RFAITRDAA 1655 ATYGYG 1937 WGQGT 2219 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG214F8 1374 RFTISRDTAK 1656 EVIYYPY 1938 WGQGT 2220 NTVYLQMNS DY QVTVSS LKPEDTAVY YCNA LG214H10 1375 RFAITRDAA 1657 ATYGYG 1939 WGQGT 2221 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA RSVPMP5C1 1376 RFTISRDNA 1658 RQDYGL 1940 WGQGT 2222 KNTVYLQID

GYRDLH QVTVSS SLQPEDTAV EYDY YYCAA RSVPMP8A1 1377 RFTISRDNA 1659 RQDYGL 1941 WGQGT 2223 KNTVYLRIDS GYRESH QVTVSS LNPEDTAVY EYDY YCAA RSVPMP8G1 1378 RFTISRDNA 1660 RQDYGL 1942 WGQGT 2224 KNTVYLRIDS GYRESH QVTVSS LNPEDTAVY EYDY YCAA RSVPMP25B3 1379 RFTISRDNA 1661 RQDYGL 1943 WGQGT 2225 KNTVYLRIDS GYRESH QVTVSS LNPEDTAVY EYDY YCAA RSVPMP8C8 1380 RFTISRDNA 1662 SKEWDI 1944 WGQGT 2226 KNTLYLQMN SASGDD QVTVSS SLEPEDTAV YDY YYCAA RSVPMP5A6 1381 RFTISRDNA 1663 DGIYSS 1945 KGQGT 2227 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP8E11 1382 RFTISRDNA 1664 DGIYSS 1946 KGQGT 2228 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP8F11 1383 RFTISRDNA 1665 DGIHSS 1947 KGQGT 2229 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP13F11 1384 RFTISRDNA 1666 DGIYSS 1948 KGQGT 2230 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP15B8 1385 RFTISRDNA 1667 DGIYSS 1949 KGQGT 2231 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP15G11 1386 RFTISRDNA 1668 DGIYSS 1950 KGQGT 2232 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP17C10 1387 RFTISRDNA 1669 DGIYSS 1951 KGQGT 2233 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP21E7 1388 RFIISRDNAK 1670 DGIYSS 1952 KGQGT 2234 NTLYLQMND QVTVSS LKSEDTAVY YCSK RSVPMP21F8 1389 RFTISRDNA 1671 DGIHSS 1953 KGRGT 2235 KNTLYLQMN QVTVSS DLKSEDTAV YYCSK RSVPMP5A2 1390 RFTISRDNA 1672 DPALGC 1954 WGQGT 2236 KNTVYLQMN YSGTYY QVTVSS SLKPEDTAV PRYDY YYCAT RSVPMP5B2 1391 RFTISWDNA 1673 DPALGC 1955 WGQGT 2237 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP5C3 1392 RFTISRDNA 1674 DPALGC 1956 WGQGT 2238 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAV RSVPMP5D2 1393 RFTISRDNA 1675 DPALGC 1957 WGQGT 2239 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAV RSVPMP5E2 1394 RFTISWDNA 1676 DPALGC 1958 YGQGT 2240 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP5F3 1395 RFTISWDNA 1677 DPALGC 1959 WGQGT 2241 KNTLYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP5G3 1396 RFTISRDNA 1678 DPALGC 1960 WGQGT 2242 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAT RSVPMP5H2 1397 RFTISWDSA 1679 DPALGC 1961 WGQGT 2243 KNTVYLQMN YSGSYY QVTVSS DLKPEDTAV PRYDY YYCAA RSVPMP5H3 1398 RFTISRDNA 1680 DPALGC 1962 WGQGT 2244 KNTVYLQMN YSGSYY QVTVSS SLQPEDTAV PRYDY YYCAA RSVPMP8C1 1399 RFTISRDNA 1681 DPALGC 1963 WGQGT 2245 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP8F2 1400 RFTISRDNA 1682 DPALGC 1964 WGQGT 2246 KNTVYLQMN YSGSYY QVTVSS SLTPEDTAV PRYDY YYCAV RSVPMP8G4 1401 RFTISRDNA 1683 DPALGC 1965 WGQGT 2247 KNTVYLQMN YSGSYY QVTVSS GLKPEDTAV PRYDY YYCAT RSVPMP13A1 1402 RFTISWDNA 1684 DPALGC 1966 WGQGT 2248 KNTVYLQMN YSGNYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP13A4 1403 RFTISWDNA 1685 DPALGC 1967 WGQGT 2249 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP13B1 1404 RFTISRDNA 1686 DPALGC 1968 WGQGT 2250 KNTVYLQMN YSGNYY QVTVSS SLTPEDTAV PRYDY YYCAA RSVPMP13B2 1405 RFTISRDNA 1687 DPALGC 1969 WGQGT 2251 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY

YYCAT RSVPMP13C1 1406 RFTISRDNA 1688 DPALGC 1970 WGQGT 2252 KNTVYLQMN YSGSYY QVTVSS SLEPEDTAV PRYDY YYCAT RSVPMP13C3 1407 RFTISWDNA 1689 DPALGC 1971 WGQGT 2253 KNMVYLQM YSGNYY QVTVSS NSLKPEDTA PRYDY VYYCAA RSVPMP13D6 1408 RFTISWDNA 1690 DPALGC 1972 WGQGT 2254 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP13E2 1409 RFTISWDNA 1691 DPALGC 1973 WGQGT 2255 KKMVYLQM YSGSYY QVTVSS NKLKPEDTA PRYDY VYYCAA RSVPMP13E3 1410 RFTISWDNA 1692 DPALGC 1974 WGQGT 2256 KNTLYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP15A5 1411 RFTISRDNT 1693 DPALGC 1975 WGQGT 2257 KNTVYLQMN YSGNYY QVTVSS SLTPEDTAIY PRYDY YCAV RSVPMP15A6 1412 RFTISWDNA 1694 DPALGC 1976 WGQGT 2258 KNTVYLQMS YSGSYY QVTVSS SLKPEDTAV PRYDY YHCAA RSVPMP15B2 1413 RFTISRDNA 1695 DPALGC 1977 WGQGT 2259 KNMVYLQM YSGSYY QVTVSS NSLKPEDTA PRYDY VYYCAT RSVPMP15B3 1414 RFTISWDNA 1696 DPALGC 1978 WGQGT 2260 KNTLYLQMN YSGSYY QVTVSS SLKPGDTAV PRYDY YYCAA RSVPMP15E5 1415 RFTISRDNA 1697 DPALGC 1979 WGQGT 2261 KNTVYLQMN YSGNYY QVTVSS NLTPEDTAV PRYDY YYCAT RSVPMP17C2 1416 RFTISRDNA 1698 DPALGC 1980 WGQGT 2262 RNTVYLQMN YSGNYY QVTVSS NLTPEDTAV PRYDY YYCAT RSVPMP17D4 1417 RFTISWDNA 1699 DPALGC 1981 WGQGT 2263 KNIVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP17G4 1418 RFTISWDSA 1700 DPALGC 1982 WGQGT 2264 KNTVYLQMN YSGSYY QVTVSS DLKPEDTAV PRYDY YYCAA RSVPMP19B2 1419 RFTISWDNA 1701 DPALGC 1983 WGQGT 2265 KKVVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP25A4 1420 RFTISWDNA 1702 DPALGC 1984 WGQGT 2266 KNMVYLQM YSGSYY QVTVSS NSLKPEDTA PRYDY VYYCAA RSVPMP25A9 1421 RFTISRDNA 1703 DPALGC 1985 WGQGT 2267 KNTVYLQMN YSGSYY QVTVSS GLKPEDTAV PRYDY YYCAT RSVPMP25B5 1422 RFTISWDNA 1704 DPALGC 1986 WGQGT 2268 KNTLYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP25G2 1423 FTISWDNAK 1705 DPALGC 1987 WGQGT 2269 NMVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP25H5 1424 RFTISWDNA 1706 DPALGC 1988 WGQGT 2270 KNTVYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP25E11 1425 RFTISRDNT 1707 DPALGC 1989 WGQGT 2271 KNTVYLQMN YSGNYY QVTVSS SLTPEDTAV PRYDY YYCAV RSVPMP8G3 1426 RFTISWDNA 1708 DPALGC 1990 WGQGT 2272 KNTLYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP13B5 1427 RFTISWDNA 1709 DPALGC 1991 WGQGT 2273 KNTLYLQMN YSGNYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP15F2 1428 RFTISWDNA 1710 DPALGC 1992 WGQGT 2274 KNTLYLQMN YSGNYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP19E2 1429 RFTISWDNA 1711 DPALGC 1993 WGQGT 2275 KNTLYLQMN YSGSYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP25D1 1430 RFTISWDNA 1712 DPALGC 1994 WGQGT 2276 KNTLYLQMT YSGSYY QVTVSS SLKPEDTAV PRYDF YYCAA RSVPMP5A1 1431 RFTISRDNA 1713 DFALGC 1995 WGQGT 2277 KNMVYLQM YSGSYV QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP5G2 1432 RFTISRDNA 1714 DFALGC 1996 WGQGT 2278 KNMVYLQM YSGSYY QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP5H1 1433 RFTISRDTAK 1715 DFALGC 1997 WGQGT 2279 NMVYLQMT YSGSYY QVTVSS SLKPEDTAV

PRYDY YYCAA RSVPMP6B1 1434 RFTISRDNA 1716 DFALGC 1998 WGQGT 2280 KNMVYLQM YSGSYY QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP8H2 1435 RFTISTDNAK 1717 DFALGC 1999 WGQGT 2281 NMVYLQMT YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP8H3 1436 RFTISRDNA 1718 DFALGC 2000 WGQGT 2282 KNMVYLQM YSGSYY QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP13A3 1437 RFTISRDTAK 1719 DFALGC 2001 WGQGT 2283 NMVYLQMT YSGSYY QVTVSS SLKPEDTAV PRYDY YYCAA RSVPMP13C5 1438 RFTISRDNA 1720 DFALGC 2002 WGQGT 2284 KNMVYLQM YSGSYY QVTVSS TSLMPEDTA PRYDY VYYCAA RSVPMP13H1 1439 RFTISRDNA 1721 DFALGC 2003 WGQGT 2285 KNMVYLQM YSGSYY QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP13H2 1440 RFTISRDNA 1722 DFALGC 2004 WGQGT 2286 KNMVYLQM YSGSYY QVTVSS TSLKPEDTAI PRYDY YYCAA RSVPMP15E6 1441 RFTISRDNA 1723 DFALGC 2005 WGQGT 2287 KNMVYLQM YSGSYY QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP17A3 1442 RFTISRDNA 1724 DFALGC 2006 WGQGT 2288 KNMVYLQM YSGSYV QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP25G8 1443 RFTISRDNA 1725 DFPLGC 2007 WGQGT 2289 KNMVYLQM YSGSYV QVTVSS TSLKPEDTA PRYDY VYYCAA RSVPMP6D1 1444 RFTISSDNA 1726 DRLSTV 2008 WGKGT 2290 KNTVYLTMN VGCLYY LVTVSS NLKPEDTAV GGSYYP YYCAA RTTIDY RSVPMP8D5 1445 RFTISSDNA 1727 DLLSTV 2009 WGKGT 2291 KNTVYLTMN VGCLYY LVTVSS SLKPEDTAV RGSYYP YYCAA RTTADY RSVPMP13B4 1446 RFTISSDNA 1728 DLLRTA 2010 RGKGT 2292 KNMVYLQM VGCLDY LVTVSS NSLKPEDTA RGTYYP VYYCAA RTTMDY RSVPMP13B6 1447 RFTISSDNA 1729 DLLSTV 2011 WGKGT 2293 KNTVYLTMN VGCLYY LVTVSS SLKPEDTAV RGSYYP YYCAA RTTADY RSVPMP13E6 1448 RFTISSDNA 1730 DLLRTA 2012 RGKGT 2294 KNTVYLQMN VGCLYY LVTVSS SLKPEDTAV RGTYYP YYCAA RTTMDY RSVPMP13F4 1449 RFTISSDNA 1731 DQLSTV 2013 WGKGT 2295 KNTVYLTMN VGCFYY LVTVSS SLKPEDTAV RGSYYP YYCAA RTTADY RSVPMP15H3 1450 RFTISRDNA 1732 DLLATA 2014 WGKGT 2296 KNTVYLQMN VGCLYY LVTVSS SLKPEDTAV RGTYYP YYCAA RTTMDY RSVPMP17E5 1451 RFTISSDNA 1733 DLLSTV 2015 WGKGT 2297 KNTVYLAMN VGCLYY LVTVSS NLKPGDTAV GGSYYP YYCAA RTTIDY RSVPMP19D3 1452 RFTISSDNA 1734 DLLRTV 2016 WGKGT 2298 KNTVYLQMN VGCLYY LVTVSS SLKPEDTAV GGRYSP YYCAA RTTTDY RSVPMP19F3 1453 RFTISSDNA 1735 DLLSTV 2017 WGKGT 2299 KNTVYLTMN VGCLYY LVTVSS NLKPEDTAV GGSYYP YYCAA RTTIDY RSVPMP25C4 1454 RFTISSDNA 1736 DLLRTA 2018 WGKGT 2300 KNTVYLQMN VGCLHY LVTVSS SLKPEDTAV RGSYYP YYCAA RTTIDY RSVPMP25E3 1455 RFTISKDNA 1737 DLLRTV 2019 WGKGT 2301 KNTVYLQMN VGCLYY LVTVSS SLKPEDTAV GGSYSP YYCAA RTTMDY RSVPMP5G4 1456 RITIFRDNAK 1738 APTLVEI 2020 WGQGT 2302 NTAYLQMNS TTTPTY QVTVSS LNPEDTAVY YCAA RSVPMP6G5 1457 RITIFRDNAK 1739 APTLVEI 2021 WGQGT 2303 NTVYLQMNS TPTPTY QVTVSS LNPEDTAVY YCAA RSVPMP8E6 1458 RITIFRDNAK 1740 APTLVEI 2022 WGQGT 2304 NTVYLQMNS TPTPTY QVTVSS LNPEDTAVY YCAA RSVPMP13A10 1459 RITIFRDNAK 1741 APTLVEI 2023 WGQGT 2305 NTAYLQMNS TTTPTY QVTVSS LNPEDTAVY YCAA RSVPMP21H10 1460 RITIFRDNAK 1742 APTLVEI 2024 WGRGT 2306 NTVYLQMNS TPTPTY RVTVSS LNPEDTAVY YCAA RSVPMP5A8 1461

RFTISRDNA 1743 TDDYINT 2025 WGQGT 2307 KNTVYLQMN TPALYRN QVTVSS SLKPEDTAA YYCAT RSVPMP5A10 1462 RFTISRDNA 1744 DSNVNT 2026 WGQGT 2308 KNTVYLQMN VKLGW QVTVSS SLRPEDTAV GRY YYCAA RSVPMP14A6 1463 RFTISRDNA 1745 DSSVNT 2027 WGQGT 2309 KNTVYLQMN VKLGW QVTVSS SLRPEDTAV GRY YYCAA RSVPMP16A6 1464 RFTISRDNA 1746 DSNVNT 2028 WGQGT 2310 KNTVYLQMN VKLGW QVTVSS SLRPEDTAV GRY YYCAA RSVPMP22D6 1465 RFTISRDNA 1747 DSNVNT 2029 WGQGT 2311 KNTVYLQMN VKLGW QVTVSS SLRPEDTAV GRY YYCAA RSVPMP8E2 1466 RFTISRDNA 1748 DVRVAE 2030 WGQGT 2312 KNTVYLQMN KHTAYE QVTVSS SLKPEDTAV ANY YYCNA RSVPMP8C6 1467 RFTISRDNA 1749 KMYGG 2031 WGQGT 2313 KNTVYLQMN NWYTY QVTVSS SLKPEDTAV YYCYL RSVPMP5C6 1468 FTMSRDNAK 1750 ATSPLF 2032 WGQGT 2314 SSVYLQMIN VASDYF QVTVSS LKPEDTAVY DASRYDY YCAA RSVPMP6D4 1469 SISRDNAKS 1751 AASTLFI 2033 WGQGT 2315 AVYLQMNNL ASDYFE QVTVSS KPEDTAVYY ASRYDY CAA RSVPMP8B10 1470 FTMSRDNAK 1752 TSPLFV 2034 WGQGT 2316 SSVYLQMIN ASDYFE QVTVSS LKPEDTAVY ASRYGY YCAA RSVPMP8E10 1471 FTMSRDNAK 1753 ASPLFV 2035 WGQGT 2317 SSVYLQMIN ASDYFE QVTVSS LKPEDTAVY ASRYGY YCAA RSVPMP15A7 1472 SISRDNAKS 1754 AASTLF 2036 WGQGT 2318 AVYLQMNNL VASDYF QVTVSS KPEDTAVYY EASRYDY CAA RSVPMP15E10 1473 FTMSRDNAK 1755 TSPLFV 2037 WGQGT 2319 SSVYLQMIN ASDYFE QVTVSS LEPEDTAVY ASRYGY YCAA RSVPMP13C7 1474 RITISRDNAK 1756 DNTAYG 2038 WGQGT 2320 NTVYLQMNS SFKADD QVTVSS LKPEDTAIYY YDY CAA RSVPMP15A9 1475 RITISRDNAK 1757 DSTAYG 2039 WGQGT 2321 NTVYLQMNS SFKADD QVTVSS LTPEDTAIYY YDY CAA RSVPMP15F11 1476 RITISRDNAK 1758 DSTAYG 2040 WGQGT 2322 NTVYLQMNS SFKADD QVTVSS LKPEDTAIYY YDY CAA RSVPMP15A1 1477 RFTISRDNA 1759 DLTDSL 2041 WGQGT 2323 KNTVYLQMN CSYYDY QVTVSS SLKPEDTAV MRPENDY YYCAT RSVPMP6H2 1478 RFTISRDNA 1760 DLTDSL 2042 WGQGT 2324 KNTVYLQMN CSYYHY QVTVSS SLKPEDTAV MRPENDY YYCAT RSVPMP17A9 1479 RFTMSRDNA 1761 NSDTYYI 2043 WGQGT 2325 KNTLYLQMN YSDIVVP QVTVSS SLEPEDTAV ERYDY YSCAA RSVPMP7G1 1480 RFTISRDNA 1762 GSEPYY 2044 WGQGT 2326 KNTVYLQMN TNTYDY QVTVSS SLKPDDTAV YYCAT RSVPMP5A9 1481 RFTISRDNA 1763 DISSGN 2045 WGQGT 2327 KNTVYLQMN SGSYIYT QVTVSS SLKPEDTAV WAYDY YYCAA RSVPMP7B2 1482 RFTISRDNA 1764 DLTSTN 2046 WGQGT 2328 KNTVYLQMN PGSYIYI QVTVSS SLKPEDTAV WAYDY YYCAA RSVPMP22A4 1483 RFTISRDNA 1765 DISSGN 2047 WGQGT 2329 KNTVYLQMS SGSYIYT QVTVSS SLKPEDTAV WAYDY YYCAA RSVPMP22E10 1484 RFTISRDNA 1766 DISSGN 2048 WGQGT 2330 KNTVYLQMN SGSYIYT QVTVSS SLKPEDTAV WAYDY YYCAA RSVPMP22H4 1485 RFTISRDNA 1767 DISSGN 2049 WGQGT 2331 KNTVYLQMN SGSYIYT QVTVSS SLKPEDTAV WAYDY YYCAA RSVPMP15C5 1486 RFIISRDNAK 1768 DGVLAT 2050 WGQGT 2332 NTVYLLMNS TLNWDY QVTVSS LQSDDTAVY YCVA RSVNC39 1487 RFIISRDNAK 1769 DGVLAT 2051 WGQGT 2333 NTVHLLMNS TLNWDY QVTVSS LQSDDTAVY YCVA RSVPMP7B9 1488 RLTVSRDNA 1770 ALLGEN 2052 WGQGT 2334 KNTAYLQMN LQWKG QVTVSS SLKPEDTAV AYDY YYCAA RSVPMP15E11 1489 RFTISRDNA 1771 DYSHTF 2053 WGQGT 2335 KNTVYLQMN VYPSMV

QVTVSS SLESEDTAV PYESDY YYCAA RSVPMP7E7 1490 RFTISRDNA 1772 GMSPNI 2054 RGQGT 2336 KNTLYLQMN EYAQGP QVTVSS SLKPEDTGV VAY YYCAK RSVPMP14H3 1491 RFTISRDNA 1773 DHKASG 2055 WGQGT 2337 KNTGYLQM SYSSLS QVTVSS NSLKPEDTA RPEEYDY VYYCAL RSVPMP24D6 1492 RFTMFSDNA 1774 LFGTSS 2056 WGQGT 2338 KNTVALQMN CTYYSR QVTVSS SLKPEDTAV RKYEYDY YYCTV RSVPMP23E5 1493 RFTISRDNA 1775 AHNTMG 2057 WGQGT 2339 KNTVHLQMN SDYEGY QVTVSS SLKPEDTAV DY YYCAA RSVPMP8A6 1494 RFTISSDNA 1776 SRRGGS 2058 WGKGT 2340 KNTVYLQMN RWYGLS LVTVSS SLKPEDTAV GSCYYG YYCAA MDY RSVPMP14E2 1495 RFTISRDNA 1777 DPYGSS 2059 WGQGT 2341 KNTLYLQMN WYGSP QVTVSS SLKPEDTAV VYDY YYCAK RSVPMP25F3 1496 RFTISSDNA 1778 GRSLYA 2060 WGQGT 2342 KNTVYLQMN KGSWW QVTVSS SLKPEDTAV LISSEYDY YYCAA RSVPMP19A6 1497 RFTVSRDNA 1779 RWYSS 2061 WGQGT 2343 QNTVYLQM MWYEY QVTVSS NSLKPDDTA VYYCYV RSVPMP23G1 1498 RFTLSRDNA 1780 PISSYV 2062 WGQGT 2344 KNTVYLQMN GGNYYS QVTVSS SLKPEDTAV AAFYHY YYCAA RSVPMP15H8 1499 RFTISRDNA 1781 GTPLNP 2063 WGRGT 2345 KNTGYLQM GAYIYD QVTVSS NSLVPDDTA WSYDY VYYCGA RSVNC41 1500 RFTISKDNA 1782 DTPLNP 2064 WGRGT 2346 KNTGYLQM GAYIYD QVTVSS NSLAPDDTA WSYDY VYYCGA RSVPMP6A8 1501 RFTISRDNA 1783 DHSRVY 2065 WGQGT 2347 KNTVYLQMN YRDYRQ QVTVSS SLKPEDTAV GRLCEE YYCAA PYDY RSVPMP25H9 1502 RFTISRDNA 1784 DARPAP 2066 WGQGT 2348 KNAVYLQMN YITNYKD QVTVSS SLKPEDSAV PRAYDY YYCAF RSVPMP8B11 1503 RFTVSRDNA 1785 GFQYYS 2067 WGQGT 2349 KNMVYLQM TITNYAR QVTVSS NSLKPEDTA ERDYDY VYYCAA RSVPMP17E1 1504 RFTISRDNA 1786 DQPPST 2068 WGQGT 2350 KETVSLQMS WLVEYF RVTVSS GLKPEDTAV DY YYCAA RSVPMP21A4 1505 RFTISRDNA 1787 DQPPST 2069 WGQGT 2351 KEIVSLQMS WLAEYF RVTVSS GLKPEDTAV DY YYCAA RSVPMP25A11 1506 RFTISRDNA 1788 DQPPST 2070 WGQGT 2352 KETVSLQMS WLVEYF RVTVSS GLKPEDTAV DY YYCAA RSVPMP25C8 1507 RFTISRDNA 1789 DQPPST 2071 WGQGT 2353 KETVSLQMN WLVEYF QVTVSS GLKPEDTAV DY YYCAA RSVNC23 1508 RFIISRDDAA 1790 DTASWN 2072 WGQGT 2354 NTAYLQMNS SGSFIY QVTVSS LKPEDTAVY DWAYDH YCAV RSVPMP20A11 1509 RFTISRDNA 1791 KENGMF 2073 WGQGT 2355 KNTVYLQMN ITATQE QVTVSS SLGPEDTAIY QSYDY TCAA RSVPMP20A9 1510 RFTISEDNA 1792 DTQFSG 2074 WGQGT 2356 NNTVYLQMH YVPKET QVTVSS SVKPEDTAT NEYDY YYCAA RSVPMP1F7 1511 RFAISRDNA 1793 DYTSSC 2075 WGKGT 2357 KSTVYLQMN PIYSGT LVTVSS SLKPEDTAV DY YYCAI RSVPMP20D6 1512 RFTISSDNA 1794 DFSLAQ 2076 WGKGT 2358 KNTVYLQMN YKTIHT LVTVSS SLKPEDTAV MPPYAM YYCAA DY RSVPMP1F1 1513 RFTMSSDNA 1795 SSRIYVY 2077 WGRGT 2359 KNTVDLQMN SDSLSE QVTVSS SLKPEDTAL GSYDY YYCAG RSVPMP3D3 1514 RFTISRDDA 1796 NPSYVY 2078 WGQGT 2360 QNAVYLQM SDYLSL QVTVSS NSLKPEDTA AGYTY VYYCAA RSVPMP3E6 1515 RFTISRDNA 1797 NRDSGT 2079 WGQGT 2361 KNTLYLQMS SYITFSL QVTVSS SLKPEDTAL TDFAS YYCAR RSVPMP1C8 1516 RFTISRDNA 1798 RKYYIH 2080 WGQGT 2362 KNTVYLQMN SDVVGN QVTVSS SLKPEDTAD DYPY YLCAA RSVPMP1A2 1517 RFTISRDNA 1799 DSLGGF 2081 WGQGT 2363 NNAVYLQM

RSASDY QVTVSS NSLQPEDTA YNTNTY IYYCAA AY RSVPMP1C5 1518 RFTISRDNA 1800 DPSDWT 2082 WGQGT 2364 KNTVYLQMN CNVLEY QVTVSS SLKPEDAAV DY YYCAA RSVPMP20G5 1519 RFTISRDNA 1801 HNY 2083 WGQGT 2365 KNTVYLQMN QVTVSS SLKPEDTAV YYCNV RSVPMP4D8 1520 RFTISRDNA 1802 GSGILN 2084 WGQGT 2366 KNTMYLQM SGSYYY QVTVSS NSLKPEDTA PWVYEY VYYCAA RSVPMP20B6 1521 RFTISRDNA 1803 EGLIIAT 2085 WGKGT 2367 KNTVYLQMN MDGGV LVTVSS SLKPEDTAV NNDMDY YICNA RSVPMP1D11 1522 RFTSSRDNA 1804 RDYEGNH 2086 WGQGT 2368 KNTAYLQMN QVTVSS SLGPEDTAV YYCNF RSVPMP20A8 1523 RFTIARDNA 1805 ALLLLPT 2087 WGQGT 2369 KNTVYLQAN TPSRVDY QVTVSS NMKPEDTAV YYCAA RSVPMP20E7 1524 RFTIARDNA 1806 ALLLLPT 2088 WGQGT 2370 KNTVYLQAN TPSRVDY QVTVSS NMKPEDTAV YYCAA RSVPMP20G8 1525 RFTITRDNA 1807 ALLLLPT 2089 WGQGT 2371 KNTVYLQAN TPSRVDY QVTVSS NMKPEDTAV YYCAA RSVPMP2D3 1526 RFTIARDNA 1808 ALLLLPT 2090 WGQGT 2372 KNTVYLQAD SPSRVDY QVTVSS NMKPEDTAV YYCAA RSVPMP2G5 1527 RFTIARDNA 1809 ALLLLPT 2091 WGQGT 2373 KNTVYLQAN TPSRVDY QVTVSS NMKPEDTAV YYCAA RSVPMP2A6 1528 RFTISRDNA 1810 YWAPW 2092 KGQGT 2374 KNTLYLQMN PMDVSR QVTVSS SLKAEDTAV LDDYDN YYCAK RSVPMP3A2 1529 RFTISRDNA 1811 DSTNRN 2093 WGQGT 2375 ENTVYLQMN SGAIYY QVTVSS SLKPEDTAV PWAYDY YTCAA RSVPMP4A8 1530 RFTISRDNA 1812 DSTNRN 2094 WGQGT 2376 ENTVHLQMN SGAVYY QVTVSS SLKPEDTAV TWAYDY YTCAA RSVPMP4F9 1531 RFTISRDNA 1813 DSTNRN 2095 WGQGT 2377 ENLVYLQMN SGAYYY QVTVSS SLKPEDTAV TWAYDH YTCVA RSVPMP1A6 1532 RFTMSRDNA 1814 DTDSSN 2096 WGQGT 2378 KNTVYLEMN SGSYLY QVTVSS NLKPEDTAV TWAYDY YYCAA RSVPMP3C2 1533 RFTISRDNA 1815 DVSSTN 2097 WGQGT 2379 KNTVYLQMN SGSYIYT QVTVSS SLKPEDTAV WAYDY YNCAA RSVPMP4H9 1534 RFTISRDNA 1816 DASSTN 2098 WGQGT 2380 KNTVYLKMN SGSFIYT QVTVSS SLKPEDTAV WAYDY YYCAV RSVPMP4B10 1535 RFTISRDNA 1817 DATNRN 2099 WGQGT 2381 ENTVYLQMN SGAYFY QVTVSS SLQPEDTAV TWAYDY YTCAA 203B1 2503 RFTISRDNA 2521 DWESSY 2539 NSQGT 2557 KNTLYLQMN AGYSP QVTVSS SLKSEDTAV YYCVK 203B2 2504 RFTISRDNA 2522 DWASD 2540 NSQGT 2558 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK 203G1 2505 RFTISRDNA 2523 DWASTY 2541 NSQGT 2559 KNTLYLQMN AGYRP QVTVSS SLKSEDTAV YYCVK 203H1 2506 RFTISRDNA 2524 KDGPLIT 2542 WGQGT 2560 KKLVYLEMN HYSTTS QVTVSS SLTVEDAAV MY YVCAA 203E12 2507 RFTISRDNA 2525 DWYND 2543 KGQGT 2561 KNTLYLQMN PNKNEY QVTVSS SLKSEDTAV YYCTR 203E1 2508 RCTISRDNA 2526 BSHTYG 2544 WGQGT 2562 NNTVALELN STYAATI QVTVSS SLKPDDTAV DYEYDY YYCAA 203A12 2509 RFTISRDNA 2527 ASGGGS 2545 WGQGT 2563 KNTVYLQMS IRSARR QVTVSS SLKPEDTAIY YDY SCAV 203A9 2510 RFTISRDNA 2528 ASGGGS 2546 WGQGT 2564 KNTVYLQMS IISARRY QVTVSS SLKPEDTAIY DY SCAV 203B12 2511 RFTISRDNV 2529 YAGSM 2547 WGQGT 2565 KNTLYLQMN WTSERDA QVTVSS SLKPEDTAV YSCEK 203D2 2512 RFTISRDNA 2530 VGNFTTY 2548 WGRGT 2566 KNTGYLQM QVTVSS NSLKPEDTA VYYCYV 203D9 2513 RFTISRDNA 2531 BQNTYG 2549 WGQGT 2567 KNTVYLQMN YMDRSD QVTVSS SLKPEDTAV YEYDY YYCAA

203G3 2514 RFTISRDNA 2532 DWASD 2550 NSQGT 2568 KNTLYLQMN YAGYSP QVTVSS SLKSEDTAV YYCVK 203G9 2515 RFTISRDNA 2533 SLTFTD 2551 RSQGT 2569 KNTLYLQMN TPDL QVTVSS SLKPEDTAL YYCRR 203G10 2516 RFTISRDNA 2534 DQNTYG 2552 WGQGT 2570 KNTVYLQMN YMDRSD QVTVSS SLKPEDTAV YEYDY YYCAA 203H9 2517 RFTISRDNA 2535 SLTLTD 2553 RSQGT 2571 KNTLYLQMN SPDL QVTVSS SLQPEDTAL YYCRR 203H10 2518 RFTISRDNA 2536 ASGGGS 2554 WGRGT 2572 KNTVYLQMS IRSARR QVTVSS SLKPEDTAIY YDY SCAV 202E4 2519 RFTISRDNA 2537 YRANL 2555 WGQGT 2573 KNTVYLQMN QVTVSS SLKPEDTAV YYCTL 189E2 2520 RFTISRDNA 2538 RGPAAH 2556 WGQGT 2573 KNTVYLQMN EVRDY QVTVSS SLKPEDTAV YYCNT PRSVPMP20C3 2606 RFTISRDDK 2614 EGLIIAT 2622 WGKGT 2630 NTVYLQMNS MNGGV LVTVSS LKPEDTAVY NYGMDY SCNA PRSVPMP20C5 2607 RFTISRDNA 2615 RTPEVH 2623 WGQGT 2631 KNMVYLQM TIRDY QVTVSS NSLKPEDTA VYYCNV PRSVPMP20B2 2608 RFTISRDNA 2616 DSTNRN 2624 WGQGT 2632 ENTVHLQMN SGAVYY QVTVSS SLKPEDTAV TWAYDY YTCAA PRSVPMP20C1 2609 RFTISGDNA 2617 DSEILNS 2625 WGQGT 2633 KNTMYLQM GAYYYP QVTVSS NSLKPEDTA WAYVY VYYCAA PRSVPMP1G8 2610 RFTISRDNA 2618 DPDPITA 2626 WGKGT 2634 NNIMYLQMN WKQSG QVTVSS LLKPEDTAD AGMDY YYCAA PRSVNMP1A4 2611 RFTISRDNA 2619 GTPLNP 2627 WGRGT 2635 KNTGYLQM GAYIYD QVTVSS NSLAPDDTA WSYDY VYYCGA PRSVPMP13E12 2612 RFTMSRDNA 2620 NSDTYYI 2628 WGQGT 2636 KNTLYLQMN YSDIVVP QVTVSS SLEPEDTAV ERYDY YSCAA PRSVPMP5C6 2613 QFTMSRDN 2621 ATSPLF 2629 WGQGT 2637 AKSSVYLQM VASDYF QVTVSS INLKPEDTAV DASRYDY YYCAA LG203E7 2826 RFTISRDNA 2862 RYGSREY 2898 WGQGT 2934 QKKIDLQMN QVTVSS SLRREDTAV YYCNA LG203G8 2827 RFTISRDNA 2863 QYGSREY 2899 WGQGT 2935 QKKIDLQMN QVTVSS GLGREDTAV YYCNA LG211A10 2828 RFTVSRDNA 2864 VSYGEYF 2900 WGKGT 2936 KNTVYLQMN LVTVSS SLKPEDTAV YYCNL LG211A8 2829 RFIFSEDEAK 2865 ALIGGY 2901 WGPGT 2937 NTVHLQMNS YSDVDA QVTVSS LKPEDTAVY WSY YCAA LG211B10 2830 RFTISRDTAK 2866 EVIYYPY 2902 WGQGT 2938 NTVYLQMNS DY QVTVSS LKPEDTAVY YCNA LG211B8 2831 RFIFSEDEAK 2867 ALIGGY 2903 WGPGT 2939 NTVHLQMNS YSDVDA QVTVSS LKPEDTAVY WSY YCAA LG211C12 2832 RFTVSRDNA 2868 VSYGEYF 2904 WGKGT 2940 KNTVYLQMN LVTVSS SLKPEDTAV YYCNV LG211C8 2833 RFAITRDAA 2869 ATYGYG 2905 WGQGT 2941 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG211D10 2834 RFTISRDSA 2870 RQIGTY 2906 WGQGT 2942 GNTVYLQM YSDYEN QVTVSS NSLKPEDTA YDY VYWCGA LG211D8 2835 RFTMSRDSA 2871 RQMGV 2907 WGQGT 2943 SDTVYLQMN YYSDYE QVTVSS SLKPEDTAV NYDY YYCGA LG211E10 2836 RFTISRDSA 2872 RQIGTY 2908 WGQGT 2944 GNTVYLQM YSDYEN QVTVSS NSLKPEDTA YDY VYWCGA LG211E12 2837 RFTFSRDNA 2873 ATLIGGY 2909 WGPGT 2945 KNTVYLQLN YSDLDN QVTVSS SLKPEDTAV YDY YHCAA LG211E8 2838 RFTMSRDSA 2874 RQMGV 2910 WGQGT 2946 SDTVYLQMN YYSDYE QVTVSS SLKPEDTAV NYDY YYCGA LG211H8 2839 RFIFSEDEAK 2875 ALIGGY 2911 WGPGT 2947 NTVHLQMNS YSDVDA QVTVSS LKPEDTAVY WSY YCAA LG212A10 2840 RFTVSRDNA 2876 VSYGEYF 2912 WGKGT 2948 KNTVYLQMN LVTVSS SLKPEDTAV YYCNV

LG212A12 2841 RFTVSRDNA 2877 VSYGEYF 2913 WGKGT 2949 KNTVYLQMN LVTVSS SLKPEDTAV YYCNV LG212A2 2842 RFTISRDNA 2878 REYGRL 2914 WGQGT 2950 KNTEYLQMN YSDSEA QVTVSS SLKPEDTAV YDY YYCAA LG212A8 2843 RFAITRDAA 2879 ATYGYG 2915 WGQGT 2951 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212B12 2844 RFTISRDNA 2880 DLYGST 2916 WSQGT 2952 KNTLYLQMN WYTDY QVTVSS SLKSEDTAV YYCAK LG212B2 2845 RFTIFRDND 2881 GGFYGL 2917 WGQGT 2953 KNTVYLQMN RTTEER QVTVSS SLKPEDTAV YDT YYCAA LG212C12 2846 RFTISRDNA 2882 DLYGSS 2918 WSQGT 2954 KNTLYLQMN WYTDY QVTVSS SLKSEDTAV YYCAT LG212D10 2847 RFAITRDAA 2883 ATYGYG 2919 WGQGT 2955 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212D12 2848 RFAITRDAA 2884 ATYGYG 2920 WGQGT 2956 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212D2 2849 RFTISRDNA 2885 DFWGST 2921 GLPGT 2957 KNTLYLQMN WS QVTVSS SLKPEDTAV YSCAT LG212E10 2850 RFTISRDTAK 2886 EVIYYPY 2922 WGQGT 2958 NTVYLQMNS DY QVTVSS LKPEDTAVY YCNA LG212E12 2851 RFTISRDNA 2887 ATYGYG 2923 WGQGT 2959 KSTVYLQMD SYTYQG QVTVSS SLKPEDTAV SYDH YYCAA LG212E6 2852 RFTISRDNA 2888 EFWPGV 2924 STPGT 2960 KNTLYLQMN YDT QVTVSS SLKAEDTAV YYCAT LG212F10 2853 RFAITRDAA 2889 ATYGYG 2925 WGQGT 2961 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212F12 2854 RFTVSRDNA 2890 VSYGEYF 2926 WGKGT 2962 KNTVYLQMN LVTVSS SLKPEDTAV YYCNL LG212F6 2855 RFTISRDNA 2891 GLYGGS 2927 WGQGT 2963 KNTLYLQMS TDDY QVTVSS SLKPEDTAV YYCAT LG212F8 2856 RFTISRDTAK 2892 EVIYYPY 2928 WGQGT 2964 NTVYLQMNS DY QVTVSS LKPEDTAVY YCNA LG212G10 2857 RFAITRDAA 2893 ATYGYG 2929 WGQGT 2965 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212G2 2858 RFAISRDNA 2894 DLYGST 2930 EDRGT 2966 KNTLYLQMN WYPG QVTVSS SLKPEDTAV YYCAT LG212H10 2859 RFAITRDAA 2895 ATYGYG 2931 WGQGT 2967 KNTVHLQMN SYTYGG QVTVSS SLKPEDTAV SYDL YYCAA LG212H2 2860 RFTISRDNA 2896 REYGRL 2932 WGQGT 2968 KNTEYLQMN YSDSEA QVTVSS SLKPEDTAV YDY YYCAA LG212H8 2861 RFIITRDSAK 2897 LGVVSN 2933 WGQGT 2969 NTIYLQMNS REY QVTVSS LQPADSGVY WCHG IV121 3324 RFTISRDNP 3389 RGPRYT 3454 WGQGT 3519 KNTMYLQM TTGWIT QVTVSS NSLKPEDTA DDY VYYCNG IV122 3325 RFTISRDNA 3390 RGPRKA 3455 WGQGT 3520 RNTVYLQMN PTGWIT QVTVSS SLKPEDTAV DDY YYCYA IV123 3326 RFTISTDNAK 3391 RGPRR 3456 WGQGT 3521 TTVFLQMNS GTAGWI QVTVSS LKPEDTAVY TDDY YCNA IV126 3327 RFTISRDNP 3392 RGPRYA 3457 WGQGT 3522 KNTLYLQMN TTGWFT QVTVSS SLEPEDTAV DDY YYCHA IV127 3328 RFTISRDNT 3393 RGPRKA 3458 WGQGT 3523 GNTAYLQM PTGWIT QVTVSS NSLKPEDTA DDY VYYCYG IV131 3329 RFTISRGNA 3394 EGPRRR 3459 WGQGT 3524 KNTVYLQMN GSTWYT QVTVSS SLKPEDTAV DNY YYCAA IV132 3330 RFTISRDNA 3395 RGPRHV 3460 WGQGT 3525 RNTVDLQM PTGWIT QVTVSS NSLKPEDTA DDY VYYCYA IV133 3331 RFTISRDNA 3396 RGPRRA 3461 WGQGT 3526 KTTVYLQMN TTGWIT QVTVSS SLKPEDTAV DDY YYCNA IV134 3332 RFTISRGNA 3397 EGPRRR 3462 WGQGT 3527 KNTVYLQMN GSTWYT QVTVSS SLKPEDTAV DNY YYCAA IV135 3333 RFTISRDNA 3398 RGPRHA 3463 WGQGT 3528

ETAVYLQMN TTGWYT QVTVSS SLKPEDTAV DDY YYCNA IV136 3334 RFTISTDNAK 3399 RGPRRA 3464 WGQGT 3529 TTVYLQMNS TTGWIT QVTVSS LKPEDTAVY DDY YCNG IV140 3335 RFTISRDNA 3400 RGPRKA 3465 WGQGT 3530 RNTVYLQMN PTGWIT QVTVSS SLKPEDTAV DDY YYCYA IV144 3336 RFTISRDSA 3401 EGPRRR 3466 WGQGT 3531 KNTIYLQMN GSTWYT QVTVSS SLKPEDTAV DTY YFCAG IV156 3337 RFTISTDNAK 3402 RGPRR 3467 WGQGT 3532 TTVFLQMNS GTAGW QVTVSS LKPEDTAVY FTDDY YCNG IV157 3338 RFTISQDNA 3403 RGPRYA 3468 WGQGT 3533 KTTVYLQMN TTGWYT QVTVSS SLKPEDTAV DDY YYCNG IV160 3339 RFTISQDNA 3404 RGPRYA 3469 WGQGT 3534 KTTVYLQMN TTGWYT QVTVSS SLKPEDTAV DDY YYCNG IV124 3340 RFTISRDNA 3405 GSTYSP 3470 WGQGT 3535 KNTVYLQMN FGDKYDY QVTVSS SLKPEDTAV YYCNA IV125 3341 RFTISRDNA 3406 GSRFNP 3471 WGQGT 3536 KNTVYLHMN FGSAYDY QVTVSS SLKPEDTAV YYCNA IV145 3342 RFTISRDNA 3407 GSRFNP 3472 WGQGT 3537 KNTVYLQMN FGSAYDY QVTVSS SLKPEDTAV YYCNA IV146 3343 RFTISRDNA 3408 GSRFNP 3473 WGQGT 3538 KNTVYLQMN FGSAYDY QVTVSS SLKPEDTAV YYCNA IV147 3344 RFTISRDNA 3409 GSRFNP 3474 WGQGT 3539 KNTVYLQMN FGSAYDY QVTVSS SLKPEDTAV YYCNA IV151 3345 RFTIFRDNA 3410 RWDYG 3475 WGQGT 3540 KNTVYLQMN LWRPST QVIVSS GLKPDDTAI YNYAY YRCAA IV153 3346 RFTISGDNA 3411 TLRSGS 3476 WGQGT 3541 KNTVYLQMS MWYQN QVTVSS SLKPEDTAV VRVNDN YYCAA PY IV154 3347 RFTISRDNT 3412 RTYAGV 3477 WGQGT 3542 RNTLTLEMN RAHTYD QVTVSS SLKPEDTAV YDY YYCAA IV155 3348 RFTISRDNA 3413 GTDAIFK 3478 WGQGT 3543 KNMVYLQM PWMLP QVTVSG NSLNPEDTAI DY YYCAA IV1 3349 RFTVSRDNA 3414 ASGYRS 3479 WGQGT 3544 GNTMYLQM PDRLSE QVTVSS NSLRPEDTA PNWVNY VYICGA IV2 3350 RFTVSRDTA 3415 ASGYRS 3480 WGQGT 3545 NNTMYLQM TDRLSD QVTVSS NSLKPEDTA PGWTNY VYICGA IV3 3351 RFIVSRDNA 3416 ASGYRS 3481 WGQGT 3546 NNTMYLQM TDRLSE QVTVSS NSLKPEDTA PAWINY VYICGA IV4 3352 RFTVSRDNA 3417 ASGYRS 3482 WGQGT 3547 NNTMYLQM TDRLST QVTVSS NSLKPEDTA PEWINY VYICGA IV6 3353 RFTVSRDNA 3418 ATGYRS 3483 WGQGT 3548 NNTMYLQM TDRLAE QVTVSS NSLKPEDTA PGWVNY VYICGA IV7 3354 RFTVSRDNA 3419 ASGYRS 3484 WGQGT 3549 NNTMYLQM TDRLSE QVTVSS NSLKPEDTA PAWINY VYICGA IV9 3355 RFTVSRDNA 3420 ATGYRS 3485 WGQGT 3550 NNTMYLQM TDRLTE QVTVSS NSLKPEDTA PAWVNY VYICGA IV10 3356 RFTVSRDNA 3421 ATGYRS 3486 WGQGT 3551 NNTMYLQM TDRLSD QVTVSS NSLKPEDTA PNWVNY VYICGA IV11 3357 RFTVSRDNA 3422 ASGYRS 3487 WGQGT 3552 NNTMYLRM TDRLSD QVTVSS NSLKPEDTA AAWINY VYICGA IV12 3358 RFTVSRDNA 3423 ASGYRS 3488 WGQGT 3553 NNTMYLQM TDRLST QVTVSS NSLKPEDTA PEWINY VYICGA IV16 3359 RFTVSRDNG 3424 ASGYRS 3489 WGQGT 3554 NNTMYLQM TDRLSE QVTVSS NSLKPEDTA PGWINY VYICGV IV24 3360 RFTVSRDTA 3425 ATGYRS 3490 WGQGT 3555 NNTMYLEM TDRLST QVTVSS NRLKPDDTA PAWINY VYICGA IV26 3361 RFTVSRDNA 3426 ASGYRS 3491 WGQGT 3556 NNTMYLQM TDRLSD QVTVSS NSLKPEDTA PAWTNY VYICGA IV30 3362 RFTVSRDNA 3427 ASGYRS 3492 WGQGT 3557 NNTMYLQM PDRLSE QVTVSS NSLKPEDTA PEWINY VYICGA IV34 3363 RFTVSRDMA 3428 ASGYRS 3493 WGQGT 3558 NNTMYLQM

TDRLSE QVTVSS NSLKPEDTA PGWVNY VYICGA IV14 3364 RFTISKDNA 3429 DRKTLA 3494 WGQGT 3559 KSTVYLDMN YYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV15 3365 RFTISKDNA 3430 DRKTLT 3495 WGQGT 3560 KSTVYLDMN YYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV17 3366 RFTISKDNA 3431 DRKTLT 3496 WGQGT 3561 KSTVYLDMN FYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV18 3367 RFTISKDNA 3432 DRKTLT 3497 WGQGT 3562 KSTVYLDMN FYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV29 3368 RFTISKDNA 3433 DRKTLT 3498 WGQGT 3563 KSTVYLDMN YYTSRL QVTVSS SLKPEDTAV RSRYEY YYCAA IV31 3369 RFTISKDNA 3434 DGKTLT 3499 WGQGT 3564 KSTVVLDMN FYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV33 3370 RFSISKDLAK 3435 DQKTLT 3500 WGQGT 3565 STVYLDMNS FYTSRL QVTVSS LKPEDTAVY RSRYDY YCAA IV35 3371 RFTISKDNA 3436 DRKTLT 3501 WGQGT 3566 KSTVYLDMN FYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV36 3372 RFTISKDYAK 3437 DQKTLT 3502 WGQGT 3567 STVYLDMNS YYTSRL QVTVSS LKPEDTAVY RSRYDY YCAA IV40 3373 RFTISKDNA 3438 DGKTLT 3503 WGQGT 3568 KRTVYLDMN YYTSRL QVTVSS SLKPEDTAV RSQYDY YYCAA IV42 3374 RFTISKDNA 3439 DRKTLT 3504 WGQGT 3569 KSTVYLDMN FYTSRL QVTVSS SLKPEDTAV RSRYDY YYCAA IV8 3375 RFTISRDNA 3440 HASYDR 3505 WGQGT 3570 RNTVYLQMN MIYSEY QVTVSS RLKSEDSAV KY YYCAA IV21 3376 RFTISRDNA 3441 HANYDR 3506 WGQGT 3571 RDTVYLQMN MINSEY QVTVSS RLNPEDSAV KY YYCAA IV23 3377 RFTISRDNA 3442 HANYDR 3507 WGQGT 3572 RDTVYLQMN MINSEY QVTVSS RLNPEDSAV KY YYCAA IV45 3378 RFTISRDNA 3443 HASYDR 3508 WGQGT 3573 RNTVYLQMN MINSEY QVTVSS RLKPEDSAV KY YYCAA IV47 3379 RFTISRDNA 3444 HANYDR 3509 WGQGT 3574 RNTVLLQMN MINSEY QVTVSS RLKPEDSAV KY YYCAA IV48 3380 RFTISRDNA 3445 HASYDR 3510 WGQGT 3575 RNTVYLQMN MINSEY QVTVSS RLKPEDSAV KY YYCAG IV50 3381 RFTISRDNA 3446 HASYDR 3511 WGQGT 3576 RNTVYLQMN MIYSEY QVTVSS RLKPEDSAV KY YYCAA IV22 3382 RFTISRDNA 3447 DPRADL 3512 WGQGT 3577 KNTLYLQMN VATMTSI QVTVSS SLKPEDTAV RY YYCAI IV37 3383 RFTISRDNA 3448 DPRADL 3513 WGQGT 3578 KNTFYLQMN VATMTSI QVTVSS SLKPEDTAV RY YYCAI IV38 3384 RFTISRDNA 3449 DPRADL 3514 WGQGT 3579 KNTLYLQMN VATMTSI QVTVSS SLKPEDTAV RY YYCAI IV5 3385 RFTISGDNA 3450 MSKPRN 3515 WGQGT 3580 GNTVDLQM LWRTDS QVTVSS NSLKPEDTA YDY VYACAA IV27 3386 RFTISRGNA 3451 MSKPYN 3516 WGQGT 3581 KNTVDLQMN LWRTDS QVTVSS SLKPEDTAV YDY YACAA IV25 3387 RFTISRDNA 3452 ARDPDL 3517 WGQGT 3582 KNTMYLQM YTGQYEY QVTVSS NALKPEDTA VYYCAA IV28 3388 RFTISRDSA 3453 GEGSAN 3518 WGQGT 3583 KNTLYLQMN WGLDF QVTVSS SLKSEDTAV GS YYCAK (“ID” refers to the SEQ ID NO as used herein)

Thus, in the preferred NANOBODIES® (V_{HH} sequences) of the invention, at least one of the CDR1, CDR2 and CDR3 sequences present is suitably chosen from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1; or from the group of CDR1, CDR2 and CDR3 sequences, respectively, that have at least 80%, preferably at least

90%, more preferably at least 95%, even more preferably at least 99% "sequence identity" (as defined herein) with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, that have 3, 2 or only 1 "amino acid difference(s)" (as defined herein) with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1.

In this context, by "suitably chosen" is meant that, as applicable, a CDR1 sequence is chosen from suitable CDR1 sequences (i.e. as defined herein), a CDR2 sequence is chosen from suitable CDR2 sequences (i.e. as defined herein), and a CDR3 sequence is chosen from suitable CDR3 sequence (i.e. as defined herein), respectively. More in particular, the CDR sequences are preferably chosen such that the NANOBODIES® (V_{HH} sequences) of the invention bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein.

In particular, in the preferred NANOBODIES® (V_{HH} sequences) of the invention, at least the CDR3 sequence present is suitably chosen from the group consisting of the CDR3 sequences listed in Table B-1 or from the group of CDR3 sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the CDR3 sequences listed in Table B-1; and/or from the group consisting of the CDR3 sequences that have 3, 2 or only 1 amino acid difference(s) with at least one of the CDR3 sequences listed in Table B-1.

Preferably, in the NANOBODIES® (V_{HH} sequences) of the invention, at least two of the CDR1, CDR2 and CDR3 sequences present are suitably chosen from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1 or from the group consisting of CDR1, CDR2 and CDR3 sequences, respectively, that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, that have 3, 2 or only 1 "amino acid difference(s)" with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1.

In particular, in the NANOBODIES® (V_{HH} sequences) of the invention, at least the CDR3 sequence present is suitably chosen from the group consisting of the CDR3 sequences listed in Table B-1 or from the group of CDR3 sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the CDR3 sequences listed in Table B-1, respectively; and at least one of the CDR1 and CDR2 sequences present is suitably chosen from the group consisting of the

CDR1 and CDR2 sequences, respectively, listed in Table B-1 or from the group of CDR1 and

CDR2 sequences, respectively, that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the CDR1 and CDR2 sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR1 and CDR2 sequences, respectively, that have 3, 2 or only 1 amino acid difference(s) with at least one of the CDR1 and CDR2 sequences, respectively, listed in Table B-1.

Most preferably, in the NANOBODIES® (V_{HH} sequences) of the invention, all three CDR1, CDR2 and CDR3 sequences present are suitably chosen from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1 or from the group of CDR1, CDR2 and CDR3 sequences, respectively, that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, that have 3, 2 or only 1 amino acid difference(s) with at least one of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1.

Even more preferably, in the NANOBODIES® (V_{HH} sequences) of the invention, at least one of the CDR1, CDR2 and CDR3 sequences present is suitably chosen from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1. Preferably, in this aspect, at least one or preferably both of the other two CDR sequences present are suitably chosen from CDR sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the corresponding CDR sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR sequences that have 3, 2 or only 1 amino acid difference(s) with at least one of the corresponding sequences, respectively, listed in Table B-1.

In particular, in the NANOBODIES® (V_{HH} sequences) of the invention, at least the CDR3 sequence present is suitably chosen from the group consisting of the CDR3 listed in Table B-1. Preferably, in this aspect, at least one and preferably both of the CDR1 and CDR2 sequences present are suitably chosen from the groups of CDR1 and CDR2 sequences, respectively, that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the CDR1 and CDR2 sequences, respectively, listed in Table B-1; and/or from the group consisting of the CDR1 and CDR2 sequences, respectively, that have 3, 2 or only 1 amino acid difference(s) with at least one of the CDR1 and CDR2 sequences, respectively, listed in Table B-1.

Even more preferably, in the NANOBODIES® (V_{HH} sequences) of the invention, at least two of the CDR1, CDR2 and CDR3 sequences present are suitably chosen from the group

consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1. Preferably, in this aspect, the remaining CDR sequence present is suitably chosen from the group of CDR sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the corresponding CDR sequences listed in Table B-1; and/or from the group consisting of CDR sequences that have 3, 2 or only 1 amino acid difference(s) with at least one of the corresponding sequences listed in Table B-1.

In particular, in the NANOBODIES® (V_{HH} sequences) of the invention, at least the CDR3 sequence is suitably chosen from the group consisting of the CDR3 sequences listed in Table B-1, and either the CDR1 sequence or the CDR2 sequence is suitably chosen from the group consisting of the CDR1 and CDR2 sequences, respectively, listed in Table B-1. Preferably, in this aspect, the remaining CDR sequence present is suitably chosen from the group of CDR sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with at least one of the corresponding CDR sequences listed in Table B-1; and/or from the group consisting of CDR sequences that have 3, 2 or only 1 amino acid difference(s) with the corresponding CDR sequences listed in Table B-1.

Even more preferably, in the NANOBODIES® (V_{HH} sequences) of the invention, all three CDR1, CDR2 and CDR3 sequences present are suitably chosen from the group consisting of the CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1.

Also, generally, the combinations of CDR's listed in Table B-1 (i.e. those mentioned on the same line in Table B-1) are preferred. Thus, it is generally preferred that, when a CDR in a NANOBODY® (V_{HH} sequence) of the invention is a CDR sequence mentioned in Table B-1 or is suitably chosen from the group of CDR sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with a CDR sequence listed in Table B-1; and/or from the group consisting of CDR sequences that have 3, 2 or only 1 amino acid difference(s) with a CDR sequence listed in Table B-1, that at least one and preferably both of the other CDR's are suitably chosen from the CDR sequences that belong to the same combination in Table B-1 (i.e. mentioned on the same line in Table B-1) or are suitably chosen from the group of CDR sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the CDR sequence(s) belonging to the same combination and/or from the group consisting of CDR sequences that have 3, 2 or only 1 amino acid difference(s) with the CDR sequence(s) belonging to the same combination. The other preferences indicated in the above paragraphs also apply to the combinations of CDR's mentioned in Table B-1.

Thus, by means of non-limiting examples, a NANOBODY® (V_{HH} sequence) of the invention

can for example comprise a CDR1 sequence that has more than 80% sequence identity with one of the CDR1 sequences mentioned in Table B-1, a CDR2 sequence that has 3, 2 or 1 amino acid difference with one of the CDR2 sequences mentioned in Table B-1 (but belonging to a different combination), and a CDR3 sequence.

Some preferred NANOBODIES® (V_{HH} sequences) of the invention may for example comprise: (1) a CDR1 sequence that has more than 80% sequence identity with one of the CDR1 sequences mentioned in Table B-1; a CDR2 sequence that has 3, 2 or 1 amino acid difference with one of the CDR2 sequences mentioned in Table B-1 (but belonging to a different combination); and a CDR3 sequence that has more than 80% sequence identity with one of the CDR3 sequences mentioned in Table B-1 (but belonging to a different combination); or (2) a CDR1 sequence that has more than 80% sequence identity with one of the CDR1 sequences mentioned in Table B-1; a CDR2 sequence, and one of the CDR3 sequences listed in Table B-1; or (3) a CDR1 sequence; a CDR2 sequence that has more than 80% sequence identity with one of the CDR2 sequence listed in Table B-1; and a CDR3 sequence that has 3, 2 or 1 amino acid differences with the CDR3 sequence mentioned in Table B-1 that belongs to the same combination as the CDR2 sequence.

Some particularly preferred NANOBODIES® (V_{HH} sequences) of the invention may for example comprise: (1) a CDR1 sequence that has more than 80% sequence identity with one of the CDR1 sequences mentioned in Table B-1; a CDR2 sequence that has 3, 2 or 1 amino acid difference with the CDR2 sequence mentioned in Table B-1 that belongs to the same combination; and a CDR3 sequence that has more than 80% sequence identity with the CDR3 sequence mentioned in Table B-1 that belongs to the same combination; (2) a CDR1 sequence; a CDR 2 listed in Table B-1 and a CDR3 sequence listed in Table B-1 (in which the CDR2 sequence and CDR3 sequence may belong to different combinations).

Some even more preferred NANOBODIES® (V_{HH} sequences) of the invention may for example comprise: (1) a CDR1 sequence that has more than 80% sequence identity with one of the CDR1 sequences mentioned in Table B-1; the CDR2 sequence listed in Table B-1 that belongs to the same combination; and a CDR3 sequence mentioned in Table B-1 that belongs to a different combination; or (2) a CDR1 sequence mentioned in Table B-1; a CDR2 sequence that has 3, 2 or 1 amino acid differences with the CDR2 sequence mentioned in Table B-1 that belongs to the same combination; and a CDR3 sequence that has more than 80% sequence identity with the CDR3 sequence listed in Table B-1 that belongs to the same or a different combination.

Particularly preferred NANOBODIES® (V_{HH} sequences) of the invention may for example comprise a CDR1 sequence mentioned in Table B-1, a CDR2 sequence that has more than 80% sequence identity with the CDR2 sequence mentioned in Table B-1 that belongs to the same combination; and the CDR3 sequence mentioned in Table B-1 that belongs to the

same combination.

In the most preferred NANOBODIES® (V_{HH} sequences) of the invention, the CDR1, CDR2 and CDR3 sequences present are suitably chosen from one of the combinations of CDR1, CDR2 and CDR3 sequences, respectively, listed in Table B-1.

According to another preferred, but non-limiting aspect of the invention (a) CDR1 has a length of between 1 and 12 amino acid residues, and usually between 2 and 9 amino acid residues, such as 5, 6 or 7 amino acid residues; and/or (b) CDR2 has a length of between 13 and 24 amino acid residues, and usually between 15 and 21 amino acid residues, such as 16 and 17 amino acid residues; and/or (c) CDR3 has a length of between 2 and 35 amino acid residues, and usually between 3 and 30 amino acid residues, such as between 6 and 23 amino acid residues.

In another preferred, but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) in which the CDR sequences (as defined herein) have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

Generally, NANOBODIES® (V_{HH} sequences) with the above CDR sequences may be as further described herein, and preferably have framework sequences that are also as further described herein. Thus, for example and as mentioned herein, such NANOBODIES® (V_{HH} sequences) may be naturally occurring NANOBODIES® (V_{HH} sequences) (from any suitable species), naturally occurring V_{HH} sequences (i.e. from a suitable species of Camelid) or synthetic or semi-synthetic amino acid sequences or NANOBODIES® (V_{HH} sequences), including but not limited to partially humanized NANOBODIES® (V_{HH} sequences) or V_{HH} sequences, fully humanized NANOBODIES® (V_{HH} sequences) or V_{HH} sequences, camelized heavy chain variable domain sequences, as well as NANOBODIES® (V_{HH} sequences) that have been obtained by the techniques mentioned herein.

Thus, in one specific, but non-limiting aspect, the invention relates to a humanized NANOBODY® (V_{HH} sequence), which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which CDR1 to CDR3 are as defined herein and in which said humanized NANOBODY® (V_{HH} sequence) comprises at least one humanizing substitution (as defined herein), and in particular at least one humanizing substitution in at least one of its framework sequences (as defined herein).

In another preferred, but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) in which the CDR sequences have at least 70% amino acid identity, preferably at

least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said NANOBODY® (V_{HH} sequence) and one or more of the sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Such NANOBODIES® (V_{HH} sequences) can be as further described herein.

In another preferred, but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) with an amino acid sequence that is chosen from the group consisting of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) or from the group consisting of amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

Another preferred, but non-limiting aspect of the invention relates to humanized variants of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), that comprise, compared to the corresponding native V_{HH} sequence, at least one humanizing substitution (as defined herein), and in particular at least one humanizing substitution in at least one of its framework sequences (as defined herein). Some preferred, but non-limiting examples of such humanized variants are the humanized NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 2999 to 3015 (see Table A-8). Thus, the invention also relates to a humanized NANOBODY® (V_{HH} sequence) with an amino acid sequence that is chosen from the group consisting of SEQ ID NO's: 2999 to 3015 (see Table A-8) or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 2999 to 3015 (see Table A-8) (in which amino acid sequences that are chosen from the latter group of amino acid sequences may contain a greater number or a smaller number of humanizing substitutions compared to the corresponding sequence of SEQ ID NO's: 2999 to 3015 (see Table A-8), as long as they retain at least one of the humanizing substitutions present in the corresponding sequence of SEQ ID NO's: 2999 to 3015 (see Table A-8)).

The polypeptides of the invention comprise or essentially consist of at least one NANOBODY® (V_{HH} sequence) of the invention. Some preferred, but non-limiting examples

of polypeptides of the invention are given in SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591 (see Table A-2, Table A-4, Table A-5, Table A-6, Table A-9, Table A-10).

It will be clear to the skilled person that the NANOBODIES® (V_{HH} sequences) that are mentioned herein as "preferred" (or "more preferred", "even more preferred", etc.) are also preferred (or more preferred, or even more preferred, etc.) for use in the polypeptides described herein. Thus, polypeptides that comprise or essentially consist of one or more "preferred" NANOBODIES® (V_{HH} sequences) of the invention will generally be preferred, and polypeptides that comprise or essentially consist of one or more "more preferred" NANOBODIES® (V_{HH} sequences) of the invention will generally be more preferred, etc. Generally, proteins or polypeptides that comprise or essentially consist of a single NANOBODY® (V_{HH} sequence) (such as a single NANOBODY® (V_{HH} sequence) of the invention) will be referred to herein as "monovalent" proteins or polypeptides or as "monovalent constructs". Proteins and polypeptides that comprise or essentially consist of two or more NANOBODIES® (V_{HH} sequences) (such as at least two NANOBODIES® (V_{HH} sequences) of the invention or at least one NANOBODY® (V_{HH} sequence) of the invention and at least one other NANOBODY® (V_{HH} sequence)) will be referred to herein as "multivalent" proteins or polypeptides or as "multivalent constructs", and these may provide certain advantages compared to the corresponding monovalent NANOBODIES® (V_{HH} sequences) of the invention. Some non-limiting examples of such multivalent constructs will become clear from the further description herein.

According to one specific, but non-limiting aspect, a polypeptide of the invention comprises or essentially consists of at least two NANOBODIES® (V_{HH} sequences) of the invention, such as two or three NANOBODIES® (V_{HH} sequences) of the invention. As further described herein, such multivalent constructs can provide certain advantages compared to a protein or polypeptide comprising or essentially consisting of a single NANOBODY® (V_{HH} sequence) of the invention, such as a much improved avidity for an envelope protein of a virus. Such multivalent constructs or polypeptides will be clear to the skilled person based on the disclosure herein.

In a preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein. The polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. In a preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein.

Generally, such a bivalent polypeptide of the invention may contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein). Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding sites).

In another preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, The polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein. In a preferred aspect, the polypeptides of the invention are directed against region aa 423-436 of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein.

Generally, such a bivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the 101F binding sites).

In another preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the

invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the sialic acid binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the VN04-2 binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a bivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb C179 binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are bivalent and are directed against the MAb 8-2 binding site on the G envelope protein of rabies and/or capable of competing with MAb 8-2 for binding to the G envelope protein.

Generally, such a bivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein. Generally, such bivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein

also apply to these bivalent polypeptides of the invention (for example, these bivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb 8-2 binding site).

In a preferred aspect, the polypeptides of the invention are capable of binding to two or more different antigenic determinants, epitopes, parts, domains of an envelope protein of a virus. In this context, the polypeptides of the invention are also referred to as "multiparatopic" (such as e.g. "biparatopic" or "triparatopic", etc.) polypeptides. The multiparatopic polypeptides of the invention can be directed against any antigenic determinants, epitopes, parts, and/or domains of the envelope protein of a virus.

For example, and generally, a biparatopic polypeptide of the invention may comprise at least one NANOBODY® (V_{HH} sequence) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain (in which said NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as further described herein). Preferably, such a biparatopic polypeptide of the invention is further such that, when it binds to the viral envelope protein, it is capable of simultaneously binding to the first antigenic determinant, epitope, part or domain (i.e. via the at least one NANOBODY® (V_{HH} sequence) of the invention capable of binding to said first antigenic determinant, epitope, part or domain) and binding to said second antigenic determinant, epitope, part or domain (i.e. via the at least one NANOBODY® (V_{HH} sequence) of the invention capable of binding to said second antigenic determinant, epitope, part or domain). Examples of such biparatopic polypeptides of the invention will become clear from the further description herein. Also, a triparatopic polypeptide of the invention may comprise at least one further NANOBODY® (V_{HH} sequence) of the invention directed against a third antigenic determinant, epitope, part or domain of the viral envelope protein (different from both the first and second antigenic determinant, epitope, part or domain), and generally multiparatopic polypeptides of the invention may contain at least two NANOBODIES® (V_{HH} sequences) of the invention directed against at least two different antigenic determinants, epitopes, parts or domains of the viral envelope protein. Generally, such biparatopic, triparatopic and multiparatopic polypeptides of the invention may be as further described herein.

In a preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein, as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. The polypeptides of the invention may be directed against antigenic site II (also

referred to as site A) of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein. In a preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against at least one other antigenic determinant, epitope, part or domain on the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the at least one other antigenic determinant, epitope, part or domain on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as against at least one other antigenic determinant on the RSV F protein. The polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein. In a preferred aspect, the polypeptides of the invention are directed against region aa 423-436 of the RSV F protein as well as against at least one other antigenic determinant on the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise

suitable linkers; are preferably such that they can simultaneously bind the 101F binding site and the at least one other antigenic determinant, epitope, part or domain on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic and are at least directed against the Synagis® binding site on the RSV F protein as well as against the 101F binding site on the RSV F protein. The polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein. The polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein. The polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein. In another preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against region aa 423-436 of the RSV F protein. In another preferred aspect, the polypeptides of the invention are directed against region aa 423-436 of the RSV F protein. In another preferred aspect, the polypeptides of the invention are directed against antigenic site II (also referred to as site A) of the RSV F protein as well as against the region aa 423-436 of the RSV F protein. In another preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein as well as against antigenic site IV-VI of the RSV F protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity

of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis® and/or 101F.

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic with both paratopes directed against the Synagis® binding site on the RSV F protein. The polypeptides of the invention may be directed against antigenic site II (also referred to as site A) of the RSV F protein (one paratope or both paratopes). In a preferred aspect, the polypeptides of the invention are directed against region aa 250-275 of the RSV F protein (one paratope or both paratopes).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic with both paratopes directed against the 101F binding site on the RSV F protein. The polypeptides of the invention may be directed against antigenic site IV-VI of the RSV F protein (one paratope or both paratopes). In a preferred aspect, the polypeptides of the invention are directed against the region aa 423-436 of the RSV F protein (one paratope or both paratopes).

Again, the above biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind both binding sites).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein

also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the sialic acid binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the VN04-2 binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as VN04-2.

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as against at least one other antigenic determinant, epitope, part or domain on the

hemagglutinin H5 envelope protein of influenza virus.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb C179 binding site and the at least one other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb C179.

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are directed against the MAb 8-2 binding site on the G envelope protein of rabies and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as against at least one other antigenic determinant, epitope, part or domain on the G envelope protein.

Generally, such a biparatopic (or multiparatopic) polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as at least one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to at least one other antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such biparatopic (or multiparatopic) polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these biparatopic (or multiparatopic) polypeptides of the invention (for example, these biparatopic and multiparatopic polypeptides of the invention may comprise suitable

linkers; and are preferably such that they can simultaneously bind the MAb 8-2 binding site and the at least one other antigenic determinant, epitope, part or domain on the G envelope protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are biparatopic (or multiparatopic) and are at least capable, upon binding to the G envelope protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb 8-2.

In another preferred aspect, the polypeptides of the invention are capable of binding to three (different) antigenic determinants, epitopes, parts, domains of an envelope protein of a virus. In this context, the polypeptides of the invention are also referred to as "trivalent" (such as e.g. "trivalent triparatopic" or "trivalent biparatopic", "trivalent monoparatopic", etc.) amino acid sequences and polypeptides. The trivalent polypeptides of the invention can be directed against any antigenic determinants, epitopes, parts, and/or domains of the envelope protein of the virus.

For example, and generally, a trivalent polypeptide of the invention may comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the same antigenic determinant, epitope, part or domain of the viral envelope protein (in which NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as further described herein). A trivalent polypeptide of the invention may comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain (in which said NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent biparatopic". A trivalent polypeptide of the invention may comprise one NANOBODY® (V_{HH} sequence) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein different from the first antigenic determinant, epitope, part or domain and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a third antigenic determinant, epitope, part or domain of the viral envelope protein different from the first and the second antigenic determinant, epitope, part or domain (in which said NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as

further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent triparatopic". A trivalent polypeptide of the invention may comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein. Such a trivalent polypeptide of the invention may also be referred to as "trivalent bispecific". A trivalent polypeptide of the invention may also comprise one NANOBODY® (V_{HH} sequence) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of the same viral envelope protein different from the first antigenic determinant, epitope, part or domain and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a third antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein (in which said NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent trispecific". A trivalent polypeptide of the invention may also comprise one NANOBODY® (V_{HH} sequence) of the invention directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, at least one NANOBODY® (V_{HH} sequence) of the invention directed against a second antigenic determinant, epitope, part or domain of a viral envelope protein different from the first viral envelope protein and at least one NANOBODY® (V_{HH} sequence) of the invention directed against a third antigenic determinant, epitope, part or domain of a viral envelope protein different from the first and the second viral envelope protein (in which said NANOBODIES® (V_{HH} sequences) may be suitably linked, for example via a suitable linker as further described herein). Such a trivalent polypeptide of the invention may also be referred to as "trivalent trispecific".

Preferably, such a trivalent polypeptide of the invention is further such that, when it binds to the viral envelope protein, it is capable of simultaneously binding to the first antigenic determinant, epitope, part or domain (i.e. via the at least one NANOBODY® (V_{HH} sequence) of the invention capable of binding to said first antigenic determinant, epitope, part or domain), binding to said second antigenic determinant, epitope, part or domain (i.e. via the at least one NANOBODY® (V_{HH} sequence) of the invention capable of binding to said second antigenic determinant, epitope, part or domain) and binding to said third antigenic determinant, epitope, part or domain (i.e. via the at least one NANOBODY® (V_{HH} sequence) of the invention capable of binding to said third antigenic determinant, epitope, part or domain). Examples of such trivalent polypeptides of the invention will become clear from the further description herein. Generally, such trivalent polypeptides of the invention may

be as further described herein.

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the two other antigenic determinants, epitopes, parts or domains on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant,

epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein. The polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the polypeptides of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis®.

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred

aspect, the polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the 101F binding site and the two other antigenic determinants, epitopes, parts or domains on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the 101F binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed

against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. polypeptides of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the polypeptides of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the 101F binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as 101F.

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. The NANOBODIES® (V_{HH} sequences) of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the NANOBODIES® (V_{HH} sequences) of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. The NANOBODIES® (V_{HH} sequences) of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, NANOBODIES® (V_{HH} sequences) of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the Synagis® binding site on the RSV F protein

and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein. The NANOBODIES® (V_{HH} sequences) of the invention that are directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the NANOBODIES® (V_{HH} sequences) of the invention that are directed against the Synagis® binding site on the RSV F protein are directed against region aa 250-275 of the RSV F protein. The NANOBODIES® (V_{HH} sequences) of the invention that are directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the NANOBODIES® (V_{HH} sequences) of the invention that are directed against the 101F binding site on the RSV F protein are directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein). Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise

suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site and the 101F binding site on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis for binding to the RSV F protein, one NANOBODY® (V_{HH} sequence) of the invention directed against the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. The NANOBODY® (V_{HH} sequence) of the invention that is directed against the Synagis® binding site on the RSV F protein may be directed against antigenic site II (also referred to as site A) of the RSV F protein. In a preferred aspect, the NANOBODY® (V_{HH} sequence) of the invention that is directed against the Synagis® binding site on the RSV F protein may be directed against region aa 250-275 of the RSV F protein. The NANOBODY® (V_{HH} sequence) of the invention that is directed against the 101F binding site on the RSV F protein may be directed against antigenic site IV-VI of the RSV F protein. In a preferred aspect, the NANOBODY® (V_{HH} sequence) of the invention that is directed against the 101F binding site on the RSV F protein may be directed against region aa 423-436 of the RSV F protein. Generally, such a trivalent polypeptide of the invention will contain one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the Synagis® binding site on the RSV F protein and/or capable of competing with Synagis® for binding to the RSV F protein (and in particular against antigenic site II (also referred to as site A) of the RSV F protein and more preferably against region aa 250-275 of the RSV F protein), one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the 101F binding site on the RSV F protein and/or capable of competing with 101F for binding to the RSV F protein (and in particular against antigenic site IV-VI of the RSV F protein and more preferably against region aa 423-436 of the RSV F protein), as well as one further NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the RSV F protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the Synagis® binding site, the 101F binding site and the other antigenic determinant, epitope, part or domain on the RSV F protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and are at least capable, upon binding to the RSV F protein, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined

herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as Synagis® and/or 101F.

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the sialic acid binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent

polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the sialic acid binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the sialic acid binding site).

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the VN04-2 binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are

trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the VN04-2 binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the VN04-2 binding site).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as VN04-2.

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb C179 binding site and the two other antigenic determinants, epitopes, parts or domains on the hemagglutinin H5 envelope protein of influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus, as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb C179 binding site and the other antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of

influenza virus).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb C179 binding site).

In another preferred, but non-limiting aspect, the amino acid sequences and (in particular) polypeptides of the invention are trivalent and are at least capable, upon binding to the hemagglutinin H5 envelope protein of influenza virus, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb C179.

In a preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise one NANOBODY® (V_{HH} sequence) of the invention directed against the MAb 8-2 binding site on the G envelope protein of rabies and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as two NANOBODIES® (V_{HH} sequences) of the invention directed against another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain at least one NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as two further NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to two other antigenic determinants, epitopes, parts or domains on the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind

the MAb 8-2 binding site and the two other antigenic determinants, epitopes, parts or domains on the G envelope protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise two NANOBODIES® (V_{HH} sequences) of the invention directed against the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as NANOBODY® (V_{HH} sequence) of the invention directed against another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain two NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein, as well as one further NANOBODY® (V_{HH} sequence) of the invention that is capable of binding to another antigenic determinant, epitope, part or domain on the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb 8-2 binding site and the other antigenic determinant, epitope, part or domain on the G envelope protein).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and comprise three NANOBODIES® (V_{HH} sequences) of the invention directed against the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein. Generally, such a trivalent polypeptide of the invention will contain three NANOBODIES® (V_{HH} sequences) of the invention that are capable of binding to the MAb 8-2 binding site on the G envelope protein and/or capable of competing with MAb 8-2 for binding to the G envelope protein. Generally, such trivalent polypeptides of the invention may be as further described herein, and the various preferred aspects of the invention as described herein also apply to these trivalent polypeptides of the invention (for example, these trivalent polypeptides of the invention may comprise suitable linkers; and are preferably such that they can simultaneously bind the MAb 8-2 binding site).

In another preferred, but non-limiting aspect, the polypeptides of the invention are trivalent and are at least capable, upon binding to the G envelope protein of rabies, to neutralize a virus (as defined herein); to modulate, reduce and/or inhibit the infectivity of a virus (as defined herein); to modulate and in particular inhibit and/or prevent viral entry (as further defined herein) in a target host cell; and/or to modulate and in particular inhibit and/or prevent viral replication (as further defined herein) in a target host cell via the same mechanism of action as MAb 8-2.

Preferred bivalent and trivalent polypeptides of the invention are given in Tables C-6, Table A-2, Table A-4, Table A-5, Table A-6, Table A-9 and Table A-10.

Preferred, but non-limiting examples of multivalent (bivalent and trivalent) NANOBODY® (V_{HH} sequence) constructs are the polypeptides of SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591.

According to another specific, but non-limiting aspect, a polypeptide of the invention comprises or essentially consists of at least one NANOBODY® (V_{HH} sequence) of the invention and at least one other binding unit (i.e. directed against another epitope, antigen, target, protein or polypeptide), which is preferably also a NANOBODY® (V_{HH} sequence). Such proteins or polypeptides are also referred to herein as "multispecific" proteins or polypeptides or as "multispecific constructs", and these may provide certain advantages compared to the corresponding monovalent NANOBODIES® (V_{HH} sequences) of the invention (as will become clear from the further discussion herein of some preferred, but-nonlimiting multispecific constructs).

According to yet another specific, but non-limiting aspect, a polypeptide of the invention comprises or essentially consists of at least one NANOBODY® (V_{HH} sequence) of the invention, optionally one or more further NANOBODIES® (V_{HH} sequences), and at least one other amino acid sequence (such as a protein or polypeptide) that confers at least one desired property to the NANOBODY® (V_{HH} sequence) of the invention and/or to the resulting fusion protein. Again, such fusion proteins may provide certain advantages compared to the corresponding monovalent NANOBODIES® (V_{HH} sequences) of the invention. Some non-limiting examples of such amino acid sequences and of such fusion constructs will become clear from the further description herein.

It is also possible to combine two or more of the above aspects, for example to provide a trivalent bispecific construct comprising two NANOBODIES® (V_{HH} sequences) of the invention and one other NANOBODY® (V_{HH} sequence), and optionally one or more other amino acid sequences. Further non-limiting examples of such constructs, as well as some constructs that are particularly preferred within the context of the present invention, will become clear from the further description herein.

In the above constructs, the one or more NANOBODIES® (V_{HH} sequences) and/or other amino acid sequences may be directly linked to each other and/or suitably linked to each other via one or more linker sequences. Some suitable but non-limiting examples of such linkers will become clear from the further description herein.

In one specific aspect of the invention, a NANOBODY® (V_{HH} sequence) of the invention or a compound, construct or polypeptide of the invention comprising at least one NANOBODY® (V_{HH} sequence) of the invention may have an increased half-life, compared to the

corresponding amino acid sequence or NANOBODY® (V_{HH} sequence) of the invention. Some preferred, but non-limiting examples of such NANOBODIES® (V_{HH} sequences), compounds and polypeptides will become clear to the skilled person based on the further disclosure herein, and for example comprise NANOBODIES® (V_{HH} sequences) sequences or polypeptides of the invention that have been chemically modified to increase the half-life thereof (for example, by means of pegylation); amino acid sequences or NANOBODIES® (V_{HH} sequences) of the invention that comprise at least one additional binding site for binding to a serum protein (such as serum albumin, see for example EP 0 368 684 B1, page 4); or polypeptides of the invention that comprise at least one NANOBODY® (V_{HH} sequence) of the invention that is linked to at least one moiety (and in particular at least one amino acid sequence) that increases the half-life of the NANOBODY® (V_{HH} sequence) of the invention. Examples of polypeptides of the invention that comprise such half-life extending moieties or amino acid sequences will become clear to the skilled person based on the further disclosure herein; and for example include, without limitation, polypeptides in which the one or more NANOBODIES® (V_{HH} sequences) of the invention are suitable linked to one or more serum proteins or fragments thereof (such as serum albumin or suitable fragments thereof) or to one or more binding units that can bind to serum proteins (such as, for example, NANOBODIES® (V_{HH} sequences) or (single) domain antibodies that can bind to serum proteins such as serum albumin, serum immunoglobulins such as IgG, or transferrin); polypeptides in which a NANOBODY® (V_{HH} sequence) of the invention is linked to an Fc portion (such as a human Fc) or a suitable part or fragment thereof; or polypeptides in which the one or more NANOBODIES® (V_{HH} sequences) of the invention are suitable linked to one or more small proteins or peptides that can bind to serum proteins (such as, without limitation, the proteins and peptides described in WO 91/01743, WO 01/45746, WO 02/076489 and WO 08/068280).

Again, as will be clear to the skilled person, such NANOBODIES® (V_{HH} sequences), compounds, constructs or polypeptides may contain one or more additional groups, residues, moieties or binding units, such as one or more further amino acid sequences and in particular one or more additional NANOBODIES® (V_{HH} sequences) (i.e. not directed against an envelope protein of a virus), so as to provide a tri- of multispecific NANOBODY® (V_{HH} sequence) construct.

Generally, the NANOBODIES® (V_{HH} sequences) of the invention (or compounds, constructs or polypeptides comprising the same) with increased half-life preferably have a half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding NANOBODY® (V_{HH} sequence) of the invention per se. For example, the NANOBODIES® (V_{HH} sequences), compounds, constructs or polypeptides of the invention with increased half-life may have a half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more

than 24, 48 or 72 hours, compared to the corresponding NANOBODY® (V_{HH} sequence) of the invention per se.

In a preferred, but non-limiting aspect of the invention, such NANOBODIES® (V_{HH} sequences), compound, constructs or polypeptides of the invention exhibit a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more. For example, compounds or polypeptides of the invention may have a half-life of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

In another one aspect of the invention, a polypeptide of the invention comprises one or more (such as two or preferably one) NANOBODIES® (V_{HH} sequences) of the invention linked (optionally via one or more suitable linker sequences) to one or more (such as two and preferably one) amino acid sequences that allow the resulting polypeptide of the invention to cross the blood brain barrier. In particular, said one or more amino acid sequences that allow the resulting polypeptides of the invention to cross the blood brain barrier may be one or more (such as two and preferably one) NANOBODIES® (V_{HH} sequences), such as the NANOBODIES® (V_{HH} sequences) described in WO 02/057445, of which FC44 (SEQ ID NO: 189 of WO 06/040153) and FC5 (SEQ ID NO: 190 of WO 06/040154) are preferred examples.

In particular, polypeptides comprising one or more NANOBODIES® (V_{HH} sequences) of the invention are preferably such that they:

- bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles);
  and/or such that they:
- bind to an envelope protein of a virus with a k_{on}-rate of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$;
  and/or such that they:
- bind to an envelope protein of a virus with a k_{off} rate between 1 s^{-1} ($t_{1/2}$=0.69 s) and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and

10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, a polypeptide that contains only one amino acid sequence or NANOBODY® (V_{HH} sequence) of the invention is preferably such that it will bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. In this respect, it will be clear to the skilled person that a polypeptide that contains two or more NANOBODIES® (V_{HH} sequences) of the invention may bind to an envelope protein of a virus with an increased avidity, compared to a polypeptide that contains only one amino acid sequence or NANOBODY® (V_{HH} sequence) of the invention.

Some preferred IC_{50} values for binding of the amino acid sequences, NANOBODIES® (V_{HH} sequences) or polypeptides of the invention to an envelope protein of a virus will become clear from the further description and examples herein.

Other polypeptides according to this preferred aspect of the invention may for example be chosen from the group consisting of amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more "sequence identity" (as defined herein) with one or more of the amino acid sequences of SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591 (see Table A-2, Table A-4, Table A-5, Table A-6, Table A-9 and Table A-10), in which the NANOBODIES® (V_{HH} sequences) comprised within said amino acid sequences are preferably as further defined herein.

Another aspect of this invention relates to a nucleic acid that encodes an amino acid sequence of the invention (such as a NANOBODY® (V_{HH} sequence) of the invention) or a polypeptide of the invention comprising the same. Again, as generally described herein for the nucleic acids of the invention, such a nucleic acid may be in the form of a genetic construct, as defined herein.

In another aspect, the invention relates to host or host cell that expresses or that is capable of expressing an amino acid sequence (such as a NANOBODY® (V_{HH} sequence)) of the invention and/or a polypeptide of the invention comprising the same; and/or that contains a nucleic acid of the invention. Some preferred but non-limiting examples of such hosts or host cells will become clear from the further description herein.

Another aspect of the invention relates to a product or composition containing or comprising at least one amino acid sequence or NANOBODY® (V_{HH} sequence) of the invention, at least one polypeptide of the invention and/or at least one nucleic acid of the invention, and optionally one or more further components of such compositions known per se, i.e. depending on the intended use of the composition. Such a product or composition may for example be a pharmaceutical composition (as described herein), a veterinary

composition or a product or composition for diagnostic use (as also described herein). Some preferred but non-limiting examples of such products or compositions will become clear from the further description herein.

The invention further relates to methods for preparing or generating the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein. Some preferred but non-limiting examples of such methods will become clear from the further description herein.

The invention further relates to applications and uses of the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein, as well as to methods for the prevention and/or treatment for diseases and disorders associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor. Some preferred but non-limiting applications and uses will become clear from the further description herein.

Other aspects, embodiments, advantages and applications of the invention will also become clear from the further description hereinbelow.

Generally, it should be noted that the term NANOBODY® (V_{HH} sequence) as used herein in its broadest sense is not limited to a specific biological source or to a specific method of preparation. For example, as will be discussed in more detail below, the NANOBODIES® (V_{HH} sequences) of the invention can generally be obtained by any of the techniques (1) to (8) mentioned on pages 61 and 62 of WO 08/020079, or any other suitable technique known per se. One preferred class of NANOBODIES® (V_{HH} sequences) correspond to the V_{HH} domains of naturally occurring heavy chain antibodies directed against an envelope protein of a virus. As further described herein, such V_{HH} sequences can generally be generated or obtained by suitably immunizing a species of Camelid with an envelope protein of a virus (i.e. so as to raise an immune response and/or heavy chain antibodies directed against an envelope protein of a virus), by obtaining a suitable biological sample from said Camelid (such as a blood sample, serum sample or sample of B-cells), and by generating V_{HH} sequences directed against an envelope protein of a virus, starting from said sample, using any suitable technique known per se. Such techniques will be clear to the skilled person and/or are further described herein.

Alternatively, such naturally occurring V_{HH} domains against an envelope protein of a virus, can be obtained from naïve libraries of Camelid V_{HH} sequences, for example by screening such a library using an envelope protein of a virus, or at least one part, fragment, antigenic determinant or epitope thereof using one or more screening techniques known per se. Such libraries and techniques are for example described in WO 99/37681, WO 01/90190, WO 03/025020 and WO 03/035694. Alternatively, improved synthetic or semi-synthetic libraries derived from naïve V_{HH} libraries may be used, such as V_{HH} libraries obtained from

naïve V_{HH} libraries by techniques such as random mutagenesis and/or CDR shuffling, as for example described in WO 00/43507.

Thus, in another aspect, the invention relates to a method for generating NANOBODIES® (V_{HH} sequences), that are directed against an envelope protein of a virus. In one aspect, said method at least comprises the steps of:

- a) providing a set, collection or library of NANOBODY® (V_{HH} sequence) sequences; and
- b) screening said set, collection or library of NANOBODY® (V_{HH} sequence) sequences for NANOBODY® (V_{HH} sequence) sequences that can bind to and/or have affinity for an envelope protein of a virus;
  and
- c) isolating the amino acid sequence(s) that can bind to and/or have affinity for an envelope protein of a virus.

In such a method, the set, collection or library of NANOBODY® (V_{HH} sequence) sequences may be a naïve set, collection or library of NANOBODY® (V_{HH} sequence) sequences; a synthetic or semi-synthetic set, collection or library of NANOBODY® (V_{HH} sequence) sequences; and/or a set, collection or library of NANOBODY® (V_{HH} sequence) sequences that have been subjected to affinity maturation.

In a preferred aspect of this method, the set, collection or library of NANOBODY® (V_{HH} sequence) sequences may be an immune set, collection or library of NANOBODY® (V_{HH} sequence) sequences, and in particular an immune set, collection or library of V_{HH} sequences, that have been derived from a species of Camelid that has been suitably immunized with an envelope protein of a virus or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

In the above methods, the set, collection or library of NANOBODY® (V_{HH} sequence) or V_{HH} sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) NANOBODY® (V_{HH} sequence) sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to WO 03/054016 and to the review by Hoogenboom in Nature Biotechnology, 23, 9, 1105-1116 (2005).

In another aspect, the method for generating NANOBODY® (V_{HH} sequence) sequences comprises at least the steps of:

- a) providing a collection or sample of cells derived from a species of Camelid that express immunoglobulin sequences;
- b) screening said collection or sample of cells for (i) cells that express an immunoglobulin sequence that can bind to and/or have affinity for an envelope protein of a virus; and (ii) cells that express heavy chain antibodies, in which substeps (i) and (ii) can be performed essentially as a single screening step or in any suitable order as two separate screening steps, so as to provide at least one cell that expresses a heavy chain antibody that can bind to and/or has affinity for an envelope protein of a virus;
  and
- c) either (i) isolating from said cell the V_{HH} sequence present in said heavy chain antibody; or (ii) isolating from said cell a nucleic acid sequence that encodes the V_{HH} sequence present in said heavy chain antibody, followed by expressing said V_{HH} domain.

In the method according to this aspect, the collection or sample of cells may for example be a collection or sample of B-cells. Also, in this method, the sample of cells may be derived from a Camelid that has been suitably immunized with an envelope protein of a virus or a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

The above method may be performed in any suitable manner, as will be clear to the skilled person. Reference is for example made to EP 0 542 810, WO 05/19824, WO 04/051268 and WO 04/106377. The screening of step b) is preferably performed using a flow cytometry technique such as FACS. For this, reference is for example made to Lieby et al., Blood, Vol. 97, No. 12, 3820. Particular reference is made to the so-called "NANOCLONE®" technique described in International application WO 06/079372 by Ablynx N.V.

In another aspect, the method for generating an amino acid sequence directed against an envelope protein of a virus may comprise at least the steps of:

- a) providing a set, collection or library of nucleic acid sequences encoding heavy chain antibodies or NANOBODY® (V_{HH} sequence) sequences;
- b) screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode a heavy chain antibody or a NANOBODY® (V_{HH} sequence) sequence that can bind to and/or has affinity for an envelope protein of a virus;
  and
- c) isolating said nucleic acid sequence, followed by expressing the V_{HH} sequence present in said heavy chain antibody or by expressing said NANOBODY® (V_{HH}

sequence) sequence, respectively.

In such a method, the set, collection or library of nucleic acid sequences encoding heavy chain antibodies or NANOBODY® (V_{HH} sequence) sequences may for example be a set, collection or library of nucleic acid sequences encoding a naïve set, collection or library of heavy chain antibodies or V_{HH} sequences; a set, collection or library of nucleic acid sequences encoding a synthetic or semi-synthetic set, collection or library of NANOBODY® (V_{HH} sequence) sequences; and/or a set, collection or library of nucleic acid sequences encoding a set, collection or library of NANOBODY® (V_{HH} sequence) sequences that have been subjected to affinity maturation.

In a preferred aspect of this method, the set, collection or library of amino acid sequences may be an immune set, collection or library of nucleic acid sequences encoding heavy chain antibodies or V_{HH} sequences derived from a Camelid that has been suitably immunized with an envelope protein of a virus or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

In the above methods, the set, collection or library of nucleotide sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) nucleotide sequences encoding amino acid sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to WO 03/054016 and to the review by Hoogenboom in Nature Biotechnology, 23, 9, 1105-1116 (2005).

As will be clear to the skilled person, the screening step of the methods described herein can also be performed as a selection step. Accordingly the term “screening” as used in the present description can comprise selection, screening or any suitable combination of selection and/or screening techniques. Also, when a set, collection or library of sequences is used, it may contain any suitable number of sequences, such as 1, 2, 3 or about 5, 10, 50, 100, 500, 1000, 5000, 10^4, 10^5, 10^6, 10^7, 10^8 or more sequences.

Also, one or more or all of the sequences in the above set, collection or library of amino acid sequences may be obtained or defined by rational, or semi-empirical approaches such as computer modelling techniques or biostatics or datamining techniques.

Furthermore, such a set, collection or library can comprise one, two or more sequences that are variants from one another (e.g. with designed point mutations or with randomized positions), compromise multiple sequences derived from a diverse set of naturally diversified sequences (e.g. an immune library)), or any other source of diverse sequences

(as described for example in Hoogenboom et al, Nat Biotechnol 23:1105, 2005 and Binz et al, Nat Biotechnol 2005, 23:1247). Such set, collection or library of sequences can be displayed on the surface of a phage particle, a ribosome, a bacterium, a yeast cell, a mammalian cell, and linked to the nucleotide sequence encoding the amino acid sequence within these carriers. This makes such set, collection or library amenable to selection procedures to isolate the desired amino acid sequences of the invention. More generally, when a sequence is displayed on a suitable host or host cell, it is also possible (and customary) to first isolate from said host or host cell a nucleotide sequence that encodes the desired sequence, and then to obtain the desired sequence by suitably expressing said nucleotide sequence in a suitable host organism. Again, this can be performed in any suitable manner known per se, as will be clear to the skilled person.

Yet another technique for obtaining V_{HH} sequences or NANOBODY® (V_{HH} sequence) sequences directed against an envelope protein of a virus involves suitably immunizing a transgenic mammal that is capable of expressing heavy chain antibodies (i.e. so as to raise an immune response and/or heavy chain antibodies directed against an envelope protein of a virus), obtaining a suitable biological sample from said transgenic mammal that contains (nucleic acid sequences encoding) said V_{HH} sequences or NANOBODY® (V_{HH} sequence) sequences (such as a blood sample, serum sample or sample of B-cells), and then generating V_{HH} sequences directed against an envelope protein of a virus, starting from said sample, using any suitable technique known per se (such as any of the methods described herein or a hybridoma technique). For example, for this purpose, the heavy chain antibody-expressing mice and the further methods and techniques described in WO 02/085945, WO 04/049794 and WO 06/008548 and Janssens et al., Proc. Natl. Acad. Sci. USA. 2006 Oct. 10; 103(41):15130-5 can be used. For example, such heavy chain antibody expressing mice can express heavy chain antibodies with any suitable (single) variable domain, such as (single) variable domains from natural sources (e.g. human (single) variable domains, Camelid (single) variable domains or shark (single) variable domains), as well as for example synthetic or semi-synthetic (single) variable domains.

The invention also relates to the V_{HH} sequences or NANOBODY® (V_{HH} sequence) sequences that are obtainable and/or obtained by the above methods, or alternatively by a method that comprises the one of the above methods and in addition at least the steps of determining the nucleotide sequence or amino acid sequence of said V_{HH} sequence or NANOBODY® (V_{HH} sequence) sequence; and of expressing or synthesizing said V_{HH} sequence or NANOBODY® (V_{HH} sequence) sequence in a manner known per se, such as by expression in a suitable host cell or host organism or by chemical synthesis.

As mentioned herein, a particularly preferred class of NANOBO NANOBODIES® (V_{HH} sequences) DIES® (V_{HH} sequences) of the invention comprises NANOBODIES® (V_{HH} sequences) with an amino acid sequence that corresponds to the amino acid sequence of a

naturally occurring V_{HH} domain, but that has been "humanized", i.e. by replacing one or more amino acid residues in the amino acid sequence of said naturally occurring V_{HH} sequence (and in particular in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a V_H domain from a conventional 4-chain antibody from a human being (e.g. indicated above), as further described on, and using the techniques mentioned on, page 63 of WO 08/020079. Another particularly preferred class of NANOBODIES® (V_{HH} sequences) of the invention comprises NANOBODIES® (V_{HH} sequences) with an amino acid sequence that corresponds to the amino acid sequence of a naturally occurring V_H domain, but that has been "camelized", i.e. by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring V_H domain from a conventional 4-chain antibody by one or more of the amino acid residues that occur at the corresponding position(s) in a V_{HH} domain of a heavy chain antibody, as further described on, and using the techniques mentioned on, page 63 of WO 08/020079.

Other suitable methods and techniques for obtaining the NANOBODIES® NANOBODIES® (V_{HH} sequences) (V_{HH} sequences) of the invention and/or nucleic acids encoding the same, starting from naturally occurring V_H sequences or preferably V_{HH} sequences, will be clear from the skilled person, and may for example include the techniques that are mentioned on page 64 of WO 08/00279. As mentioned herein, NANOBODIES® (V_{HH} sequences) may in particular be characterized by the presence of one or more "Hallmark residues" (as described herein) in one or more of the framework sequences.

Thus, according to one preferred, but non-limiting aspect of the invention, a NANOBODY® (V_{HH} sequence) in its broadest sense can be generally defined as a polypeptide comprising:

- a) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 108 according to the Kabat numbering is Q;
  and/or:
- b) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 45 according to the Kabat numbering is a charged amino acid (as defined herein) or a cysteine residue, and position 44 is preferably an E;
  and/or:
- c) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S, and is in particular chosen from the group consisting of R and S.

Thus, in a first preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which

- a) the amino acid residue at position 108 according to the Kabat numbering is Q;
  and/or in which:
- b) the amino acid residue at position 45 according to the Kabat numbering is a charged amino acid or a cysteine and the amino acid residue at position 44 according to the Kabat numbering is preferably E;
  and/or in which:
- c) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S, and is in particular chosen from the group consisting of R and S;
  and in which:
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In particular, a NANOBODY® (V_{HH} sequence) in its broadest sense can be generally defined as a polypeptide comprising:

- a) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 108 according to the Kabat numbering is Q;
  and/or:
- b) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 44 according to the Kabat numbering is E and in which the amino acid residue at position 45 according to the Kabat numbering is an R;
  and/or:
- c) an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S, and is in particular chosen from the group consisting of R and S.

Thus, according to a preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which

- a) the amino acid residue at position 108 according to the Kabat numbering is Q;
  and/or in which:
- b) the amino acid residue at position 44 according to the Kabat numbering is E and in which the amino acid residue at position 45 according to the Kabat numbering is an R; and/or in which:
- c) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S, and is in particular chosen from the group consisting of R and S;
  and in which:
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In particular, a NANOBODY® (V_{HH} sequence) against an envelope protein of a virus according to the invention may have the structure:

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which

- a) the amino acid residue at position 108 according to the Kabat numbering is Q;
  and/or in which:
- b) the amino acid residue at position 44 according to the Kabat numbering is E and in which the amino acid residue at position 45 according to the Kabat numbering is an R;
  and/or in which:
- c) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S, and is in particular chosen from the group consisting of R and S;
  and in which:
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In particular, according to one preferred, but non-limiting aspect of the invention, a NANOBODY® (V_{HH} sequence) can generally be defined as a polypeptide comprising an

amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which;

- a-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of A, G, E, D, G, Q, R, S, L; and is preferably chosen from the group consisting of G, E or Q; and
- a-2) the amino acid residue at position 45 according to the Kabat numbering is chosen from the group consisting of L, R or C; and is preferably chosen from the group consisting of L or R; and
- a-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of W, R or S; and is preferably W or R, and is most preferably W;
- a-4) the amino acid residue at position 108 according to the Kabat numbering is Q;
or in which:
- b-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of E and Q; and
- b-2) the amino acid residue at position 45 according to the Kabat numbering is R; and
- b-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of W, R and S; and is preferably W;
- b-4) the amino acid residue at position 108 according to the Kabat numbering is chosen from the group consisting of Q and L; and is preferably Q;
or in which:
- c-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of A, G, E, D, Q, R, S and L; and is preferably chosen from the group consisting of G, E and Q; and
- c-2) the amino acid residue at position 45 according to the Kabat numbering is chosen from the group consisting of L, R and C; and is preferably chosen from the group consisting of L and R; and
- c-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S; and is in particular chosen from the group consisting of R and S; and
- c-4) the amino acid residue at position 108 according to the Kabat numbering is chosen from the group consisting of Q and L; is preferably Q;
and in which
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

Thus, in another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- a-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of A, G, E, D, G, Q, R, S, L; and is preferably chosen from the group consisting of G, E or Q;
  and in which:
- a-2) the amino acid residue at position 45 according to the Kabat numbering is chosen from the group consisting of L, R or C; and is preferably chosen from the group consisting of L or R;
  and in which:
- a-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of W, R or S; and is preferably W or R, and is most preferably W;
  and in which
- a-4) the amino acid residue at position 108 according to the Kabat numbering is Q;
  and in which:
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- b-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of E and Q;
  and in which:
- b-2) the amino acid residue at position 45 according to the Kabat numbering is R;
  and in which:
- b-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of W, R and S; and is preferably W;
  and in which:
- b-4) the amino acid residue at position 108 according to the Kabat numbering is chosen from the group consisting of Q and L; and is preferably Q;
  and in which:

- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- c-1) the amino acid residue at position 44 according to the Kabat numbering is chosen from the group consisting of A, G, E, D, Q, R, S and L; and is preferably chosen from the group consisting of G, E and Q;
  and in which:
- c-2) the amino acid residue at position 45 according to the Kabat numbering is chosen from the group consisting of L, R and C; and is preferably chosen from the group consisting of L and R;
  and in which:
- c-3) the amino acid residue at position 103 according to the Kabat numbering is chosen from the group consisting of P, R and S; and is in particular chosen from the group consisting of R and S;
  and in which:
- c-4) the amino acid residue at position 108 according to the Kabat numbering is chosen from the group consisting of Q and L; is preferably Q;
  and in which:
- d) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.
    - Two particularly preferred, but non-limiting groups of the NANOBODIES® (V_{HH} sequences) of the invention are those according to a) above; according to (a-1) to (a-4) above; according to b) above; according to (b-1) to (b-4) above; according to (c) above; and/or according to (c-1) to (c-4) above, in which either:
- i) the amino acid residues at positions 44-47 according to the Kabat numbering form the sequence GLEW (or a GLEW-like sequence as described herein) and the amino acid residue at position 108 is Q;
  or in which:
- ii) the amino acid residues at positions 43-46 according to the Kabat numbering form the sequence KERE or KQRE (or a KERE-like sequence as described) and the amino

acid residue at position 108 is Q or L, and is preferably Q.

Thus, in another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- i) the amino acid residues at positions 44-47 according to the Kabat numbering form the sequence GLEW (or a GLEW-like sequence as defined herein) and the amino acid residue at position 108 is Q;
  and in which:
- ii) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may have the structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- i) the amino acid residues at positions 43-46 according to the Kabat numbering form the sequence KERE or KQRE (or a KERE-like sequence) and the amino acid residue at position 108 is Q or L, and is preferably Q;
  and in which:
- ii) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In the NANOBODIES® (V_{HH} sequences) of the invention in which the amino acid residues at positions 43-46 according to the Kabat numbering form the sequence KERE or KQRE, the amino acid residue at position 37 is most preferably F. In the NANOBODIES® (V_{HH} sequences) of the invention in which the amino acid residues at positions 44-47 according to the Kabat numbering form the sequence GLEW, the amino acid residue at position 37 is chosen from the group consisting of Y, H, I, L, V or F, and is most preferably V.

Thus, without being limited hereto in any way, on the basis of the amino acid residues present on the positions mentioned above, the NANOBODIES® (V_{HH} sequences) of the

invention can generally be classified on the basis of the following three groups:

- i) The "GLEW-group": NANOBODIES® (V_{HH} sequences) with the amino acid sequence GLEW at positions 44-47 according to the Kabat numbering and Q at position 108 according to the Kabat numbering. As further described herein, NANOBODIES® (V_{HH} sequences) within this group usually have a V at position 37, and can have a W, P, R or S at position 103, and preferably have a W at position 103. The GLEW group also comprises some GLEW-like sequences such as those mentioned in Table B-2 below. More generally, and without limitation, NANOBODIES® (V_{HH} sequences) belonging to the GLEW-group can be defined as NANOBODIES® (V_{HH} sequences) with a G at position 44 and/or with a W at position 47, in which position 46 is usually E and in which preferably position 45 is not a charged amino acid residue and not cysteine;
- ii) The "KERE-group": NANOBODIES® (V_{HH} sequences) with the amino acid sequence KERE or KQRE (or another KERE-like sequence) at positions 43-46 according to the Kabat numbering and Q or L at position 108 according to the Kabat numbering. As further described herein, NANOBODIES® (V_{HH} sequences) within this group usually have a F at position 37, an L or F at position 47; and can have a W, P, R or S at position 103, and preferably have a W at position 103. More generally, and without limitation, NANOBODIES® (V_{HH} sequences) belonging to the KERE-group can be defined as NANOBODIES® (V_{HH} sequences) with a K, Q or R at position 44 (usually K) in which position 45 is a charged amino acid residue or cysteine, and position 47 is as further defined herein;
- iii) The "103 P, R, S-group": NANOBODIES® (V_{HH} sequences) with a P, R or S at position 103. These NANOBODIES® (V_{HH} sequences) can have either the amino acid sequence GLEW at positions 44-47 according to the Kabat numbering or the amino acid sequence KERE or KQRE at positions 43-46 according to the Kabat numbering, the latter most preferably in combination with an F at position 37 and an L or an F at position 47 (as defined for the KERE-group); and can have Q or L at position 108 according to the Kabat numbering, and preferably have Q.

Also, where appropriate, NANOBODIES® (V_{HH} sequences) may belong to (i.e. have characteristics of) two or more of these classes. For example, one specifically preferred group of NANOBODIES® (V_{HH} sequences) has GLEW or a GLEW-like sequence at positions 44-47; P, R or S (and in particular R) at position 103; and Q at position 108 (which may be humanized to L).

More generally, it should be noted that the definitions referred to above describe and apply to NANOBODIES® (V_{HH} sequences) in the form of a native (i.e. non-humanized) V_{HH} sequence, and that humanized variants of these NANOBODIES® (V_{HH} sequences) may contain other amino acid residues than those indicated above (i.e. one or more humanizing substitutions as defined herein). For example, and without limitation, in some humanized

NANOBODIES® (V_{HH} sequences) of the GLEW-group or the 103 P, R, S-group, Q at position 108 may be humanized to 108 L. As already mentioned herein, other humanizing substitutions (and suitable combinations thereof) will become clear to the skilled person based on the disclosure herein. In addition, or alternatively, other potentially useful humanizing substitutions can be ascertained by comparing the sequence of the framework regions of a naturally occurring V_{HH} sequence with the corresponding framework sequence of one or more closely related human V_H sequences, after which one or more of the potentially useful humanizing substitutions (or combinations thereof) thus determined can be introduced into said V_{HH} sequence (in any manner known per se, as further described herein) and the resulting humanized V_{HH} sequences can be tested for affinity for the target, for stability, for ease and level of expression, and/or for other desired properties. In this way, by means of a limited degree of trial and error, other suitable humanizing substitutions (or suitable combinations thereof) can be determined by the skilled person based on the disclosure herein. Also, based on the foregoing, (the framework regions of) a NANOBODY® (V_{HH} sequence) may be partially humanized or fully humanized.

Thus, in another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may be a NANOBODY® (V_{HH} sequence) belonging to the GLEW-group (as defined herein), and in which CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may be a NANOBODY® (V_{HH} sequence) belonging to the KERE-group (as defined herein), and CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

Thus, in another preferred, but non-limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention may be a NANOBODY® (V_{HH} sequence) belonging to the 103 P, R, S-group (as defined herein), and in which CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

Also, more generally and in addition to the 108Q, 43E/44R and 103 P,R,S residues mentioned above, the NANOBODIES® (V_{HH} sequences) of the invention can contain, at one or more positions that in a conventional V_H domain would form (part of) the V_H/V_L interface, one or more amino acid residues that are more highly charged than the amino acid residues that naturally occur at the same position(s) in the corresponding naturally occurring V_H sequence, and in particular one or more charged amino acid residues (as mentioned in Table A-2 on page 48 of the International application WO 08/020079). Such

substitutions include, but are not limited to, the GLEW-like sequences mentioned in Table B-2 below; as well as the substitutions that are described in the International Application WO 00/29004 for so-called "microbodies", e.g. so as to obtain a NANOBODY® (V_{HH} sequence) with Q at position 108 in combination with KLEW at positions 44-47. Other possible substitutions at these positions will be clear to the skilled person based upon the disclosure herein.

In one aspect of the NANOBODIES® (V_{HH} sequences) of the invention, the amino acid residue at position 83 is chosen from the group consisting of L, M, S, V and W; and is preferably L.

Also, in one aspect of the NANOBODIES® (V_{HH} sequences) of the invention, the amino acid residue at position 83 is chosen from the group consisting of R, K, N, E, G, I, T and Q; and is most preferably either K or E (for NANOBODIES® (V_{HH} sequences) corresponding to naturally occurring V_{HH} domains) or R (for "humanized" NANOBODIES® (V_{HH} sequences), as described herein). The amino acid residue at position 84 is chosen from the group consisting of P, A, R, S, D T, and V in one aspect, and is most preferably P (for NANOBODIES® (V_{HH} sequences) corresponding to naturally occurring V_{HH} domains) or R (for "humanized" NANOBODIES® (V_{HH} sequences), as described herein).

Furthermore, in one aspect of the NANOBODIES® (V_{HH} sequences) of the invention, the amino acid residue at position 104 is chosen from the group consisting of G and D; and is most preferably G.

Collectively, the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108, which in the NANOBODIES® (V_{HH} sequences) are as mentioned above, will also be referred to herein as the "Hallmark Residues". The Hallmark Residues and the amino acid residues at the corresponding positions of the most closely related human V_H domain, V_H3, are summarized in Table B-2.

Some especially preferred but non-limiting combinations of these Hallmark Residues as occur in naturally occurring V_{HH} domains are mentioned in Table B-3. For comparison, the corresponding amino acid residues of the human V_H3 called DP-47 have been indicated in italics.

TABLE B-2 Hallmark Residues in Nanobodies Position Human V_H3 Hallmark Residues 11 L, V; L, M, S, V, W; preferably L predominantly L 37 V, I, F; usually V $F^{(1)}$, Y, H, I, L or V, preferably $F^{(1)}$ or Y $44^{(8)}$ G $G^{(2)}$, $E^{(3)}$, A, D, Q, R, S, L; preferably $G^{(2)}$, $E^{(3)}$ or Q; most preferably $G^{(2)}$ or $E^{(3)}$. $45^{(8)}$ L $L^{(2)}$, $R^{(3)}$, C, I, L, P, Q, V; preferably $L^{(2)}$ or $R^{(3)}$ $47^{(8)}$ W, Y $W^{(2)}$, $L^{(1)}$ or $F^{(1)}$, A, G, I, M, R, S, V or Y; preferably $W^{(2)}$, $L^{(1)}$, $F^{(1)}$ or R 83 R or K; usually R R, $K^{(5)}$, N, $E^{(5)}$, G, I, M, Q or T; preferably K or R; most preferably K 84 A, T, D; $P^{(5)}$, A, L, R, S, T, D, V; preferably P predominantly A 103 W $W^{(4)}$, $P^{(6)}$, $R^{(6)}$, S; preferably W 104 G G or D;

preferably G 108 L, M or T; Q, L[7] or R; preferably Q or L[7] predominantly L Notes: [1]In particular, but not exclusively, in combination with KERE or KQRE at positions 43-46. [2]Usually as GLEW at positions 44-47. [3]Usually as KERE or KQRE at positions 43-46, e.g. as KEREL, KEREF, KQREL, KQREF or KEREG at positions 43-47. Alternatively, also sequences such as TERE (for example TEREL), KECE (for example KECEL or KECER), RERE (for example REREG), QERE (for example QEREG), KGRE (for example KGREG), KDRE (for example KDREV) are possible. Some other possible, but less preferred sequences include for example DECKL and NVCEL. [4]With both GLEW at positions 44-47 and KERE or KQRE at positions 43-46. [5]Often as KP or EP at positions 83-84 of naturally occurring V_{HH} domains. [6]In particular, but not exclusively, in combination with GLEW at positions 44-47. [7]With the proviso that when positions 44-47 are GLEW, position 108 is always Q in (non-humanized) V_{HH} sequences that also contain a W at position 103. The GLEW group also contains GLEW-like sequences at positions 44-47, such as for example GVEW, EPEW, GLER, DQEW, DLEW, GIEW, ELEW, GPEW, EWLP, GPER, GLER and ELEW.

TABLE B-3 Some preferred but non-limiting combinations of Hallmark Residues in naturally occurring Nanobodies. For humanization of these combinations, reference is made to the specification. 11 37 44 45 47 83 84 103 104 108 *DP-47 (human) M V G L W R A W G L* “KERE” group L F E R L K P W G Q L F E R F E P W G Q L F E R F K P W G Q L Y Q R L K P W G Q L F L R V K P Q G Q L F Q R L K P W G Q L F E R F K P W G Q “GLEW” group L V G L W K S W G Q M V G L W K P R G Q

In the NANOBODIES® (V_{HH} sequences), each amino acid residue at any other position than the Hallmark Residues can be any amino acid residue that naturally occurs at the corresponding position (according to the Kabat numbering) of a naturally occurring V_{HH} domain.

Such amino acid residues will be clear to the skilled person. Tables B-4 to B-7 mention some non-limiting residues that can be present at each position (according to the Kabat numbering) of the FR1, FR2, FR3 and FR4 of naturally occurring V_{HH} domains. For each position, the amino acid residue that most frequently occurs at each position of a naturally occurring V_{HH} domain (and which is the most preferred amino acid residue for said position in a NANOBODY® (V_{HH} sequence)) is indicated in bold; and other preferred amino acid residues for each position have been underlined (note: the number of amino acid residues that are found at positions 26-30 of naturally occurring V_{HH} domains supports the hypothesis underlying the numbering by Chothia (supra) that the residues at these positions already form part of CDR1.)

In Tables B-4 to B-7, some of the non-limiting residues that can be present at each position of a human V_H3 domain have also been mentioned. Again, for each position, the amino acid

residue that most frequently occurs at each position of a naturally occurring human V_H3 domain is indicated in bold; and other preferred amino acid residues have been underlined.

For reference only, Tables B-4 to B-7 also contain data on the V_{HH} entropy ("V_{HH} Ent.") and V_{HH} variability ("V_{HH} Var.") at each amino acid position for a representative sample of 1118 V_{HH} sequences (data kindly provided by David Lutje Hulsing and Prof. Theo Verrips of Utrecht University). The values for the V_{HH} entropy and the V_{HH} variability provide a measure for the variability and degree of conservation of amino acid residues between the 1118 V_{HH} sequences analyzed: low values (i.e. <1, such as <0.5) indicate that an amino acid residue is highly conserved between the V_{HH} sequences (i.e. little variability). For example, the G at position 8 and the G at position 9 have values for the V_{HH} entropy of 0.1 and 0 respectively, indicating that these residues are highly conserved and have little variability (and in case of position 9 is G in all 1118 sequences analysed), whereas for residues that form part of the CDR's generally values of 1.5 or more are found (data not shown). Note that (1) the amino acid residues listed in the second column of Tables B-4 to B-7 are based on a bigger sample than the 1118 V_{HH} sequences that were analysed for determining the V_{HH} entropy and V_{HH} variability referred to in the last two columns; and (2) the data represented below support the hypothesis that the amino acid residues at positions 27-30 and maybe even also at positions 93 and 94 already form part of the CDR's (although the invention is not limited to any specific hypothesis or explanation, and as mentioned above, herein the numbering according to Kabat is used). For a general explanation of sequence entropy, sequence variability and the methodology for determining the same, see Oliveira et al., PROTEINS: Structure, Function and Genetics, 52: 544-552 (2003).

TABLE B-4 Non-limiting examples of amino acid residues in FR1 (for the footnotes, see the footnotes to Table B-2) Amino acid residue(s): V_{HH} V_{HH} Pos. Human V_H3 Camelid V_{HH}'s Ent. Var. 1 **E**, Q **Q**, A, E — — 2 **V V** 0.2 1 3 **Q Q**, K 0.3 2 4 **L L** 0.1 1 5 **V**, L **Q**, E, L, V 0.8 3 6 **E E**, D, Q, A 0.8 4 7 **S**, T **S**, F 0.3 2 8 **G**, R **G** 0.1 1 9 **G G** 0 1 10 **G**, V **G**, D, R 0.3 2 11 Hallmark residue: L, M, S, V, W; preferably L 0.8 2 12 **V**, I **V**, A 0.2 2 13 **Q**, K, R **Q**, E, K, P, R 0.4 4 14 **P A**, Q, A, G, P, S, T, V 1 5 15 **G G** 0 1 16 **G**, R **G**, A, E, D 0.4 3 17 **S S**, F 0.5 2 18 **L L**, V 0.1 1 19 **R**, K **R**, K, L, N, S, T 0.6 4 20 **L L**, F, I, V 0.5 4 21 **S S**, A, F, T 0.2 3 22 **C C** 0 1 23 **A**, T **A**, D, E, P, S, T, V 1.3 5 24 **A A**, I, L, S, T, V 1 6 25 **S S**, A, F, P, T 0.5 5 26 **G G**, A, D, E, R, S, T, V 0.7 7 27 **F** S, F, R, L, P, G, N, 2.3 13 28 **T** N, T, E, D, S, I, R, A, G, R, F, Y 1.7 11 29 **F**, V F, L, D, S, I, G, V, A 1.9 11 30 **S**, D, G N, S, E, G, A, D, M, T 1.8 11

TABLE B-5 Non-limiting examples of amino acid residues in FR2 (for the footnotes, see the footnotes to Table B-2) Amino acid residue(s): V_{HH} V_{HH} Pos. Human V_H3 Camelid V_{HH}'s Ent. Var. 36 **W W** 0.1 1 37 Hallmark residue: $F^{(1)}$, H, I, L, Y 1.1 6 or V, preferably $F^{(1)}$ or Y 38 **R R** 0.2 1 39 **Q Q**, H, P, R 0.3 2 40 **A A**, F, G, L, P, T, V 0.9 7 41 **P**, S, T **P**, A, L, S 0.4 3 42 **G G**, E 0.2 2 43 **K K**, D, E, N, Q, R, T, V 0.7 6 44 Hallmark residue: $G^{(2)}$, $E^{(3)}$, A, D, Q, 1.3 5 R, S, L; preferably

$G^{(2)}$, $E^{(3)}$ or Q; most preferably $G^{(2)}$ or $E^{(3)}$. 45 Hallmark residue: $L^{(2)}$, $R^{(3)}$, C, I, L, P, Q, V; 0.6 4 preferably $L^{(2)}$ or $R^{(3)}$ 46 **E**, V **E**, D, K, Q, V 0.4 2 47 Hallmark residue: $W^{(2)}$, $L^{(1)}$ or $F^{(1)}$, A, G, I, 1.9 9 M, R, S, V or Y; preferably $W^{(2)}$, $L^{(1)}$, $F^{(1)}$ or R 48 **V V**, I, L 0.4 3 49 **S**, A, G **A**, S, G, T, V 0.8 3

TABLE B-6 Non-limiting examples of amino acid residues in FR3 (for the footnotes, see the footnotes to Table B-2) Amino acid residue(s): V_{HH} V_{HH} Pos. Human V_H3 Camelid V_{HH}'s Ent. Var. 66 **R R** 0.1 1 67 **F F**, L, V 0.1 1 68 **T T**, A, N, S 0.5 4 69 **I I**, L, M, V 0.4 4 70 **S S**, A, F, T 0.3 4 71 **R R**, G, H, I, L, K, Q, S, T, W 1.2 8 72 **D**, E **D**, E, G, N, V 0.5 4 73 **N**, D, G **N**, A, D, F, I, K, L, R, S, T, V, Y 1.2 9 74 **A**, S **A**, D, G, N, P, S, T, V 1 7 75 **K K**, A, E, K, L, N, Q, R 0.9 6 76 **N**, S **N**, D, K, R, S, T, Y 0.9 6 77 S, T, I **T**, A, E, I, M, P, S 0.8 5 78 **L**, A **V**, L, A, F, G, I, M 1.2 5 79 **Y**, H **Y**, A, D, F, H, N, S, T 1 7 80 **L L**, F, V 0.1 1 81 **Q Q**, E, I, L, R, T 0.6 5 82 **M M**, I, L, V 0.2 2 82a **N**, G **N**, D, G, H, S, T 0.8 4 82b **S S**, N, D, G, R, T 1 6 82c **L L**, P, V 0.1 2 83 Hallmark residue: R, $K^{(5)}$, N, $E^{(5)}$, G, I, M, Q or T; 0.9 7 preferably K or R; most preferably K 84 Hallmark residue: $P^{(5)}$, A, D, L, R, S, T, V; 0.7 6 preferably P 85 **E**, G **E**, D, G, Q 0.5 3 86 **D D** 0 1 87 **T**, M **T**, A, S 0.2 3 88 **A A**, G, S 0.3 2 89 **V**, L **V**, A, D, I, L, M, N, R, T 1.4 6 90 **Y Y**, F 0 1 91 **Y**, H **Y**, D, F, H, L, S, T, V 0.6 4 92 **C C** 0 1 93 **A**, K, T **A**, N, G, H, K, N, R, S, T, V, Y 1.4 10 94 **K**, R, T **A**, V, C, F, G, I, K, L, R, S or T 1.6 9

TABLE B-7 Non-limiting examples of amino acid residues in FR4 (for the footnotes, see the footnotes to Table B-2) Amino acid residue(s): V_{HH} V_{HH} Pos. Human V_H3 Camelid V_{HH}'s Ent. Var. 103 Hallmark residue: $W^{(4)}$, $P^{(6)}$, $R^{(6)}$, S; preferably W 0.4 2 104 Hallmark residue: G or D; preferably G 0.1 1 105 **Q**, R **Q**, E, K, P, R 0.6 4 106 **G G** 0.1 1 107 **T T**, A, I 0.3 2 108 Hallmark residue: Q, $L^{(7)}$ or R: preferably Q or $L^{(7)}$ 0.4 3 109 **V V** 0.1 1 110 **T T**, I, A 0.2 1 111 **V V**, A, I 0.3 2 112 **S S**, F 0.3 1 113 **S S**, A, L, P, T 0.4 3

Thus, in another preferred, but not limiting aspect, a NANOBODY® (V_{HH} sequence) of the invention can be defined as an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- i) one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2;
  and in which:
- ii) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

The above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein.

In particular, a NANOBODY® (V_{HH} sequence) of the invention can be an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

- i) (preferably) one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2 (it being understood that V_{HH} sequences will contain one or more Hallmark residues; and that partially humanized NANOBODIES® (V_{HH} sequences) will usually, and preferably, contain one or more Hallmark residues [although it is also within the scope of the invention to provide—where suitable in accordance with the invention—partially humanized NANOBODIES® (V_{HH} sequences) in which all Hallmark residues, but not one or more of the other amino acid residues, have been humanized]; and that in fully humanized NANOBODIES® (V_{HH} sequences), where suitable in accordance with the invention, all amino acid residues at the positions of the Hallmark residues will be amino acid residues that occur in a human V_H3 sequence. As will be clear to the skilled person based on the disclosure herein that such V_{HH} sequences, such partially humanized NANOBODIES® (V_{HH} sequences) with at least one Hallmark residue, such partially humanized NANOBODIES® (V_{HH} sequences) without Hallmark residues and such fully humanized NANOBODIES® (V_{HH} sequences) all form aspects of this invention); and in which:
- ii) said amino acid sequence has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences (indicated with X in the sequences of SEQ ID NO's: 1 to 22) are disregarded;
  and in which:
- iii) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

The above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein.

TABLE B-8 Representative amino acid sequences for NANOBODIES® (V_{HH} sequences) of the KERE, GLEW and P, R, S 103 group. The CDRs are indicated with XXXXX KERE SEQ ID NO: 1
EVQLVESGGGLVQPGGSLRLSCAASGIPFSXXXXXWFRQAPGKQRDSVAXXXXXRFTISRDNAKNTVYI
sequence no. 1 NSLKPEDTAVYRCYFXXXXXWGQGTQVTVSS KERE SEQ ID NO: 2
QVKLEESGGGLVQAGGSLRLSCVGSGRTFSXXXXXWFRLAPGKEREFVAXXXXXRFTISRDTASNRGYI
sequence no. 2 NNLTPEDTAVYYCAAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 3
AVQLVDSGGGLVQAGDSLKLSCALTGGAFTXXXXXWFRQTPGREREFVAXXXXXRFTISRDNAKNMVY
sequence no. 3 NSLIPEDAAVYSCAAXXXXXWGQGTLVTVSS KERE SEQ ID NO: 4
QVQLVESGGGLVEAGGSLRLSCTASESPFRXXXXXWFRQTSGQEREFVAXXXXXRFTISRDDAKNTVW
sequence no. 4 STLKPEDTAVYYCAAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 5
AVQLVESGGGLVQGGGSLRLACAASERIFDXXXXXWYRQGPGNERELVAXXXXXRFTISMDYTKQTVY
sequence no. 5 NSLRPEDTGLYYCKIXXXXXWGQGTQVTVSS KERE SEQ ID NO: 6
DVKFVESGGGLVQAGGSLRLSCVASGFNFDXXXXXWFRQAPGKEREEVAXXXXXRFTISSEKDKNSVY
sequence no. 6 NSLKPEDTALYICAGXXXXXWGRGTQVTVSS KERE SEQ ID NO: 7
QVRLAESGGGLVQSGGSLRLSCVASGSTYTXXXXXWYRQYPGKQRALVAXXXXXRFTIARDSTKDTFCI
sequence no. 7 NNLKPEDTAVYYCYAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 8
EVQLVESGGGLVQAGGSLRLSCAASGFTSDXXXXXWFRQAPGKPREGVSXXXXXRFTISTDNAKNTVH
sequence no. 8 NRVNAEDTALYYCAVXXXXXWGRGTRVIVSS KERE SEQ ID NO: 9
QVQLVESGGGLVQPGGSLRLSCQASGDISTXXXXXWYRQVPGKLREFVAXXXXXRFTISGDNAKRAIYL
sequence no. 9 NLKPDDTAVYYCNRXXXXXWGQGTQVTVSP KERE SEQ ID NO: 10
QVPVVESGGGLVQAGDSLRLFCAVPSFTSTXXXXXWFRQAPGKEREFVAXXXXXRFTISRNATKNTLTI
sequence no. 10 SLKPEDTAVYYCAAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 11
EVQLVESGGGLVQAGDSLRLFCTVSGGTASXXXXXWFRQAPGEKREFVAXXXXXRFTIARENAGNMVY
sequence no. 11 NNLKPDDTALYTCAAXXXXXWGRGTQVTVSS KERE SEQ ID NO: 12
AVQLVESGGDSVQPGDSQTLSCAASGRTNSXXXXXWFRQAPGKERVFLAXXXXXRFTISRDSAKNMM
sequence no. 12 LQMNNLKPQDTAVYYCAAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 13
AVQLVESGGGLVQAGGSLRLSCVVSGLTSSXXXXXWFRQTPWQERDFVAXXXXXRFTISRDNYKDTVL
sequence no. 13 EMNFLKPEDTAIYYCAAXXXXXWGQGTQVTVSS KERE SEQ ID NO: 14
AVQLVESGGGLVQAGASLRLSCATSTRTLDXXXXXWFRQAPGRDREFVAXXXXXRFTVSRDSAENTVA
sequence no. 14 QMNSLKPEDTAVYYCAAXXXXXWGQGTRVTVSS KERE SEQ ID NO:

15
QVQLVESGGGLVQPGGSLRLSCTVSRLTAHXXXXXWFRQAPGKEREAVSXXXXXRFTISRDYAGNTAFL
sequence no. 15 QMDSLKPEDTGVYYCATXXXXXWGQGTQVTVSS KERE SEQ ID NO:
16
EVQLVESGGELVQAGGSLKLSCTASGRNFVXXXXXWFRRAPGKEREFVAXXXXXRFTVSRDNGKNTAY
sequence no. 16 LRMNSLKPEDTADYYCAVXXXXXLGSGTQVTVSS GLEW SEQ ID NO:
17
AVQLVESGGGLVQPGGSLRLSCAASGFTFSXXXXXWVRQAPGKVLEWVSXXXXXRFTISRDNAKNTLY
sequence no. 1 QMNSLKPEDTAVYYCVKXXXXXGSQGTQVTVSS GLEW SEQ ID NO: 18
EVQLVESGGGLVQPGGSLRLSCVCVSSGCTXXXXXWVRQAPGKAEEWVSXXXXXRFKISRDNAKKTLY
sequence no. 2 LQMNSLGPEDTAMYYCQRXXXXXRGQGTQVTVSS GLEW SEQ ID NO:
19
EVQLVESGGGLALPGGSLTLSCVFSGSTFSXXXXXWVRHTPGKAEEWVSXXXXXRFTISRDNAKNTLY
sequence no. 3 EMNSLSPEDTAMYYCGRXXXXXRSKGIQVTVSS P, R, S 103 SEQ ID
NO: 20
AVQLVESGGGLVQAGGSLRLSCAASGRTFSXXXXXWFRQAPGKEREFVAXXXXXRFTISRDNAKNTVY
sequence no. 1 QMNSLKPEDTAVYYCAAXXXXXRGQGTQVTVSS P, R, S 103 SEQ
ID NO: 21
DVQLVESGGDLVQPGGSLRLSCAASGFSFDXXXXXWLRQTPGKGLEWVGXXXXXRFTISRDNAKNML
sequence no. 2 LHLNNLKSEDTAVYYCRRXXXXXLGQGTQVTVSS P, R, S 103 SEQ
ID NO: 22
EVQLVESGGGLVQPGGSLRLSCVCVSSGCTXXXXXWVRQAPGKAEEWVSXXXXXRFKISRDNAKKTLY
sequence no. 3 LQMNSLGPEDTAMYYCQRXXXXXRGQGTQVTVSS

In particular, a NANOBODY® (V_{HH} sequence) of the invention of the KERE group can be an amino acid sequence with the (general) structure

FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4

in which:

- i) the amino acid residue at position 45 according to the Kabat numbering is a charged amino acid (as defined herein) or a cysteine residue, and position 44 is preferably an E;
  and in which:
- ii) FR1 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-9 Representative FW1 sequences for NANOBODIES® (V_{HH} sequences) of the KERE-group. KERE FW1 sequence no. 1 SEQ ID NO: 23
QVQRVESGGGLVQAGGSLRLSCAASGRTSS KERE FW1 sequence no. 2 SEQ ID

NO: 24 QVQLVESGGGLVQTGDSLSLSCSASGRTFS KERE FW1 sequence no. 3 SEQ ID NO: 25 QVKLEESGGGLVQAGDSLRLSCAATGRAFG KERE FW1 sequence no. 4 SEQ ID NO: 26 AVQLVESGGGLVQPGESLGLSCVASGRDFV KERE FW1 sequence no. 5 SEQ ID NO: 27 EVQLVESGGGLVQAGGSLRLSCEVLGRTAG KERE FW1 sequence no. 6 SEQ ID NO: 28 QVQLVESGGGWVQPGGSLRLSCAASETILS KERE FW1 sequence no. 7 SEQ ID NO: 29 QVQLVESGGGTVQPGGSLNLSCVASGNTFN KERE FW1 sequence no. 8 SEQ ID NO: 30 EVQLVESGGGLAQPGGSLQLSCSAPGFTLD KERE FW1 sequence no. 9 SEQ ID NO: 31 AQELEESGGGLVQAGGSLRLSCAASGRTFN

and in which:

- iii) FR2 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-10 Representative FW2 sequences for NANOBODIES® (V_{HH} sequences) of the KERE-group. KERE FW2 sequence SEQ ID NO: 41 WFRQAPGKEREFVA no. 1 KERE FW2 sequence SEQ ID NO: 42 WFRQTPGREREFVA no. 2 KERE FW2 sequence SEQ ID NO: 43 WYRQAPGKQREMVA no. 3 KERE FW2 sequence SEQ ID NO: 44 WYRQGPGKQRELVA no. 4 KERE FW2 sequence SEQ ID NO: 45 WIRQAPGKEREGVS no. 5 KERE FW2 sequence SEQ ID NO: 46 WFREAPGKEREGIS no. 6 KERE FW2 sequence SEQ ID NO: 47 WYRQAPGKERDLVA no. 7 KERE FW2 sequence SEQ ID NO: 48 WFRQAPGKQREEVS no. 8 KERE FW2 sequence SEQ ID NO: 49 WFRQPPGKVREFVG no. 9

and in which:

- iv) FR3 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-11 Representative FW3 sequences for NANOBODIES® (V_{HH} sequences) of the KERE-group. (V_{HH} sequences) of the KERE-group. SEQ ID NO: 50 RFTISRDNAKNTVYLQMNSLKPEDTAVYRCYF KERE FW3 sequence no. 2 SEQ ID NO: 51 RFAISRDNNKNTGYLQMNSLEPEDTAVYYCAA KERE FW3 sequence no. 3 SEQ ID NO: 52 RFTVARNNAKNTVNLEMNSLKPEDTAVYYCAA KERE FW3 sequence no. 4 SEQ ID NO: 53 RFTISRDIAKNTVDLLMNNLEPEDTAVYYCAA KERE FW3 sequence no. 5 SEQ ID

NO: 54 RLTISRDNAVDTMYLQMNSLKPEDTAVYYCAA KERE FW3 sequence no. 6 SEQ ID NO: 55 RFTISRDNAKNTVYLQMDNVKPEDTAIYYCAA KERE FW3 sequence no. 7 SEQ ID NO: 56 RFTISKDSGKNTVYLQMTSLKPEDTAVYYCAT KERE FW3 sequence no. 8 SEQ ID NO: 57 RFTISRDSAKNMMYLQMNNLKPQDTAVYYCAA KERE FW3 sequence no. 9 SEQ ID NO: 58 RFTISRENDKSTVYLQLNSLKPEDTAVYYCAA KERE FW3 sequence no. 10 SEQ ID NO: 59 RFTISRDYAGNTAYLQMNSLKPEDTGVYYCAT

and in which:

- v) FR4 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-12 Representative FW4 sequences for NANOBODIES® (V_{HH} sequences)of the KERE-group. KERE FW4 sequence no. 1 SEQ ID NO: 60 WGQGTQVTVSS KERE FW4 sequence no. 2 SEQ ID NO: 61 WGKGTLVTVSS KERE FW4 sequence no. 3 SEQ ID NO: 62 RGQGTRVTVSS KERE FW4 sequence no. 4 SEQ ID NO: 63 WGLGTQVTISS

and in which:

- vi) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In the above NANOBODIES® (V_{HH} sequences), one or more of the further Hallmark residues are preferably as described herein (for example, when they are V_{HH} sequences or partially humanized NANOBODIES® (V_{HH} sequences)).

Also, the above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein.

With regard to framework 1, it will be clear to the skilled person that, when an amino acid sequence as outlined above is generated by expression of a nucleotide sequence, the first four amino acid sequences (i.e. amino acid residues 1-4 according to the Kabat numbering)

may often be determined by the primer(s) that have been used to generate said nucleic acid. Thus, for determining the degree of amino acid identity, the first four amino acid residues are preferably disregarded.

Also, with regard to framework 1, and although amino acid positions 27 to 30 are according to the Kabat numbering considered to be part of the framework regions (and not the CDR's), it has been found by analysis of a database of more than 1000 V_{HH} sequences that the positions 27 to 30 have a variability (expressed in terms of V_{HH} entropy and V_{HH} variability—see Tables B-4 to B-7) that is much greater than the variability on positions 1 to 26. Because of this, for determining the degree of amino acid identity, the amino acid residues at positions 27 to 30 are preferably also disregarded.

In view of this, a NANOBODY® (V_{HH} sequence) of the KERE class may be an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which:

- i) the amino acid residue at position 45 according to the Kabat numbering is a charged amino acid (as defined herein) or a cysteine residue, and position 44 is preferably an E;
  and in which:
- ii) FR1 is an amino acid sequence that, on positions 5 to 26 of the Kabat numbering, has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-13 Representative FW1 sequences (amino acid residues 5 to 26) for NANOBODIES® (V_{HH} sequences) of the KERE-group. KERE FW1 sequence no. 10 SEQ ID NO: 32 VESGGGLVQPGGSLRLSCAASG KERE FW1 sequence no. 11 SEQ ID NO: 33 VDSGGGLVQAGDSLKLSCALTG KERE FW1 sequence no. 12 SEQ ID NO: 34 VDSGGGLVQAGDSLRLSCAASG KERE FW1 sequence no. 13 SEQ ID NO: 35 VDSGGGLVEAGGSLRLSCQVSE KERE FW1 sequence no. 14 SEQ ID NO: 36 QDSGGGSVQAGGSLKLSCAASG KERE FW1 sequence no. 15 SEQ ID NO: 37 VQSGGRLVQAGDSLRLSCAASE KERE FW1 sequence no. 16 SEQ ID NO: 38 VESGGTLVQSGDSLKLSCASST KERE FW1 sequence no. 17 SEQ ID NO: 39 MESGGDSVQSGGSLTLSCVASG KERE FW1 sequence no. 18 SEQ ID NO: 40 QASGGGLVQAGGSLRLSCSASV

and in which:

- iii) FR2, FR3 and FR4 are as mentioned herein for FR2, FR3 and FR4 of NANOBODIES® (V_{HH} sequences) of the KERE-class;

and in which:

- iv) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

The above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein.

A NANOBODY® (V_{HH} sequence) of the GLEW class may be an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which

- i) preferably, when the NANOBODY® (V_{HH} sequence) of the GLEW-class is a non-humanized NANOBODY® (V_{HH} sequence), the amino acid residue in position 108 is Q;
- ii) FR1 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-14 Representative FW1 sequences for Nanobodies of the GLEW-group. GLEW FW1 sequence no. 1 SEQ ID NO: 64 QVQLVESGGGLVQPGGSLRLSCAASGFTFS GLEW FW1 sequence no. 2 SEQ ID NO: 65 EVHLVESGGGLVRPGGSLRLSCAAFGFIFK GLEW FW1 sequence no. 3 SEQ ID NO: 66 QVKLEESGGGLAQPGGSLRLSCVASGFTFS GLEW FW1 sequence no. 4 SEQ ID NO: 67 EVQLVESGGGLVQPGGSLRLSCVCVSSGCT GLEW FW1 sequence no. 5 SEQ ID NO: 68 EVQLVESGGGLALPGGSLTLSCVFSGSTFS

and in which:

- iii) FR2 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-15 Representative FW2 sequences for NANOBODIES® (V_{HH} sequences) of the GLEW-group. GLEW FW2 sequence SEQ ID NO: 72 WVRQAPGKVLEWVS no. 1 GLEW FW2 sequence SEQ ID NO: 73 WVRRPPGKGLEWVS no. 2 GLEW FW2 sequence SEQ ID NO: 74 WVRQAPGMGLEWVS no. 3 GLEW FW2 sequence SEQ ID NO: 75 WVRQAPGKEPEWVS no. 4 GLEW FW2 sequence SEQ ID NO: 76

WVRQAPGKDQEWVS no. 5 GLEW FW2 sequence SEQ ID NO: 77
WVRQAPGKAEEWVS no. 6 GLEW FW2 sequence SEQ ID NO: 78
WVRQAPGKGLEWVA no. 7 GLEW FW2 sequence SEQ ID NO: 79
WVRQAPGRATEWVS no. 8

and in which:

- iv) FR3 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-16 Representative FW3 sequences for NANOBODIES® (V_{HH} sequences) of the GLEW-group. GLEW FW3 sequence no. 1 SEQ ID NO: 80 RFTISRDNAKNTLYLQMNSLKPEDTAVYYCVK GLEW FW3 sequence no. 2 SEQ ID NO: 81 RFTISRDNARNTLYLQMDSLIPEDTALYYCAR GLEW FW3 sequence no. 3 SEQ ID NO: 82 RFTSSRDNAKSTLYLQMNDLKPEDTALYYCAR GLEW FW3 sequence no. 4 SEQ ID NO: 83 RFIISRDNAKNTLYLQMNSLGPEDTAMYYCQR GLEW FW3 sequence no. 5 SEQ ID NO: 84 RFTASRDNAKNTLYLQMNSLKSEDTARYYCAR GLEW FW3 sequence no. 6 SEQ ID NO: 85 RFTISRDNAKNTLYLQMDDLQSEDTAMYYCGR

and in which:

- v) FR4 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-17 Representative FW4 sequences for NANOBODIES® (V_{HH} sequences) of the GLEW-group. GLEW FW4 sequence no. 1 SEQ ID NO: 86 GSQGTQVTVSS GLEW FW4 sequence no. 2 SEQ ID NO: 87 LRGGTQVTVSS GLEW FW4 sequence no. 3 SEQ ID NO: 88 RGQGTLVTVSS GLEW FW4 sequence no. 4 SEQ ID NO: 89 RSRGIQVTVSS GLEW FW4 sequence no. 5 SEQ ID NO: 90 WGKGTQVTVSS GLEW FW4 sequence no. 6 SEQ ID NO: 91 WGQGTQVTVSS

and in which:

- vi) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In the above NANOBODIES® (V_{HH} sequences), one or more of the further Hallmark residues are preferably as described herein (for example, when they are V_{HH} sequences or partially humanized NANOBODIES® (V_{HH} sequences)).

With regard to framework 1, it will again be clear to the skilled person that, for determining the degree of amino acid identity, the amino acid residues on positions 1 to 4 and 27 to 30 are preferably disregarded.

In view of this, a NANOBODY® (V_{HH} sequence) of the GLEW class may be an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which:

- i) preferably, when the NANOBODY® (V_{HH} sequence) of the GLEW-class is a non-humanized NANOBODY® (V_{HH} sequence), the amino acid residue in position 108 is Q;
  and in which:
- ii) FR1 is an amino acid sequence that, on positions 5 to 26 of the Kabat numbering, has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-18 Representative FW1 sequences (amino acid residues 5 to 26) for NANOBODIES® (V_{HH} sequences) KERE-group. GLEW FW1 SEQ ID NO: 69 VESGGGLVQPGGSLRLSCAASG sequence no. 6 GLEW FW1 SEQ ID NO: 70 EESGGGLAQPGGSLRLSCVASG sequence no. 7 GLEW FW1 SEQ ID NO: 71 VESGGGLALPGGSLTLSCVFSG sequence no. 8

and in which:

- iii) FR2, FR3 and FR4 are as mentioned herein for FR2, FR3 and FR4 of NANOBODIES® (V_{HH} sequences) of the GLEW-class;
  and in which:
- iv) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

The above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein. In the above NANOBODIES® (V_{HH} sequences), one or more of the

further Hallmark residues are preferably as described herein (for example, when they are V_{HH} sequences or partially humanized NANOBODIES® (V_{HH} sequences)).

A NANOBODY® (V_{HH} sequence) of the P, R, S 103 class may be an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which

- i) the amino acid residue at position 103 according to the Kabat numbering is different from W;
  and in which:
- ii) preferably the amino acid residue at position 103 according to the Kabat numbering is P, R or S, and more preferably R;
  and in which:
- iii) FR1 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-19 Representative FW1 sequences for NANOBODIES® (V_{HH} sequences) of the P, R, S 103-group. P, R, S 103 FW1 sequence no. 1 SEQ ID NO: 92 AVQLVESGGGLVQAGGSLRLSCAASGRTFS P, R, S 103 FW1 sequence no. 2 SEQ ID NO: 93 QVQLQESGGGMVQPGGSLRLSCAASGFDFG P, R, S 103 FW1 sequence no. 3 SEQ ID NO: 94 EVHLVESGGGLVRPGGSLRLSCAAFGFIFK P, R, S 103 FW1 sequence no. 4 SEQ ID NO: 95 QVQLAESGGGLVQPGGSLKLSCAASRTIVS P, R, S 103 FW1 sequence no. 5 SEQ ID NO: 96 QEHLVESGGGLVDIGGSLRLSCAASERIFS P, R, S 103 FW1 sequence no. 6 SEQ ID NO: 97 QVKLEESGGGLAQPGGSLRLSCVASGFTFS P, R, S 103 FW1 sequence no. 7 SEQ ID NO: 98 EVQLVESGGGLVQPGGSLRLSCVCVSSGCT P, R, S 103 FW1 sequence no. 8 SEQ ID NO: 99 EVQLVESGGGLALPGGSLTLSCVFSGSTFS

and in which

- iv) FR2 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-20 Representative FW2 sequences for NANOBODIES® (V_{HH} sequences) of the P, R, S 103-group. P, R, S 103 FW2 sequence no. 1 SEQ ID NO: 102 WFRQAPGKEREFVA P, R, S 103 FW2 sequence no. 2 SEQ ID NO: 103 WVRQAPGKVLEWVS P, R, S 103 FW2 sequence no. 3 SEQ ID NO: 104 WVRRPPGKGLEWVS P, R, S 103 FW2 sequence no. 4 SEQ ID NO: 105 WIRQAPGKEREGVS P, R, S 103 FW2 sequence no. 5

SEQ ID NO: 106 WVRQYPGKEPEWVS P, R, S 103 FW2 sequence no. 6
SEQ ID NO: 107 WFRQPPGKEHEFVA P, R, S 103 FW2 sequence no. 7
SEQ ID NO: 108 WYRQAPGKRTELVA P, R, S 103 FW2 sequence no. 8
SEQ ID NO: 109 WLRQAPGQGLEWVS P, R, S 103 FW2 sequence no. 9
SEQ ID NO: 110 WLRQTPGKGLEWVG P, R, S 103 FW2 sequence no. 10
SEQ ID NO: 111 WVRQAPGKAEEFVS

and in which:

- v) FR3 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-21 Representative FW3 sequences for NANOBODIES® (V_{HH} sequences) of the P, R, S 103-group. P, R, S 103 FW3 sequence no. 1 SEQ ID NO: 112 RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA P, R, S 103 FW3 sequence no. 2 SEQ ID NO: 113 RFTISRDNARNTLYLQMDSLIPEDTALYYCAR P, R, S 103 FW3 sequence no. 3 SEQ ID NO: 114 RFTISRDNAKNEMYLQMNNLKTEDTGVYWCGA P, R, S 103 FW3 sequence no. 4 SEQ ID NO: 115 RFTISSDSNRNMIYLQMNNLKPEDTAVYYCAA P, R, S 103 FW3 sequence no. 5 SEQ ID NO: 116 RFTISRDNAKNMLYLHLNNLKSEDTAVYYCRR P, R, S 103 FW3 sequence no. 6 SEQ ID NO: 117 RFTISRDNAKKTVYLRLNSLNPEDTAVYSCNL P, R, S 103 FW3 sequence no. 7 SEQ ID NO: 118 RFKISRDNAKKTLYLQMNSLGPEDTAMYYCQR P, R, S 103 FW3 sequence no. 8 SEQ ID NO: 119 RFTVSRDNGKNTAYLRMNSLKPEDTADYYCAV

and in which:

- vi) FR4 is an amino acid sequence that has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-22 Representative FW4 sequences for NANOBODIES® (V_{HH} sequences) of the P, R, S 103-group. P, R, S 103 FW4 SEQ ID NO: 120 RGQGTQVTVSS sequence no. 1 P, R, S 103 FW4 SEQ ID NO: 121 LRGGTQVTVSS sequence no. 2 P, R, S 103 FW4 SEQ ID NO: 122 GNKGTLVTVSS sequence no. 3 P, R, S 103 FW4 SEQ ID NO: 123 SSPGTQVTVSS sequence no. 4 P, R, S 103 FW4 SEQ ID NO: 124 SSQGTLVTVSS sequence no. 5 P, R, S 103 FW4 SEQ ID NO: 125 RSRGIQVTVSS sequence no. 6

and in which:

- vii) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

In the above NANOBODIES® (V_{HH} sequences), one or more of the further Hallmark residues are preferably as described herein (for example, when they are V_{HH} sequences or partially humanized NANOBODIES® (V_{HH} sequences)).

With regard to framework 1, it will again be clear to the skilled person that, for determining the degree of amino acid identity, the amino acid residues on positions 1 to 4 and 27 to 30 are preferably disregarded.

In view of this, a NANOBODY® (V_{HH} sequence) of the P,R,S 103 class may be an amino acid sequence that is comprised of four framework regions/sequences interrupted by three complementarity determining regions/sequences, in which:

- i) the amino acid residue at position 103 according to the Kabat numbering is different from W;
  and in which:
- ii) preferably the amino acid residue at position 103 according to the Kabat numbering is P, R or S, and more preferably R;
  and in which:
- iii) FR1 is an amino acid sequence that, on positions 5 to 26 of the Kabat numbering, has at least 80% amino acid identity with at least one of the following amino acid sequences:

TABLE B-23 Representative FW1 sequences (amino acid residues 5 to 26) for NANOBODIES® (V_{HH} sequences) of the P, R, S 103-group. P, R, S 103 FW1 SEQ ID VESGGGLVQAGGSLRLSCAASG sequence no. 9 NO: 100 P, R, S 103 FW1 SEQ ID AESGGGLVQPGGSLKLSCAASR sequence no. 10 NO: 101

and in which:

- iv) FR2, FR3 and FR4 are as mentioned herein for FR2, FR3 and FR4 of NANOBODIES® (V_{HH} sequences) of the P,R,S 103 class;
  and in which:
- v) CDR1, CDR2 and CDR3 are as defined herein, and are preferably as defined

according to one of the preferred aspects herein, and are more preferably as defined according to one of the more preferred aspects herein.

The above NANOBODIES® (V_{HH} sequences) may for example be V_{HH} sequences or may be humanized NANOBODIES® (V_{HH} sequences). When the above NANOBODY® (V_{HH} sequence) sequences are V_{HH} sequences, they may be suitably humanized, as further described herein. When the NANOBODIES® (V_{HH} sequences) are partially humanized NANOBODIES® (V_{HH} sequences), they may optionally be further suitably humanized, again as described herein.

In the above NANOBODIES® (V_{HH} sequences), one or more of the further Hallmark residues are preferably as described herein (for example, when they are V_{HH} sequences or partially humanized NANOBODIES® (V_{HH} sequences)).

In another preferred, but non-limiting aspect, the invention relates to a NANOBODY® (V_{HH} sequence) as described above, in which the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said NANOBODY® (V_{HH} sequence) and one or more of the sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), in which the amino acid residues that form the framework regions are disregarded. Such NANOBODIES® (V_{HH} sequences) can be as further described herein.

As already mentioned herein, another preferred but non-limiting aspect of the invention relates to a NANOBODY® (V_{HH} sequence) with an amino acid sequence that is chosen from the group consisting of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

Also, in the above NANOBODIES® (V_{HH} sequences):

- i) any amino acid substitution (when it is not a humanizing substitution as defined herein) is preferably, and compared to the corresponding amino acid sequence of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1), a conservative amino acid substitution, (as defined herein);

and/or:

- ii) its amino acid sequence preferably contains either only amino acid substitutions, or otherwise preferably no more than 5, preferably no more than 3, and more preferably only 1 or 2 amino acid deletions or insertions, compared to the corresponding amino acid sequence of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1);
  and/or
- iii) the CDR's may be CDR's that are derived by means of affinity maturation, for example starting from the CDR's of to the corresponding amino acid sequence of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

Preferably, the CDR sequences and FR sequences in the NANOBODIES® (V_{HH} sequences) of the invention are such that the NANOBODIES® (V_{HH} sequences) of the invention (and polypeptides of the invention comprising the same):

- - bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles);
  and/or such that they:
  - bind to an envelope protein of a virus with a k_{on}-rate of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$;
    and/or such that they:
  - bind to an envelope protein of a virus with a k_{off} rate between 1 s^{-1} (t_{v2}=0.69 s) and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, CDR sequences and FR sequences present in the NANOBODIES® (V_{HH} sequences) of the invention are such that the Nanobodies of the invention will bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

According to one non-limiting aspect of the invention, a NANOBODY® (V_{HH} sequence) may be as defined herein, but with the proviso that it has at least “one amino acid difference” (as defined herein) in at least one of the framework regions compared to the corresponding framework region of a naturally occurring human V_H domain, and in particular compared to

the corresponding framework region of DP-47. More specifically, according to one non-limiting aspect of the invention, a NANOBODY® (V_{HH} sequence) may be as defined herein, but with the proviso that it has at least "one amino acid difference" (as defined herein) at at least one of the Hallmark residues (including those at positions 108, 103 and/or 45) compared to the corresponding framework region of a naturally occurring human V_H domain, and in particular compared to the corresponding framework region of DP-47. Usually, a NANOBODY® (V_{HH} sequence) will have at least one such amino acid difference with a naturally occurring V_H domain in at least one of FR2 and/or FR4, and in particular at at least one of the Hallmark residues in FR2 and/or FR4 (again, including those at positions 108, 103 and/or 45).

Also, a humanized NANOBODY® (V_{HH} sequence) of the invention may be as defined herein, but with the proviso that it has at least "one amino acid difference" (as defined herein) in at least one of the framework regions compared to the corresponding framework region of a naturally occurring V_{HH} domain. More specifically, according to one non-limiting aspect of the invention, a humanized NANOBODY® (V_{HH} sequence) may be as defined herein, but with the proviso that it has at least "one amino acid difference" (as defined herein) at at least one of the Hallmark residues (including those at positions 108, 103 and/or 45) compared to the corresponding framework region of a naturally occurring V_{HH} domain. Usually, a humanized NANOBODY® (V_{HH} sequence) will have at least one such amino acid difference with a naturally occurring V_{HH} domain in at least one of FR2 and/or FR4, and in particular at at least one of the Hallmark residues in FR2 and/or FR4 (again, including those at positions 108, 103 and/or 45).

As will be clear from the disclosure herein, it is also within the scope of the invention to use natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the NANOBODIES® (V_{HH} sequences) of the invention as defined herein, and in particular analogs of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1). Thus, according to one aspect of the invention, the term "NANOBODY® (V_{HH} sequence) of the invention" in its broadest sense also covers such analogs.

Generally, in such analogs, one or more amino acid residues may have been replaced, deleted and/or added, compared to the NANOBODIES® (V_{HH} sequences) of the invention as defined herein. Such substitutions, insertions or deletions may be made in one or more of the framework regions and/or in one or more of the CDR's. When such substitutions, insertions or deletions are made in one or more of the framework regions, they may be made at one or more of the Hallmark residues and/or at one or more of the other positions in the framework residues, although substitutions, insertions or deletions at the Hallmark residues are generally less preferred (unless these are suitable humanizing substitutions as

described herein).

By means of non-limiting examples, a substitution may for example be a conservative substitution (as described herein) and/or an amino acid residue may be replaced by another amino acid residue that naturally occurs at the same position in another V_{HH} domain (see Tables B-4 to B-7 for some non-limiting examples of such substitutions), although the invention is generally not limited thereto. Thus, any one or more substitutions, deletions or insertions, or any combination thereof, that either improve the properties of the NANOBODY® (V_{HH} sequence) of the invention or that at least do not detract too much from the desired properties or from the balance or combination of desired properties of the NANOBODY® (V_{HH} sequence) of the invention (i.e. to the extent that the NANOBODY® (V_{HH} sequence) is no longer suited for its intended use) are included within the scope of the invention. A skilled person will generally be able to determine and select suitable substitutions, deletions or insertions, or suitable combinations of thereof, based on the disclosure herein and optionally after a limited degree of routine experimentation, which may for example involve introducing a limited number of possible substitutions and determining their influence on the properties of the NANOBODIES® (V_{HH} sequences) thus obtained.

For example, and depending on the host organism used to express the NANOBODY® (V_{HH} sequence) or polypeptide of the invention, such deletions and/or substitutions may be designed in such a way that one or more sites for post-translational modification (such as one or more glycosylation sites or myristilation sites) are removed, as will be within the ability of the person skilled in the art. Alternatively, substitutions or insertions may be designed so as to introduce one or more sites for attachment of functional groups (as described herein), for example to allow site-specific pegylation (again as described herein).

As can be seen from the data on the V_{HH} entropy and V_{HH} variability given in Tables B-4 to B-7 above, some amino acid residues in the framework regions are more conserved than others. Generally, although the invention in its broadest sense is not limited thereto, any substitutions, deletions or insertions are preferably made at positions that are less conserved. Also, generally, amino acid substitutions are preferred over amino acid deletions or insertions.

The analogs are preferably such that they can bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein for the NANOBODIES® (V_{HH} sequences) of the invention.

The analogs are preferably also such that they retain the favourable properties the NANOBODIES® (V_{HH} sequences), as described herein.

Also, according to one preferred aspect, the analogs have a degree of sequence identity of at least 70%, preferably at least 80%, more preferably at least 90%, such as at least 95% or 99% or more; and/or preferably have at most 20, preferably at most 10, even more preferably at most 5, such as 4, 3, 2 or only 1 amino acid difference (as defined herein), with one of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

Also, the framework sequences and CDR's of the analogs are preferably such that they are in accordance with the preferred aspects defined herein. More generally, as described herein, the analogs will have (a) a Q at position 108; and/or (b) a charged amino acid or a cysteine residue at position 45 and preferably an E at position 44, and more preferably E at position 44 and R at position 45; and/or (c) P, R or S at position 103.

One preferred class of analogs of the NANOBODIES® (V_{HH} sequences) of the invention comprise NANOBODIES® (V_{HH} sequences) that have been humanized (i.e. compared to the sequence of a naturally occurring NANOBODY® (V_{HH} sequence) of the invention). As mentioned in the background art cited herein, such humanization generally involves replacing one or more amino acid residues in the sequence of a naturally occurring V_{HH} with the amino acid residues that occur at the same position in a human V_H domain, such as a human V_H3 domain. Examples of possible humanizing substitutions or combinations of humanizing substitutions will be clear to the skilled person, for example from the Tables herein, from the possible humanizing substitutions mentioned in the background art cited herein, and/or from a comparison between the sequence of a NANOBODY® (V_{HH} sequence) and the sequence of a naturally occurring human V_H domain.

The humanizing substitutions should be chosen such that the resulting humanized NANOBODIES® (V_{HH} sequences) still retain the favourable properties of NANOBODIES® (V_{HH} sequences) as defined herein, and more preferably such that they are as described for analogs in the preceding paragraphs. A skilled person will generally be able to determine and select suitable humanizing substitutions or suitable combinations of humanizing substitutions, based on the disclosure herein and optionally after a limited degree of routine experimentation, which may for example involve introducing a limited number of possible humanizing substitutions and determining their influence on the properties of the NANOBODIES® (V_{HH} sequences) thus obtained.

Generally, as a result of humanization, the NANOBODIES® (V_{HH} sequences) of the invention may become more “human-like”, while still retaining the favorable properties of the NANOBODIES® (V_{HH} sequences) of the invention as described herein. As a result, such humanized NANOBODIES® (V_{HH} sequences) may have several advantages, such as a reduced immunogenicity, compared to the corresponding naturally occurring V_{HH} domains. Again, based on the disclosure herein and optionally after a limited degree of routine

experimentation, the skilled person will be able to select humanizing substitutions or suitable combinations of humanizing substitutions which optimize or achieve a desired or suitable balance between the favourable properties provided by the humanizing substitutions on the one hand and the favourable properties of naturally occurring V_{HH} domains on the other hand.

The NANOBODIES® (V_{HH} sequences) of the invention may be suitably humanized at any framework residue(s), such as at one or more Hallmark residues (as defined herein) or at one or more other framework residues (i.e. non-Hallmark residues) or any suitable combination thereof. One preferred humanizing substitution for NANOBODIES® (V_{HH} sequences) of the "P,R,S-103 group" or the "KERE group" is Q108 into L108. NANOBODIES® (V_{HH} sequences) of the "GLEW class" may also be humanized by a Q108 into L108 substitution, provided at least one of the other Hallmark residues contains a camelid (camelizing) substitution (as defined herein). For example, as mentioned above, one particularly preferred class of humanized NANOBODIES® (V_{HH} sequences) has GLEW or a GLEW-like sequence at positions 44-47; P, R or S (and in particular R) at position 103, and an L at position 108.

The humanized and other analogs, and nucleic acid sequences encoding the same, can be provided in any manner known per se, for example using one or more of the techniques mentioned on pages 103 and 104 of WO 08/020079.

As mentioned there, it will be also be clear to the skilled person that the NANOBODIES® (V_{HH} sequences) of the invention (including their analogs) can be designed and/or prepared starting from human V_H sequences (i.e. amino acid sequences or the corresponding nucleotide sequences), such as for example from human V_H3 sequences such as DP-47, DP-51 or DP-29, i.e. by introducing one or more camelizing substitutions (i.e. changing one or more amino acid residues in the amino acid sequence of said human V_H domain into the amino acid residues that occur at the corresponding position in a V_{HH} domain), so as to provide the sequence of a NANOBODY® (V_{HH} sequence) of the invention and/or so as to confer the favourable properties of a NANOBODY® (V_{HH} sequence) to the sequence thus obtained. Again, this can generally be performed using the various methods and techniques referred to in the previous paragraph, using an amino acid sequence and/or nucleotide sequence for a human V_H domain as a starting point.

Some preferred, but non-limiting camelizing substitutions can be derived from Tables B-4 to B-7. It will also be clear that camelizing substitutions at one or more of the Hallmark residues will generally have a greater influence on the desired properties than substitutions at one or more of the other amino acid positions, although both and any suitable combination thereof are included within the scope of the invention. For example, it is possible to introduce one or more camelizing substitutions that already confer at least

some the desired properties, and then to introduce further camelizing substitutions that either further improve said properties and/or confer additional favourable properties. Again, the skilled person will generally be able to determine and select suitable camelizing substitutions or suitable combinations of camelizing substitutions, based on the disclosure herein and optionally after a limited degree of routine experimentation, which may for example involve introducing a limited number of possible camelizing substitutions and determining whether the favourable properties of NANOBODIES® (V_{HH} sequences) are obtained or improved (i.e. compared to the original V_H domain).

Generally, however, such camelizing substitutions are preferably such that the resulting amino acid sequence at least contains (a) a Q at position 108; and/or (b) a charged amino acid or a cysteine residue at position 45 and preferably also an E at position 44, and more preferably E at position 44 and R at position 45; and/or (c) P, R or S at position 103; and optionally one or more further camelizing substitutions. More preferably, the camelizing substitutions are such that they result in a NANOBODY® (V_{HH} sequence) of the invention and/or in an analog thereof (as defined herein), such as in a humanized analog and/or preferably in an analog that is as defined in the preceding paragraphs.

As will also be clear from the disclosure herein, it is also within the scope of the invention to use parts or fragments, or combinations of two or more parts or fragments, of the NANOBODIES® (V_{HH} sequences) of the invention as defined herein, and in particular parts or fragments of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1). Thus, according to one aspect of the invention, the term "NANOBODY® (V_{HH} sequence) of the invention" in its broadest sense also covers such parts or fragments.

Generally, such parts or fragments of the NANOBODIES® (V_{HH} sequences) of the invention (including analogs thereof) have amino acid sequences in which, compared to the amino acid sequence of the corresponding full length NANOBODY® (V_{HH} sequence) of the invention (or analog thereof), one or more of the amino acid residues at the N-terminal end, one or more amino acid residues at the C-terminal end, one or more contiguous internal amino acid residues, or any combination thereof, have been deleted and/or removed.

The parts or fragments are preferably such that they can bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein for the NANOBODIES® (V_{HH} sequences) of the invention.

Any part or fragment is preferably such that it comprises at least 10 contiguous amino acid residues, preferably at least 20 contiguous amino acid residues, more preferably at least 30 contiguous amino acid residues, such as at least 40 contiguous amino acid residues, of the

amino acid sequence of the corresponding full length NANOBODY® (V_{HH} sequence) of the invention.

Also, any part or fragment is such preferably that it comprises at least one of CDR1, CDR2 and/or CDR3 or at least part thereof (and in particular at least CDR3 or at least part thereof). More preferably, any part or fragment is such that it comprises at least one of the CDR's (and preferably at least CDR3 or part thereof) and at least one other CDR (i.e. CDR1 or CDR2) or at least part thereof, preferably connected by suitable framework sequence(s) or at least part thereof. More preferably, any part or fragment is such that it comprises at least one of the CDR's (and preferably at least CDR3 or part thereof) and at least part of the two remaining CDR's, again preferably connected by suitable framework sequence(s) or at least part thereof.

According to another particularly preferred, but non-limiting aspect, such a part or fragment comprises at least CDR3, such as FR3, CDR3 and FR4 of the corresponding full length NANOBODY® (V_{HH} sequence) of the invention, i.e. as for example described in the International application WO 03/050531 (Lasters et al.).

As already mentioned above, it is also possible to combine two or more of such parts or fragments (i.e. from the same or different NANOBODIES® (V_{HH} sequences) of the invention), i.e. to provide an analog (as defined herein) and/or to provide further parts or fragments (as defined herein) of a NANOBODY® (V_{HH} sequence) of the invention. It is for example also possible to combine one or more parts or fragments of a NANOBODY® (V_{HH} sequence) of the invention with one or more parts or fragments of a human V_H domain.

According to one preferred aspect, the parts or fragments have a degree of sequence identity of at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80%, such as at least 90%, 95% or 99% or more with one of the NANOBODIES® (V_{HH} sequences) of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1).

The parts and fragments, and nucleic acid sequences encoding the same, can be provided and optionally combined in any manner known per se. For example, such parts or fragments can be obtained by inserting a stop codon in a nucleic acid that encodes a full-sized NANOBODY® (V_{HH} sequence) of the invention, and then expressing the nucleic acid thus obtained in a manner known per se (e.g. as described herein). Alternatively, nucleic acids encoding such parts or fragments can be obtained by suitably restricting a nucleic acid that encodes a full-sized NANOBODY® (V_{HH} sequence) of the invention or by synthesizing such a nucleic acid in a manner known per se. Parts or fragments may also be provided using techniques for peptide synthesis known per se.

The invention in its broadest sense also comprises derivatives of the NANOBODIES® (V_{HH}

sequences) of the invention. Such derivatives can generally be obtained by modification, and in particular by chemical and/or biological (e.g. enzymatical) modification, of the NANOBODIES® (V_{HH} sequences) of the invention and/or of one or more of the amino acid residues that form the NANOBODIES® (V_{HH} sequences) of the invention.

Examples of such modifications, as well as examples of amino acid residues within the NANOBODY® (V_{HH} sequence) sequence that can be modified in such a manner (i.e. either on the protein backbone but preferably on a side chain), methods and techniques that can be used to introduce such modifications and the potential uses and advantages of such modifications will be clear to the skilled person.

For example, such a modification may involve the introduction (e.g. by covalent linking or in an other suitable manner) of one or more functional groups, residues or moieties into or onto the NANOBODY® (V_{HH} sequence) of the invention, and in particular of one or more functional groups, residues or moieties that confer one or more desired properties or functionalities to the NANOBODY® (V_{HH} sequence) of the invention. Example of such functional groups will be clear to the skilled person.

For example, such modification may comprise the introduction (e.g. by covalent binding or in any other suitable manner) of one or more functional groups that increase the half-life, the solubility and/or the absorption of the NANOBODY® (V_{HH} sequence) of the invention, that reduce the immunogenicity and/or the toxicity of the NANOBODY® (V_{HH} sequence) of the invention, that eliminate or attenuate any undesirable side effects of the NANOBODY® (V_{HH} sequence) of the invention, and/or that confer other advantageous properties to and/or reduce the undesired properties of the NANOBODIES® (V_{HH} sequences) and/or polypeptides of the invention; or any combination of two or more of the foregoing. Examples of such functional groups and of techniques for introducing them will be clear to the skilled person, and can generally comprise all functional groups and techniques mentioned in the general background art cited hereinabove as well as the functional groups and techniques known per se for the modification of pharmaceutical proteins, and in particular for the modification of antibodies or antibody fragments (including ScFv's and single domain antibodies), for which reference is for example made to Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Co., Easton, Pa. (1980). Such functional groups may for example be linked directly (for example covalently) to a NANOBODY® (V_{HH} sequence) of the invention, or optionally via a suitable linker or spacer, as will again be clear to the skilled person.

One of the most widely used techniques for increasing the half-life and/or reducing the immunogenicity of pharmaceutical proteins comprises attachment of a suitable pharmacologically acceptable polymer, such as poly(ethyleneglycol) (PEG) or derivatives thereof (such as methoxypoly(ethyleneglycol) or mPEG). Generally, any suitable form of

pegylation can be used, such as the pegylation used in the art for antibodies and antibody fragments (including but not limited to (single) domain antibodies and ScFv's); reference is made to for example Chapman, Nat. Biotechnol., 54, 531-545 (2002); Veronese and Harris (2002) Adv. Drug Deliv. Rev. 54: 453-456, Harris and Chess, Nat. Rev. Drug. Discov., 2, (2003) and in WO 04/060965. Various reagents for pegylation of proteins are also commercially available, for example from Nektar Therapeutics, USA.

Preferably, site-directed pegylation is used, in particular via a cysteine-residue (see for example Yang et al., Protein Engineering, 16, 10, 761-770 (2003). For example, for this purpose, PEG may be attached to a cysteine residue that naturally occurs in a NANOBODY® (V_{HH} sequence) of the invention, a NANOBODY® (V_{HH} sequence) of the invention may be modified so as to suitably introduce one or more cysteine residues for attachment of PEG, or an amino acid sequence comprising one or more cysteine residues for attachment of PEG may be fused to the N- and/or C-terminus of a NANOBODY® (V_{HH} sequence) of the invention, all using techniques of protein engineering known per se to the skilled person.

Preferably, for the NANOBODIES® (V_{HH} sequences) and proteins of the invention, a PEG is used with a molecular weight of more than 5000, such as more than 10,000 and less than 200,000, such as less than 100,000; for example in the range of 20,000-80,000.

Another, usually less preferred modification comprises N-linked or O-linked glycosylation, usually as part of co-translational and/or post-translational modification, depending on the host cell used for expressing the NANOBODY® (V_{HH} sequence) or polypeptide of the invention.

An also usually less preferred modification comprises myristilation, usually as part of co-translational and/or post-translational modification, depending on the host cell used for expressing the NANOBODY® (V_{HH} sequence) or polypeptide of the invention.

Yet another modification may comprise the introduction of one or more detectable labels or other signal-generating groups or moieties, depending on the intended use of the labelled NANOBODY® (V_{HH} sequence). Suitable labels and techniques for attaching, using and detecting them will be clear to the skilled person, and for example include, but are not limited to, the fluorescent labels, phosphorescent labels, chemiluminescent labels, bioluminescent labels, radio-isotopes, metals, metal chelates, metallic cations, chromophores and enzymes, such as those mentioned on page 109 of WO 08/020079. Other suitable labels will be clear to the skilled person, and for example include moieties that can be detected using NMR or ESR spectroscopy.

Such labelled NANOBODIES® (V_{HH} sequences) and polypeptides of the invention may for example be used for in vitro, in vivo or in situ assays (including immunoassays known per se such as ELISA, RIA, EIA and other “sandwich assays”, etc.) as well as in vivo diagnostic

and imaging purposes, depending on the choice of the specific label.

As will be clear to the skilled person, another modification may involve the introduction of a chelating group, for example to chelate one of the metals or metallic cations referred to above. Suitable chelating groups for example include, without limitation, diethyl-enetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

Yet another modification may comprise the introduction of a functional group that is one part of a specific binding pair, such as the biotin-(strept)avidin binding pair. Such a functional group may be used to link the NANOBODY® (V_{HH} sequence) of the invention to another protein, polypeptide or chemical compound that is bound to the other half of the binding pair, i.e. through formation of the binding pair. For example, a NANOBODY® (V_{HH} sequence) of the invention may be conjugated to biotin, and linked to another protein, polypeptide, compound or carrier conjugated to avidin or streptavidin. For example, such a conjugated NANOBODY® (V_{HH} sequence) may be used as a reporter, for example in a diagnostic system where a detectable signal-producing agent is conjugated to avidin or streptavidin. Such binding pairs may for example also be used to bind the NANOBODY® (V_{HH} sequence) of the invention to a carrier, including carriers suitable for pharmaceutical purposes. One non-limiting example are the liposomal formulations described by Cao and Suresh, Journal of Drug Targetting, 8, 4, 257 (2000). Such binding pairs may also be used to link a therapeutically active agent to the NANOBODY® (V_{HH} sequence) of the invention.

For some applications, in particular for those applications in which it is intended to kill a cell that expresses the target against which the NANOBODIES® (V_{HH} sequences) of the invention are directed (e.g. in the treatment of cancer), or to reduce or slow the growth and/or proliferation such a cell, the NANOBODIES® (V_{HH} sequences) of the invention may also be linked to a toxin or to a toxic residue or moiety. Examples of toxic moieties, compounds or residues which can be linked to a NANOBODY® (V_{HH} sequence) of the invention to provide—for example—a cytotoxic compound will be clear to the skilled person and can for example be found in the prior art cited above and/or in the further description herein. One example is the so-called ADEPT™ technology described in WO 03/055527.

Other potential chemical and enzymatical modifications will be clear to the skilled person. Such modifications may also be introduced for research purposes (e.g. to study function-activity relationships). Reference is for example made to Lundblad and Bradshaw, Biotechnol. Appl. Biochem., 26, 143-151 (1997).

Preferably, the derivatives are such that they bind to an envelope protein of a virus with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein for the NANOBODIES® (V_{HH} sequences)

of the invention.

As mentioned above, the invention also relates to proteins or polypeptides that essentially consist of or comprise at least one NANOBODY® (V_{HH} sequence) of the invention. By "essentially consist of" is meant that the amino acid sequence of the polypeptide of the invention either is exactly the same as the amino acid sequence of a NANOBODY® (V_{HH} sequence) of the invention or corresponds to the amino acid sequence of a NANOBODY® (V_{HH} sequence) of the invention which has a limited number of amino acid residues, such as 1-20 amino acid residues, for example 1-10 amino acid residues and preferably 1-6 amino acid residues, such as 1, 2, 3, 4, 5 or 6 amino acid residues, added at the amino terminal end, at the carboxy terminal end, or at both the amino terminal end and the carboxy terminal end of the amino acid sequence of the NANOBODY® (V_{HH} sequence). Said amino acid residues may or may not change, alter or otherwise influence the (biological) properties of the NANOBODY® (V_{HH} sequence) and may or may not add further functionality to the NANOBODY® (V_{HH} sequence). For example, such amino acid residues:

- can comprise an N-terminal Met residue, for example as result of expression in a heterologous host cell or host organism.
- may form a signal sequence or leader sequence that directs secretion of the NANOBODY® (V_{HH} sequence) from a host cell upon synthesis. Suitable secretory leader peptides will be clear to the skilled person, and may be as further described herein. Usually, such a leader sequence will be linked to the N-terminus of the NANOBODY® (V_{HH} sequence), although the invention in its broadest sense is not limited thereto;
- may form a sequence or signal that allows the NANOBODY® (V_{HH} sequence) to be directed towards and/or to penetrate or enter into specific organs, tissues, cells, or parts or compartments of cells, and/or that allows the NANOBODY® (V_{HH} sequence) to penetrate or cross a biological barrier such as a cell membrane, a cell layer such as a layer of epithelial cells, a tumor including solid tumors, or the blood-brain-barrier. Examples of such amino acid sequences will be clear to the skilled person and include those mentioned in paragraph c) on page 112 of WO 08/020079.
- may form a "tag", for example an amino acid sequence or residue that allows or facilitates the purification of the NANOBODY® (V_{HH} sequence), for example using affinity techniques directed against said sequence or residue. Thereafter, said sequence or residue may be removed (e.g. by chemical or enzymatical cleavage) to provide the NANOBODY® (V_{HH} sequence) sequence (for this purpose, the tag may optionally be linked to the NANOBODY® (V_{HH} sequence) sequence via a cleavable linker sequence or contain a cleavable motif). Some preferred, but non-limiting examples of such residues are multiple histidine residues, glutathione residues and a myc-tag (see for example SEQ ID NO:31 of

WO 06/12282).

- may be one or more amino acid residues that have been functionalized and/or that can serve as a site for attachment of functional groups. Suitable amino acid residues and functional groups will be clear to the skilled person and include, but are not limited to, the amino acid residues and functional groups mentioned herein for the derivatives of the NANOBODIES® (V_{HH} sequences) of the invention.

According to another aspect, a polypeptide of the invention comprises a NANOBODY® (V_{HH} sequence) of the invention, which is fused at its amino terminal end, at its carboxy terminal end, or both at its amino terminal end and at its carboxy terminal end to at least one further amino acid sequence, i.e. so as to provide a fusion protein comprising said NANOBODY® (V_{HH} sequence) of the invention and the one or more further amino acid sequences. Such a fusion will also be referred to herein as a "NANOBODY® (V_{HH} sequence) fusion".

The one or more further amino acid sequence may be any suitable and/or desired amino acid sequences. The further amino acid sequences may or may not change, alter or otherwise influence the (biological) properties of the NANOBODY® (V_{HH} sequence), and may or may not add further functionality to the NANOBODY® (V_{HH} sequence) or the polypeptide of the invention. Preferably, the further amino acid sequence is such that it confers one or more desired properties or functionalities to the NANOBODY® (V_{HH} sequence) or the polypeptide of the invention.

For example, the further amino acid sequence may also provide a second binding site, which binding site may be directed against any desired protein, polypeptide, antigen, antigenic determinant or epitope (including but not limited to the same protein, polypeptide, antigen, antigenic determinant or epitope against which the NANOBODY® (V_{HH} sequence) of the invention is directed, or a different protein, polypeptide, antigen, antigenic determinant or epitope).

Example of such amino acid sequences will be clear to the skilled person, and may generally comprise all amino acid sequences that are used in peptide fusions based on conventional antibodies and fragments thereof (including but not limited to ScFv's and single domain antibodies). Reference is for example made to the review by Holliger and Hudson, Nature Biotechnology, 23, 9, 1126-1136 (2005).

For example, such an amino acid sequence may be an amino acid sequence that increases the half-life, the solubility, or the absorption, reduces the immunogenicity or the toxicity, eliminates or attenuates undesirable side effects, and/or confers other advantageous properties to and/or reduces the undesired properties of the polypeptides of the invention, compared to the NANOBODY® (V_{HH} sequence) of the invention per se. Some non-limiting examples of such amino acid sequences are serum proteins, such as human serum albumin

(see for example WO 00/27435) or haptenic molecules (for example haptens that are recognized by circulating antibodies, see for example WO 98/22141).

In particular, it has been described in the art that linking fragments of immunoglobulins (such as V_H domains) to serum albumin or to fragments thereof can be used to increase the half-life. Reference is for made to WO 00/27435 and WO 01/077137. According to the invention, the NANOBODY® (V_{HH} sequence) of the invention is preferably either directly linked to serum albumin (or to a suitable fragment thereof) or via a suitable linker, and in particular via a suitable peptide linked so that the polypeptide of the invention can be expressed as a genetic fusion (protein). According to one specific aspect, the NANOBODY® (V_{HH} sequence) of the invention may be linked to a fragment of serum albumin that at least comprises the domain III of serum albumin or part thereof. Reference is for example made to WO 07/112940 of Ablynx N.V.

Alternatively, the further amino acid sequence may provide a second binding site or binding unit that is directed against a serum protein (such as, for example, human serum albumin or another serum protein such as IgG), so as to provide increased half-life in serum. Such amino acid sequences for example include the NANOBODIES® (V_{HH} sequences) described below, as well as the small peptides and binding proteins described in WO 91/01743, WO 01/45746 and WO 02/076489 and the dAb's described in WO 03/002609 and WO 04/003019. Reference is also made to Harmsen et al., Vaccine, 23 (41); 4926-42, 2005, as well as to EP 0 368 684, as well as to WO 08/028977, WO 08/043821, WO 08/043822 and WO 08/068280.

Such amino acid sequences may in particular be directed against serum albumin (and more in particular human serum albumin) and/or against IgG (and more in particular human IgG). For example, such amino acid sequences may be amino acid sequences that are directed against (human) serum albumin and amino acid sequences that can bind to amino acid residues on (human) serum albumin that are not involved in binding of serum albumin to FcRn (see for example WO 06/0122787) and/or amino acid sequences that are capable of binding to amino acid residues on serum albumin that do not form part of domain III of serum albumin (see again for example WO 06/0122787); amino acid sequences that have or can provide an increased half-life (see for example WO 08/028977 by Ablynx N.V.)); amino acid sequences against human serum albumin that are cross-reactive with serum albumin from at least one species of mammal, and in particular with at least one species of primate (such as, without limitation, monkeys from the genus *Macaca* (such as, and in particular, cynomolgus monkeys (*Macaca fascicularis*) and/or rhesus monkeys (*Macaca mulatta*)) and baboon (*Papio ursinus*), reference is again made to WO 08/028977; amino acid sequences that can bind to serum albumin in a pH independent manner (see for example WO2008/043821) and/or amino acid sequences that are conditional binders (see for example WO 08/043822).

According to another aspect, the one or more further amino acid sequences may comprise one or more parts, fragments or domains of conventional 4-chain antibodies (and in particular human antibodies) and/or of heavy chain antibodies. For example, although usually less preferred, a NANOBODY® (V_{HH} sequence) of the invention may be linked to a conventional (preferably human) V_H or V_L domain or to a natural or synthetic analog of a V_H or V_L domain, again optionally via a linker sequence (including but not limited to other (single) domain antibodies, such as the dAb's described by Ward et al.).

The at least one NANOBODY® (V_{HH} sequence) may also be linked to one or more (preferably human) C_H1, C_H2 and/or C_H3 domains, optionally via a linker sequence. For instance, a NANOBODY® (V_{HH} sequence) linked to a suitable C_H1 domain could for example be used—together with suitable light chains—to generate antibody fragments/structures analogous to conventional Fab fragments or $F(ab')_2$ fragments, but in which one or (in case of an $F(ab')_2$ fragment) one or both of the conventional V_H domains have been replaced by a NANOBODY® (V_{HH} sequence) of the invention. Also, two NANOBODIES® (V_{HH} sequences) could be linked to a C_H2 and/or C_H3 domain (optionally via a linker) to provide a construct with increased half-life in vivo.

According to one specific aspect of a polypeptide of the invention, one or more NANOBODIES® (V_{HH} sequences) of the invention may be linked (optionally via a suitable linker or hinge region) to one or more constant domains (for example, 2 or 3 constant domains that can be used as part of/to form an Fc portion), to an Fc portion and/or to one or more antibody parts, fragments or domains that confer one or more effector functions to the polypeptide of the invention and/or may confer the ability to bind to one or more Fc receptors. For example, for this purpose, and without being limited thereto, the one or more further amino acid sequences may comprise one or more C_H2 and/or C_H3 domains of an antibody, such as from a heavy chain antibody (as described herein) and more preferably from a conventional human 4-chain antibody; and/or may form (part of) and Fc region, for example from IgG (e.g. from IgG1, IgG2, IgG3 or IgG4), from IgE or from another human Ig such as IgA, IgD or IgM. For example, WO 94/04678 describes heavy chain antibodies comprising a Camelid V_{HH} domain or a humanized derivative thereof (i.e. a NANOBODY® (V_{HH} sequence)), in which the Camelidae C_H2 and/or C_H3 domain have been replaced by human C_H2 and C_H3 domains, so as to provide an immunoglobulin that consists of 2 heavy chains each comprising a NANOBODY® (V_{HH} sequence) and human C_H2 and C_H3 domains (but no C_H1 domain), which immunoglobulin has the effector function provided by the C_H2 and C_H3 domains and which immunoglobulin can function without the presence of any light chains. Other amino acid sequences that can be suitably linked to the NANOBODIES® (V_{HH} sequences) of the invention so as to provide an effector function will be clear to the skilled person, and may be chosen on the basis of the desired effector function(s). Reference is for example made to WO 04/058820, WO 99/42077, WO 02/056910 and WO 05/017148, as well as the review by Holliger and Hudson, supra; and

to the non-prepublished US provisional application by Ablynx N.V. entitled "Constructs comprising single variable domains and an Fc portion derived from IgE" which has a filing date of Dec. 4, 2007 (see also PCT/EP2008/066366). Coupling of a NANOBODY® (V_{HH} sequence) of the invention to an Fc portion may also lead to an increased half-life, compared to the corresponding NANOBODY® (V_{HH} sequence) of the invention. For some applications, the use of an Fc portion and/or of constant domains (i.e. C_H2 and/or C_H3 domains) that confer increased half-life without any biologically significant effector function may also be suitable or even preferred. Other suitable constructs comprising one or more NANOBODIES® (V_{HH} sequences) and one or more constant domains with increased half-life in vivo will be clear to the skilled person, and may for example comprise two NANOBODIES® (V_{HH} sequences) linked to a C_H3 domain, optionally via a linker sequence. Generally, any fusion protein or derivatives with increased half-life will preferably have a molecular weight of more than 50 kD, the cut-off value for renal absorption.

In another one specific, but non-limiting, aspect, in order to form a polypeptide of the invention, one or more amino acid sequences of the invention may be linked (optionally via a suitable linker or hinge region) to naturally occurring, synthetic or semisynthetic constant domains (or analogs, variants, mutants, parts or fragments thereof) that have a reduced (or essentially no) tendency to self-associate into dimers (i.e. compared to constant domains that naturally occur in conventional 4-chain antibodies). Such monomeric (i.e. not self-associating) Fc chain variants, or fragments thereof, will be clear to the skilled person. For example, Helm et al., J Biol Chem 1996 271 7494, describe monomeric Fc chain variants that can be used in the polypeptide chains of the invention.

Also, such monomeric Fc chain variants are preferably such that they are still capable of binding to the complement or the relevant Fc receptor(s) (depending on the Fc portion from which they are derived), and/or such that they still have some or all of the effector functions of the Fc portion from which they are derived (or at a reduced level still suitable for the intended use). Alternatively, in such a polypeptide chain of the invention, the monomeric Fc chain may be used to confer increased half-life upon the polypeptide chain, in which case the monomeric Fc chain may also have no or essentially no effector functions.

Bivalent/multivalent, bispecific/multispecific or biparatopic/multiparatopic polypeptides of the invention may also be linked to Fc portions, in order to provide polypeptide constructs of the type that is described in the non-prepublished US provisional application U.S. 61/005,331 entitled "immunoglobulin constructs" filed on Dec. 4, 2007 (see also PCT/EP2008/066368).

The further amino acid sequences may also form a signal sequence or leader sequence that directs secretion of the NANOBODY® (V_{HH} sequence) or the polypeptide of the invention

from a host cell upon synthesis (for example to provide a pre-, pro- or prepro-form of the polypeptide of the invention, depending on the host cell used to express the polypeptide of the invention).

The further amino acid sequence may also form a sequence or signal that allows the NANOBODY® (V_{HH} sequence) or polypeptide of the invention to be directed towards and/or to penetrate or enter into specific organs, tissues, cells, or parts or compartments of cells, and/or that allows the NANOBODY® (V_{HH} sequence) or polypeptide of the invention to penetrate or cross a biological barrier such as a cell membrane, a cell layer such as a layer of epithelial cells, a tumor including solid tumors, or the blood-brain-barrier. Suitable examples of such amino acid sequences will be clear to the skilled person, and for example include, but are not limited to, those mentioned on page 118 of WO 08/020079. For some applications, in particular for those applications in which it is intended to kill a cell that expresses the target against which the NANOBODIES® (V_{HH} sequences) of the invention are directed (e.g. in the treatment of cancer), or to reduce or slow the growth and/or proliferation of such a cell, the NANOBODIES® (V_{HH} sequences) of the invention may also be linked to a (cyto)toxic protein or polypeptide. Examples of such toxic proteins and polypeptides which can be linked to a NANOBODY® (V_{HH} sequence) of the invention to provide—for example—a cytotoxic polypeptide of the invention will be clear to the skilled person and can for example be found in the prior art cited above and/or in the further description herein. One example is the so-called ADEPT™ technology described in WO 03/055527.

According to one preferred, but non-limiting aspect, said one or more further amino acid sequences comprise at least one further NANOBODY® (V_{HH} sequence), so as to provide a polypeptide of the invention that comprises at least two, such as three, four, five or more NANOBODIES® (V_{HH} sequences), in which said NANOBODIES® (V_{HH} sequences) may optionally be linked via one or more linker sequences (as defined herein). As described on pages 119 and 120 of WO 08/020079, polypeptides of the invention that comprise two or more NANOBODIES® (V_{HH} sequences), of which at least one is a NANOBODY® (V_{HH} sequence) of the invention, will also be referred to herein as "multivalent" polypeptides of the invention, and the NANOBODIES® (V_{HH} sequences) present in such polypeptides will also be referred to herein as being in a "multivalent format". For example, "bivalent" and "trivalent" polypeptides of the invention may be as further described on pages 119 and 120 of WO 08/020079.

Polypeptides of the invention that contain at least two NANOBODIES® (V_{HH} sequences), in which at least one NANOBODY® (V_{HH} sequence) is directed against a first antigen (i.e. against an envelope protein of a virus) and at least one NANOBODY® (V_{HH} sequence) is directed against a second antigen (i.e. different from an envelope protein of a virus), will also be referred to as "multispecific" polypeptides of the invention, and the NANOBODIES®

(V_{HH} sequences) present in such polypeptides will also be referred to herein as being in a "multispecific format". Thus, for example, a "bispecific" polypeptide of the invention is a polypeptide that comprises at least one NANOBODY® (V_{HH} sequence) directed against a first antigen (i.e. an envelope protein of a virus) and at least one further NANOBODY® (V_{HH} sequence) directed against a second antigen (i.e. different from the envelope protein of a virus), whereas a "trispecific" polypeptide of the invention is a polypeptide that comprises at least one NANOBODY® (V_{HH} sequence) directed against a first antigen (i.e. an envelope protein of a virus), at least one further NANOBODY® (V_{HH} sequence) directed against a second antigen (i.e. different from said envelope protein of a virus) and at least one further NANOBODY® (V_{HH} sequence) directed against a third antigen (i.e. different from both said envelope protein of a virus and the second antigen); etc.

Accordingly, in its simplest form, a bispecific polypeptide of the invention is a bivalent polypeptide of the invention (as defined herein), comprising a first NANOBODY® (V_{HH} sequence) directed against an envelope protein of a virus and a second NANOBODY® (V_{HH} sequence) directed against a second antigen, in which said first and second NANOBODY® (V_{HH} sequence) may optionally be linked via a linker sequence (as defined herein); whereas a trispecific polypeptide of the invention in its simplest form is a trivalent polypeptide of the invention (as defined herein), comprising a first NANOBODY® (V_{HH} sequence) directed against an envelope protein of a virus, a second NANOBODY® (V_{HH} sequence) directed against a second antigen and a third NANOBODY® (V_{HH} sequence) directed against a third antigen, in which said first, second and third NANOBODY® (V_{HH} sequence) may optionally be linked via one or more, and in particular one and more, in particular two, linker sequences.

However, as will be clear from the description hereinabove, the invention is not limited thereto, in the sense that a multispecific polypeptide of the invention may comprise at least one NANOBODY® (V_{HH} sequence) against an envelope protein of a virus, and any number of NANOBODIES® (V_{HH} sequences) directed against one or more antigens different from said envelope protein of a virus.

Furthermore, although it is encompassed within the scope of the invention that the specific order or arrangement of the various NANOBODIES® (V_{HH} sequences) in the polypeptides of the invention may have some influence on the properties of the final polypeptide of the invention (including but not limited to the affinity, specificity or avidity for the envelope protein of a virus, or against the one or more other antigens), said order or arrangement is usually not critical and may be suitably chosen by the skilled person, optionally after some limited routine experiments based on the disclosure herein. Thus, when reference is made to a specific multivalent or multispecific polypeptide of the invention, it should be noted that this encompasses any order or arrangements of the relevant NANOBODIES® (V_{HH} sequences), unless explicitly indicated otherwise.

Finally, it is also within the scope of the invention that the polypeptides of the invention contain two or more NANOBODIES® (V_{HH} sequences) and one or more further amino acid sequences (as mentioned herein).

As further described herein, a polypeptide of the invention may contain two or more amino acid sequences and/or NANOBODIES® (V_{HH} sequences) of the invention that are directed against an envelope protein of a virus. Generally, such polypeptides will bind to an envelope protein of a virus with increased avidity compared to a single amino acid sequence or NANOBODY® (V_{HH} sequence) of the invention. Such a polypeptide may for example comprise two amino acid sequences and/or NANOBODIES® (V_{HH} sequences) of the invention that are directed against the same antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus (which may or may not be an interaction site); or comprise at least one "first" amino acid sequence of the invention that is directed against a first same antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) of an envelope protein of a virus (which may or may not be an interaction site); and at least one "second" amino acid sequence and/or NANOBODY® (V_{HH} sequence) of the invention that is directed against a second antigenic determinant, epitope, part, domain, subunit or conformation (where applicable) different from the first (and which again may or may not be an interaction site). Preferably, in such "biparatopic" polypeptides of the invention, at least one amino acid sequence and/or NANOBODY® (V_{HH} sequence) of the invention is directed against an interaction site (as defined herein), although the invention in its broadest sense is not limited thereto.

It is thus also within the scope of the invention that, where applicable, a polypeptide of the invention can bind to two or more antigenic determinants, epitopes, parts, domains, subunits or conformations of an envelope protein of a virus. In such a case, the antigenic determinants, epitopes, parts, domains or subunits of said envelope protein of a virus to which the amino acid sequences and/or polypeptides of the invention bind may be essentially the same (for example, if an envelope protein of a virus contains repeated structural motifs or occurs in a multimeric form) or may be different (and in the latter case, the amino acid sequences and polypeptides of the invention are said to be "bi- and/or multiparatopic" and may bind to such different antigenic determinants, epitopes, parts, domains, subunits of said envelope protein of a virus with an affinity and/or specificity which may be the same or different). Accordingly, bi- or multiparatopic polypeptides of the present invention are directed against and/or specifically bind to at least two epitopes of an envelope protein of a virus, and are for example (but not limited to) polypeptides that are directed against and/or can specifically bind to three or even more epitopes of the same envelope protein of a virus.

Also, the polypeptides of the present invention may be directed against and/or can

specifically bind to at least one particular envelope protein of a virus and at least one further epitope of another target, which is different from said at least one particular envelope protein. For example (but not limited to), the polypeptides of the present invention may be directed against and/or can specifically bind to at least one particular envelope protein of a virus and at least one further epitope of a virus, for instance at least one further epitope of a viral protein, such as at least one further epitope of another particular viral envelope protein. Thus, the polypeptides according to the invention may be directed against and/or may specifically bind to at least two (or even more) epitopes of at least two different envelope proteins. Also, said at least one further epitope of a virus may or may not be involved in one or more of the viral-mediated biological pathways, in which an envelope protein of a virus and/or its viral receptor is involved; more specifically said at least one further epitope of a virus may or may not be involved in viral entry in a target host cell, such as virion attachment to a target host cell and/or viral fusion with a target host cell or said at least one further epitope of a virus may or may not be involved in viral replication in a target host cell, such as viral transcription and/or viral translation and/or viral packaging and/or the formation of functional virions and/or budding of nascent virions from the target host cell membrane.

Generally, bi-, tri- and multivalent (as defined herein), bi-, tri- and multispecific (as defined herein) and bi-, tri- and multiparatopic (as defined herein) polypeptides according to the invention may be useful for the prevention and/or treatment of viral diseases by specifically binding to at least one epitope of an envelope protein of a virus and at least one further epitope (which may or may not be different from said at least one epitope) of a target, wherein said target may or may not be different from said envelope protein.

Preferably, bi-, tri- and multivalent (as defined herein) and bi-, tri- and multiparatopic polypeptides (as defined herein) according to the invention may be useful for the prevention and/or treatment of viral diseases by specifically binding to at least two (or even more) epitopes (which may be the same or different) on the same envelope protein of a virus.

Alternatively, the polypeptides of the present invention may be directed against and/or can specifically bind to at least one epitope of an envelope protein of a virus and at least one further epitope of another target, which is different from said particular envelope protein and which is for instance a further epitope of a virus, such as a further epitope of a viral protein or a further epitope of another particular viral envelope protein.

Preferably, such bi-, tri- and multivalent, bi-, tri- and multispecific, and bi-, tri- and multiparatopic polypeptides, as discussed hereabove, will bind to (an envelope protein of) a virus with increased avidity compared to a single amino acid sequence and/or NANOBODY® (V_{HH} sequence) of the invention.

More specifically, bi-, tri- and multivalent, bi-, tri- and multiparatopic and bi-, tri- and multispecific polypeptides according to the invention may be useful in targeting multiple viral receptor binding sites on the same and on different envelope proteins, respectively, which can result in an increased potency of viral neutralization (as defined herein) compared to a single amino acid sequence of the invention. Also, bi-, tri- and multivalent and bi-, tri- and multiparatopic polypeptides according to the invention (i.e. that are directed against and/or specifically bind to at least two epitopes of the same envelope protein) may be useful in preventing viral escape and/or viral evasion.

Also, bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be useful in binding different genotypes, different subtypes and/or different strains and/or clades of a certain virus. Also, bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be useful in preventing viral escape and/or viral evasion.

In a specific aspect of the invention, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1 as well as influenza subtype H1N1. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1 as well as influenza subtype H3N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H1N1 as well as influenza subtype H3N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1 as well as influenza subtype H2N2. In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H2N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1 as well as influenza subtype H3N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H2N2 as well as influenza subtype H3N2. Yet in another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against influenza virus and may bind influenza subtype H5N1, influenza subtype H1N1, influenza subtype H2N2, as well as influenza subtype H3N2.

In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-,

and multiparatopic polypeptides according to the invention are directed against the G envelope protein of rabies and may bind rabies genotype 1 as well as genotype 5.

In yet another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention may be directed against RSV and may bind different escape mutants of RSV (such as e.g. described in Lopez et al. 1998, J. Virol. 72: 6922-6928) and/or one or more escape mutants specific for antigen site II, specific for antigen site IV-VI and/or specific for the combination of both antigenic sites.

In this respect it was observed in the present invention that bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention show improved binding and/or in vitro and/or in vivo neutralization of different genotypes, different subtypes and/or different strains and/or clades of a certain virus. Also, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of viral escape mutants.

In one specific aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of certain subtypes of influenza (such as H1, H2, H3 and H5). The bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of different clades of influenza virus. The bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved competition with sialic acid for binding hemaglutinin H5 of influenza virus.

In another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of different strains of rabies. The bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention also showed improved binding and/or neutralization of different genotypes of rabies (such as genotype 1 and genotype 5).

In yet another aspect, the bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of different strains of RSV (such as Long, A-2 and B-1). The bi-, tri-, and multivalent, bi-, tri-, and multispecific and/or bi-, tri-, and multiparatopic polypeptides according to the invention showed improved binding and/or neutralization of different escape mutants of RSV (such as e.g. the escape mutants described in Lopez et al. 1998, J. Virol. 72: 6922-6928, one or more escape mutants specific for antigen site II, escape mutants specific for antigen site IV-VI, escape mutants specific for the combination of both antigenic sites).

Finally, bi-, tri- and multivalent, bi-, tri- and multispecific and bi-, tri- and multiparatopic polypeptides according to the invention may be useful in preventing and/or inhibiting viral infection and/or viral fusion of a virion with its target host cell (as defined herein) or may be useful in neutralizing a virus by inducing virion aggregation of said virus.

For multivalent and multispecific polypeptides containing one or more V_{HH} domains and their preparation, reference is also made to Conrath et al., J. Biol. Chem., Vol. 276, 10. 7346-7350, 2001; Muyldermans, Reviews in Molecular Biotechnology 74 (2001), 277-302; as well as to for example WO 96/34103 and WO 99/23221. Some other examples of some specific multispecific and/or multivalent polypeptide of the invention can be found in the applications by Ablynx N.V. referred to herein.

In one aspect, the NANOBODIES® (V_{HH} sequences) of the invention may be attached to non-NANOBODY® (V_{HH} sequence) polypeptides. The non-NANOBODY® (V_{HH} sequence) polypeptides may be polypeptides that provide the NANOBODIES® (V_{HH} sequences) with an additional functionality. For example, the non-NANOBODY® (V_{HH} sequence) polypeptides may provide the NANOBODIES® (V_{HH} sequences) of the invention with increased stability and/or in vivo half-life. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide may be a non-antigen binding fragment of an antibody. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide may be a Fc fragment of human IgG1. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide may also comprises the hinge regions of the Fc fragment. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide may be coupled to the NANOBODY® (V_{HH} sequence) by one or more linkers. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide may be coupled to multiple NANOBODIES® (V_{HH} sequences). In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are coupled at each side of the non-NANOBODY® (V_{HH} sequence) polypeptide (see FIG. 59). In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are coupled at one side of the non-NANOBODY® (V_{HH} sequence) polypeptide (see FIG. 60). In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide is coupled to a bi-, tri- or multivalent, bi-, tri-, or multiparatopic or bi-, tri-, or multispecific polypeptide as described above. In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide is coupled, at one side of the non-NANOBODY® (V_{HH} sequence) polypeptide, to a bi-, tri- or multivalent, bi-, tri-, or multiparatopic or bi-, tri-, or multispecific polypeptide as described above (FIGS. 60 and 61). In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide is coupled, at both sides of the non-NANOBODY® (V_{HH} sequence) polypeptide, to a bi-, tri- or multivalent, bi-, tri-, or multiparatopic or bi-, tri-, or multispecific polypeptide as described above (FIG. 62). In some embodiments, the non-NANOBODY® (V_{HH} sequence) polypeptide is coupled, at one side of the non-NANOBODY® (V_{HH} sequence) polypeptide, to a NANOBODY® (V_{HH} sequence) as described above and, at one side of the non-NANOBODY® (V_{HH} sequence) polypeptide, to a bi-, tri- or multivalent, bi-, tri-, or multiparatopic or bi-,

tri-, or multispecific polypeptide as described above (FIG. 63). In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are directed against the same antigen. In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are directed against a different epitope on the same antigen. In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are directed against the same epitope on the same antigen. In some embodiments, the multiple NANOBODIES® (V_{HH} sequences) are identical. Non-limiting examples of NANOBODY® (V_{HH} sequence) constructs comprising IgG1 Fc fragments are provided in FIG. 46, Table A-5 and Example 53. Preferred NANOBODIES® (V_{HH} sequences) of the invention that comprise an Fc fragment are SEQ ID NO's: 2641 to 2659 and 2978 to 2988 (Table A-5).

In this respect, the present invention in general also relates to NANOBODY® (V_{HH} sequence) constructs (also referred to as "polypeptide chain construct of the invention") that comprise two polypeptide chains (each, a "polypeptide chain of the invention"), in which each polypeptide chain comprises two or more single variable domains that are linked, usually via a suitable hinge region or linker, to one or more constant domains that, in the final construct, together form an Fc portion. The single variable domains may be linked at one side of the constant domain or the single variable domains may be linked at both sides of the constant domain.

Thus, the polypeptide chain construct provided by the invention generally comprises an Fc portion (as defined herein) in which each of the two polypeptide chains that form the Fc portion is linked, optionally via a suitable linker or hinge region, to two or more single variable domains (also as defined herein). More specifically, in one aspect, one variable domain may be linked at each side of the Fc portion. In another aspect, two variable domains may be linked at one side of the Fc portion. In another aspect, three variable domains may be linked at one side of the Fc portion. In another aspect, two variable domains may be linked at each side of the Fc portion. In another aspect, three variable domains may be linked at each side of the Fc portion. In another aspect, two variable domains may be linked at one side of the Fc portion and one variable domain may be linked at the other side of the Fc portion.

The polypeptide chains of the invention, and their use in forming the polypeptide chain construct s of the invention, form further aspects of the invention. Also, in one specific aspect of the invention, as further described herein, these polypeptide chains of the invention may also be used as such (i.e. without interaction with another polypeptide chain and/or not as part of a construct of the invention).

Preferably, in the polypeptide chain constructs of the invention, each polypeptide chain of the invention comprises two, three or four single variable domains, and more preferably only two or three single variable domains, and even more preferably only two single

variable domains. In other words, the polypeptide chain constructs of the invention preferably comprise a total of four (i.e. two in each polypeptide chain), six (i.e. three in each polypeptide chain) or eight (i.e. four in each polypeptide chain) single variable domains and more preferably a total of four single variable domains (i.e. two in each polypeptide chain) or six (i.e. three in each polypeptide chain), and even more preferably a total of four single variable domains (i.e. two in each polypeptide chain).

Also, each polypeptide chain of the invention will usually comprise either two constant domains (for example, in case of an Fc portion that is derived from IgG, IgA or IgD) or three constant domains (for example, in case of an Fc portion that is derived from IgM or IgE), such that, in the final construct, the constant domains of the two polypeptide chains form an Fc portion, for example an Fc portion that is derived from IgG (e.g. IgG1, IgG2, IgG3 or IgG4), IgA, IgD, IgE or IgM, or a variant, analog, mutant, part or fragment thereof (including chimeric Fc portions), that may or may not have effector functions, as further described herein.

For the sake of convenience, and as these polypeptide chain constructs are generally preferred in practice, the invention will now be described in more detail with reference to polypeptide chain constructs that comprise four constant domains (i.e. two in each polypeptide chain), in which the variable domains are linked to each other via a suitable linker and are linked to the constant domains via a suitable linker or hinge region. However, it will be clear to the skilled person that the teaching of the present invention can equally be applied to polypeptide chain constructs of the invention that comprise six constant domains (for example, in case of an Fc portion that is derived from IgM or IgE), and/or in which the constant domains are directly linked to each other and/or directly linked to the variable domains (for example, when the Fc portion is derived from IgE, a hinge region between the Fc portion and the variable domains may not be required).

Polypeptide chain construct of the invention with four single variable domains and four constant domains (for example forming an Fc portion derived from an IgG or IgA, or an analog, mutant or variant thereof) are schematically shown in the non-limiting FIGS. 59 and 60.

In FIG. 59, the polyp eptide chain constructs comprise two polyp eptide chains (1) and (2), which each comprise two constant domains (3) and (4), a “first” single variable domain (5) and a “second” single variable domain (6). The first single variable domain (5) is linked, optionally via a suitable linker or hinge region (7) to the constant domain (3). The second single variable domain (6) is linked, optionally via a suitable linker or hinge region (8) to the constant domain (4). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

In FIG. 60, the polypeptide chain constructs comprise two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5) and a "second" single variable domain (6). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domains, optionally (and usually) via a suitable linker or hinge region (8). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

An example of a polypeptide chain construct of the invention with more than four single variable domains is schematically shown in the non-limiting FIGS. 61, **62** and **63**.

FIG. 61 shows a polypeptide chain construct of the invention with six single variable domains and four constant domains (for example forming an Fc portion derived from an IgG or IgA, or an analog, mutant or variant thereof). The construct comprise two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5), a "second" single variable domain (6) and a "third" single variable domain (10). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domains, optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (11) is linked, optionally via a suitable linker (12), to the second single variable domain (6). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 62 shows a polypeptide chain construct of the invention with eight single variable domains and four constant domains (for example forming an Fc portion derived from an IgG or IgA, or an analog, mutant or variant thereof). The construct comprise two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5), a "second" single variable domain (6), a "third" single variable domain (10) and a "fourth" single variable domain (13). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (10) is linked, optionally via a suitable linker (12), to the fourth single variable domain (13), and is also linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 63 shows a polypeptide chain construct of the invention with six single variable

domains and four constant domains (for example forming an Fc portion derived from an IgG or IgA, or an analog, mutant or variant thereof). The construct comprise two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5), a "second" single variable domain (6) and a "third" single variable domain (10). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (10) is linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

In polypeptide chain constructs with more than six or eight single variable domains, each chain (1) and (2) can contain one or more additional single variable domains (not shown), which can be linked to the present single variable domain, again optionally via suitable linkers.

In the polypeptide chain constructs of the invention, all of the single variable domains that are present in the construct may each be directed against a different target, antigen, antigenic determinant or epitope. However, this is generally less preferred. Preferably, both of the "first" single variable domains that are present in each of the polypeptide chain are directed against the same target or antigen, and both of the "second" single variable domains that are present in each of the polypeptide chain are directed against the same target or antigen (and so on for the "third", "fourth" and further single variable domains).

In this aspect of the invention, the first single variable domains and second single variable domains (and so on for the "third", "fourth" and further single variable domains) may be directed against a different target or antigen (such that the constructs of the invention are capable of simultaneously binding to two or more different targets or antigens); or may be directed against the same target or antigen (such that all single variable domains present in the construct are capable of binding to the same target or antigen).

As further described herein, when two or more single variable domains in a polypeptide chain construct of the invention are capable of binding to the same target or antigen, they may bind to the same epitope, antigenic determinant, part, domain or subunit of the target or antigen, or to different epitopes, antigenic determinants, parts, domains or subunits of the target or antigen.

One preferred, but non-limiting example of a multispecific polypeptide of the invention comprises at least one NANOBODY® (V_{HH} sequence) of the invention and at least one NANOBODY® (V_{HH} sequence) that provides for an increased half-life. Such NANOBODIES® (V_{HH} sequences) may for example be NANOBODIES® (V_{HH} sequences) that are directed

against a serum protein, and in particular a human serum protein, such as human serum albumin, thyroxine-binding protein, (human) transferrin, fibrinogen, an immunoglobulin such as IgG, IgE or IgM, or against one of the serum proteins listed in WO 04/003019. Of these, NANOBODIES® (V_{HH} sequences) that can bind to serum albumin (and in particular human serum albumin) or to IgG (and in particular human IgG, see for example NANOBODY® (V_{HH} sequence) VH-1 described in the review by Muyldermans, supra) are particularly preferred (although for example, for experiments in mice or primates, NANOBODIES® (V_{HH} sequences) against or cross-reactive with mouse serum albumin (MSA) or serum albumin from said primate, respectively, can be used. However, for pharmaceutical use, NANOBODIES® (V_{HH} sequences) against human serum albumin or human IgG will usually be preferred). NANOBODIES® (V_{HH} sequences) that provide for increased half-life and that can be used in the polypeptides of the invention include the NANOBODIES® (V_{HH} sequences) directed against serum albumin that are described in WO 04/041865, in WO 06/122787 and in the further patent applications by Ablynx N.V., such as those mentioned above.

For example, some preferred NANOBODIES® (V_{HH} sequences) that provide for increased half-life for use in the present invention include NANOBODIES® (V_{HH} sequences) that can bind to amino acid residues on (human) serum albumin that are not involved in binding of serum albumin to FcRn (see for example WO 06/0122787); NANOBODIES® (V_{HH} sequences) that are capable of binding to amino acid residues on serum albumin that do not form part of domain III of serum albumin (see for example WO 06/0122787); NANOBODIES® (V_{HH} sequences) that have or can provide an increased half-life (see for example WO 2008/028977); NANOBODIES® (V_{HH} sequences) against human serum albumin that are cross-reactive with serum albumin from at least one species of mammal, and in particular with at least one species of primate (such as, without limitation, monkeys from the genus *Macaca* (such as, and in particular, cynomolgus monkeys (*Macaca fascicularis*) and/or rhesus monkeys (*Macaca mulatta*)) and baboon (*Papio ursinus*)) (see for example WO 2008/028977)); NANOBODIES® (V_{HH} sequences) that can bind to serum albumin in a pH independent manner (see for example WO 08/043821) and/or NANOBODIES® (V_{HH} sequences) that are conditional binders (see for example WO 08/043822).

Some particularly preferred NANOBODIES® (V_{HH} sequences) that provide for increased half-life and that can be used in the polypeptides of the invention include the NANOBODIES® (V_{HH} sequences) ALB-1 to ALB-10 disclosed in WO 06/122787 (see Tables II and III) of which ALB-8 (SEQ ID NO: 62 in WO 06/122787) is particularly preferred.

According to a specific, but non-limiting aspect of the invention, the polypeptides of the invention contain, besides the one or more NANOBODIES® (V_{HH} sequences) of the invention, at least one NANOBODY® (V_{HH} sequence) against human serum albumin.

Generally, any polypeptides of the invention with increased half-life that contain one or more NANOBODIES® (V_{HH} sequences) of the invention, and any derivatives of NANOBODIES® (V_{HH} sequences) of the invention or of such polypeptides that have an increased half-life, preferably have a half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding NANOBODY® (V_{HH} sequence) of the invention per se. For example, such a derivative or polypeptides with increased half-life may have a half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding NANOBODY® (V_{HH} sequence) of the invention per se.

In a preferred, but non-limiting aspect of the invention, such derivatives or polypeptides may exhibit a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more. For example, such derivatives or polypeptides may have a half-life of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

According to one aspect of the invention the polypeptides are capable of binding to one or more molecules which can increase the half-life of the polypeptide in vivo.

The polypeptides of the invention are stabilised in vivo and their half-life increased by binding to molecules which resist degradation and/or clearance or sequestration. Typically, such molecules are naturally occurring proteins which themselves have a long half-life in vivo.

Another preferred, but non-limiting example of a multispecific polypeptide of the invention comprises at least one NANOBODY® (V_{HH} sequence) of the invention and at least one NANOBODY® (V_{HH} sequence) that directs the polypeptide of the invention towards, and/or that allows the polypeptide of the invention to penetrate or to enter into specific organs, tissues, cells, or parts or compartments of cells, and/or that allows the NANOBODY® (V_{HH} sequence) to penetrate or cross a biological barrier such as a cell membrane, a cell layer such as a layer of epithelial cells, a tumor including solid tumors, or the blood-brain-barrier. Examples of such NANOBODIES® (V_{HH} sequences) include NANOBODIES® (V_{HH} sequences) that are directed towards specific cell-surface proteins, markers or epitopes of the desired organ, tissue or cell (for example cell-surface markers associated with tumor cells), and the single-domain brain targeting antibody fragments described in WO 02/057445 and WO 06/040153, of which FC44 (SEQ ID NO: 189 of WO 06/040153) and

FC5 (SEQ ID NO: 190 of WO 06/040154) are preferred examples.

In the polypeptides of the invention, the one or more NANOBODIES® (V_{HH} sequences) and the one or more polypeptides may be directly linked to each other (as for example described in WO 99/23221) and/or may be linked to each other via one or more suitable spacers or linkers, or any combination thereof.

Suitable spacers or linkers for use in multivalent, multiparatopic and multispecific polypeptides and polypeptide chains will be clear to the skilled person, and may generally be any linker or spacer used in the art to link amino acid sequences. Preferably, said linker or spacer is suitable for use in constructing proteins or polypeptides that are intended for pharmaceutical use.

Some particularly preferred spacers include the spacers and linkers that are used in the art to link antibody fragments or antibody domains. These include the linkers mentioned in the general background art cited above, as well as for example linkers that are used in the art to construct diabodies or ScFv fragments (in this respect, however, its should be noted that, whereas in diabodies and in ScFv fragments, the linker sequence used should have a length, a degree of flexibility and other properties that allow the pertinent V_H and V_L domains to come together to form the complete antigen-binding site, there is no particular limitation on the length or the flexibility of the linker used in the polypeptide of the invention, since each NANOBODY® (V_{HH} sequence) by itself forms a complete antigen-binding site).

For example, a linker may be a suitable amino acid sequence, and in particular amino acid sequences of between 1 and 50, preferably between 1 and 30, such as between 1 and 10 amino acid residues. Some preferred examples of such amino acid sequences include gly-ser linkers, for example of the type $(gly_xser_y)_z$, such as (for example $(gly_4ser)_3$ or $(gly_3ser_2)_3$, as described in WO 99/42077 and the GS30, GS15, GS9 and GS7 linkers described in the applications by Ablynx mentioned herein (see for example WO 06/040153 and WO 06/122825), as well as hinge-like regions, such as the hinge regions of naturally occurring heavy chain antibodies or similar sequences (such as described in WO 94/04678).

Some other particularly preferred linkers are poly-alanine (such as AAA), as well as the linkers GS30 (SEQ ID NO: 85 in WO 06/122825) and GS9 (SEQ ID NO: 84 in WO 06/122825). Other preferred linkers may comprise or consist of a hinge region, a (Gly_x-Ser_y) repeat or a combination of (Gly_x-Ser_y) with a hinge region (such as e.g. used in the construes of Table A-5 and/or depicted in Table A-7).

Other suitable linkers generally comprise organic compounds or polymers, in particular those suitable for use in proteins for pharmaceutical use. For instance, poly(ethyleneglycol) moieties have been used to link antibody domains, see for example WO 04/081026.

It is encompassed within the scope of the invention that the length, the degree of flexibility and/or other properties of the linker(s) used (although not critical, as it usually is for linkers used in ScFv fragments) may have some influence on the properties of the final polypeptide of the invention, including but not limited to the affinity, specificity or avidity for the envelope protein, or for one or more of the other antigens. Based on the disclosure herein, the skilled person will be able to determine the optimal linker(s) for use in a specific polypeptide of the invention, optionally after some limited routine experiments.

For example, in multivalent polypeptides of the invention that comprise NANOBODIES® (V_{HH} sequences) directed against a multimeric antigen (such as a multimeric receptor or other protein), the length and flexibility of the linker are preferably such that it allows each NANOBODY® (V_{HH} sequence) of the invention present in the polypeptide to bind to the antigenic determinant on each of the subunits of the multimer. Similarly, in a multispecific polypeptide of the invention that comprises NANOBODIES® (V_{HH} sequences) directed against two or more different antigenic determinants on the same antigen (for example against different epitopes of an antigen and/or against different subunits of a multimeric receptor, channel or protein), the length and flexibility of the linker are preferably such that it allows each NANOBODY® (V_{HH} sequence) to bind to its intended antigenic determinant. Again, based on the disclosure herein, the skilled person will be able to determine the optimal linker(s) for use in a specific polypeptide of the invention, optionally after some limited routine experiments.

It is also within the scope of the invention that the linker(s) used confer one or more other favourable properties or functionality to the polypeptides of the invention, and/or provide one or more sites for the formation of derivatives and/or for the attachment of functional groups (e.g. as described herein for the derivatives of the NANOBODIES® (V_{HH} sequences) of the invention). For example, linkers containing one or more charged amino acid residues (see Table A-2 on page 48 of the International application WO 08/020079) can provide improved hydrophilic properties, whereas linkers that form or contain small epitopes or tags can be used for the purposes of detection, identification and/or purification. Again, based on the disclosure herein, the skilled person will be able to determine the optimal linkers for use in a specific polypeptide of the invention, optionally after some limited routine experiments.

Finally, when two or more linkers are used in the polypeptides of the invention, these linkers may be the same or different. Again, based on the disclosure herein, the skilled person will be able to determine the optimal linkers for use in a specific polypeptide of the invention, optionally after some limited routine experiments.

Usually, for easy of expression and production, a polypeptide of the invention will be a linear polypeptide. However, the invention in its broadest sense is not limited thereto. For

example, when a polypeptide of the invention comprises three of more NANOBODIES® (V_{HH} sequences), it is possible to link them by use of a linker with three or more "arms", which each "arm" being linked to a NANOBODY® (V_{HH} sequence), so as to provide a "star-shaped" construct. It is also possible, although usually less preferred, to use circular constructs.

The invention also comprises derivatives of the polypeptides of the invention, which may be essentially analogous to the derivatives of the NANOBODIES® (V_{HH} sequences) of the invention, i.e. as described herein.

The invention also comprises proteins or polypeptides that "essentially consist" of a polypeptide of the invention (in which the wording "essentially consist of" has essentially the same meaning as indicated hereinabove).

According to one aspect of the invention, the polypeptide of the invention is in essentially isolated form, as defined herein.

The amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and nucleic acids of the invention can be prepared in a manner known per se, as will be clear to the skilled person from the further description herein. For example, the NANOBODIES® (V_{HH} sequences) and polypeptides of the invention can be prepared in any manner known per se for the preparation of antibodies and in particular for the preparation of antibody fragments (including but not limited to (single) domain antibodies and ScFv fragments). Some preferred, but non-limiting methods for preparing the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides and nucleic acids include the methods and techniques described herein.

As will be clear to the skilled person, one particularly useful method for preparing an amino acid sequence, NANOBODY® (V_{HH} sequence) and/or a polypeptide of the invention generally comprises the steps of:

- i) the expression, in a suitable host cell or host organism (also referred to herein as a "host of the invention") or in another suitable expression system of a nucleic acid that encodes said amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention (also referred to herein as a "nucleic acid of the invention"), optionally followed by:
- ii) isolating and/or purifying the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention thus obtained.

In particular, such a method may comprise the steps of:

- i) cultivating and/or maintaining a host of the invention under conditions that are such that said host of the invention expresses and/or produces at least one amino

acid sequence, NANOBODY® (V_{HH} sequence) and/or polypeptide of the invention;

- optionally followed by:

- ii) isolating and/or purifying the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention thus obtained.

A nucleic acid of the invention can be in the form of single or double stranded DNA or RNA, and is preferably in the form of double stranded DNA. For example, the nucleotide sequences of the invention may be genomic DNA, cDNA or synthetic DNA (such as DNA with a codon usage that has been specifically adapted for expression in the intended host cell or host organism).

According to one aspect of the invention, the nucleic acid of the invention is in essentially isolated form, as defined herein.

The nucleic acid of the invention may also be in the form of, be present in and/or be part of a vector, such as for example a plasmid, cosmid or YAC, which again may be in essentially isolated form.

The nucleic acids of the invention can be prepared or obtained in a manner known per se, based on the information on the amino acid sequences for the polypeptides of the invention given herein, and/or can be isolated from a suitable natural source. To provide analogs, nucleotide sequences encoding naturally occurring V_{HH} domains can for example be subjected to site-directed mutagenesis, so as to provide a nucleic acid of the invention encoding said analog. Also, as will be clear to the skilled person, to prepare a nucleic acid of the invention, also several nucleotide sequences, such as at least one nucleotide sequence encoding a NANOBODY® (V_{HH} sequence) and for example nucleic acids encoding one or more linkers can be linked together in a suitable manner.

Techniques for generating the nucleic acids of the invention will be clear to the skilled person and may for instance include, but are not limited to, automated DNA synthesis; site-directed mutagenesis; combining two or more naturally occurring and/or synthetic sequences (or two or more parts thereof), introduction of mutations that lead to the expression of a truncated expression product; introduction of one or more restriction sites (e.g. to create cassettes and/or regions that may easily be digested and/or ligated using suitable restriction enzymes), and/or the introduction of mutations by means of a PCR reaction using one or more "mismatched" primers, using for example a sequence of a naturally occurring form of an envelope protein of a virus as a template. These and other techniques will be clear to the skilled person, and reference is again made to the standard handbooks, such as Sambrook et al. and Ausubel et al., mentioned above, as well as the Examples below.

The nucleic acid of the invention may also be in the form of, be present in and/or be part of

a genetic construct, as will be clear to the person skilled in the art and as described on pages 131-134 of WO 08/020079 (incorporated herein by reference). Such genetic constructs generally comprise at least one nucleic acid of the invention that is optionally linked to one or more elements of genetic constructs known per se, such as for example one or more suitable regulatory elements (such as a suitable promoter(s), enhancer(s), terminator(s), etc.) and the further elements of genetic constructs referred to herein. Such genetic constructs comprising at least one nucleic acid of the invention will also be referred to herein as "genetic constructs of the invention".

The genetic constructs of the invention may be DNA or RNA, and are preferably double-stranded DNA. The genetic constructs of the invention may also be in a form suitable for transformation of the intended host cell or host organism, in a form suitable for integration into the genomic DNA of the intended host cell or in a form suitable for independent replication, maintenance and/or inheritance in the intended host organism. For instance, the genetic constructs of the invention may be in the form of a vector, such as for example a plasmid, cosmid, YAC, a viral vector or transposon. In particular, the vector may be an expression vector, i.e. a vector that can provide for expression in vitro and/or in vivo (e.g. in a suitable host cell, host organism and/or expression system).

In a preferred but non-limiting aspect, a genetic construct of the invention comprises

- i) at least one nucleic acid of the invention; operably connected to
- ii) one or more regulatory elements, such as a promoter and optionally a suitable terminator;
  and optionally also
- iii) one or more further elements of genetic constructs known per se;

in which the terms "operably connected" and "operably linked" have the meaning given on pages 131-134 of WO 08/020079; and in which the "regulatory elements", "promoter", "terminator" and "further elements" are as described on pages 131-134 of WO 08/020079; and in which the genetic constructs may further be as described on pages 131-134 of WO 08/020079.

The nucleic acids of the invention and/or the genetic constructs of the invention may be used to transform a host cell or host organism, i.e. for expression and/or production of the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention. Suitable hosts or host cells will be clear to the skilled person, and may for example be any suitable fungal, prokaryotic or eukaryotic cell or cell line or any suitable fungal, prokaryotic or eukaryotic organism, for example those described on pages 134 and 135 of WO 08/020079; as well as all other hosts or host cells known per se for the expression and production of antibodies and antibody fragments (including but not limited to (single) domain antibodies and ScFv fragments), which will be clear to the skilled person. Reference

is also made to the general background art cited hereinabove, as well as to for example WO 94/29457; WO 96/34103; WO 99/42077; Frenken et al., (1998), supra; Riechmann and Muyldermans, (1999), supra; van der Linden, (2000), supra; Thomassen et al., (2002), supra; Joosten et al., (2003), supra; Joosten et al., (2005), supra; and the further references cited herein.

The amino acid sequences, NANOBODIES® (V_{HH} sequences) and polypeptides of the invention can also be introduced and expressed in one or more cells, tissues or organs of a multicellular organism, for example for prophylactic and/or therapeutic purposes (e.g. as a gene therapy), as further described on pages 135 and 136 of in WO 08/020079 and in the further references cited in WO 08/020079.

For expression of the NANOBODIES® (V_{HH} sequences) in a cell, they may also be expressed as so-called "intrabodies", as for example described in WO 94/02610, WO 95/22618 and U.S. Pat. No. 7,004,940; WO 03/014960; in Cattaneo, A. & Biocca, S. (1997) Intracellular Antibodies: Development and Applications. Landes and Springer-Verlag; and in Kontermann, Methods 34, (2004), 163-170.

The amino acid sequences, NANOBODIES® (V_{HH} sequences) and polypeptides of the invention can for example also be produced in the milk of transgenic mammals, for example in the milk of rabbits, cows, goats or sheep (see for example U.S. Pat. No. 6,741,957, U.S. Pat. No. 6,304,489 and U.S. Pat. No. 6,849,992 for general techniques for introducing transgenes into mammals), in plants or parts of plants including but not limited to their leaves, flowers, fruits, seed, roots or tubers (for example in tobacco, maize, soybean or alfalfa) or in for example pupae of the silkworm *Bombix mori.*

Furthermore, the amino acid sequences, NANOBODIES® (V_{HH} sequences) and polypeptides of the invention can also be expressed and/or produced in cell-free expression systems, and suitable examples of such systems will be clear to the skilled person. Some preferred, but non-limiting examples include expression in the wheat germ system; in rabbit reticulocyte lysates; or in the *E. coli* Zubay system.

As mentioned above, one of the advantages of the use of NANOBODIES® (V_{HH} sequences) is that the polypeptides based thereon can be prepared through expression in a suitable bacterial system, and suitable bacterial expression systems, vectors, host cells, regulatory elements, etc., will be clear to the skilled person, for example from the references cited above. It should however be noted that the invention in its broadest sense is not limited to expression in bacterial systems.

Preferably, in the invention, an (in vivo or in vitro) expression system, such as a bacterial expression system, is used that provides the polypeptides of the invention in a form that is suitable for pharmaceutical use, and such expression systems will again be clear to the

skilled person. As also will be clear to the skilled person, polypeptides of the invention suitable for pharmaceutical use can be prepared using techniques for peptide synthesis.

For production on industrial scale, preferred heterologous hosts for the (industrial) production of NANOBODIES® (V_{HH} sequences) or NANOBODY® (V_{HH} sequence)-containing protein therapeutics include strains of *E. coli, Pichia pastoris, S. cerevisiae* that are suitable for large scale expression/production/fermentation, and in particular for large scale pharmaceutical (i.e. GMP grade) expression/production/fermentation. Suitable examples of such strains will be clear to the skilled person. Such strains and production/expression systems are also made available by companies such as Biovitrum (Uppsala, Sweden).

Alternatively, mammalian cell lines, in particular Chinese hamster ovary (CHO) cells, can be used for large scale expression/production/fermentation, and in particular for large scale pharmaceutical expression/production/fermentation. Again, such expression/production systems are also made available by some of the companies mentioned above.

The choice of the specific expression system would depend in part on the requirement for certain post-translational modifications, more specifically glycosylation. The production of a NANOBODY® (V_{HH} sequence)-containing recombinant protein for which glycosylation is desired or required would necessitate the use of mammalian expression hosts that have the ability to glycosylate the expressed protein. In this respect, it will be clear to the skilled person that the glycosylation pattern obtained (i.e. the kind, number and position of residues attached) will depend on the cell or cell line that is used for the expression. Preferably, either a human cell or cell line is used (i.e. leading to a protein that essentially has a human glycosylation pattern) or another mammalian cell line is used that can provide a glycosylation pattern that is essentially and/or functionally the same as human glycosylation or at least mimics human glycosylation. Generally, prokaryotic hosts such as *E. coli* do not have the ability to glycosylate proteins, and the use of lower eukaryotes such as yeast usually leads to a glycosylation pattern that differs from human glycosylation. Nevertheless, it should be understood that all the foregoing host cells and expression systems can be used in the invention, depending on the desired amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide to be obtained.

Thus, according to one non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is glycosylated. According to another non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is non-glycosylated.

According to one preferred, but non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is produced in a bacterial cell, in particular a bacterial cell suitable for large scale pharmaceutical production, such as cells of the strains mentioned above.

According to another preferred, but non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is produced in a yeast cell, in particular a yeast cell suitable for large scale pharmaceutical production, such as cells of the species mentioned above.

According to yet another preferred, but non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is produced in a mammalian cell, in particular in a human cell or in a cell of a human cell line, and more in particular in a human cell or in a cell of a human cell line that is suitable for large scale pharmaceutical production, such as the cell lines mentioned hereinabove. As further described on pages 138 and 139 of WO 08/020079, when expression in a host cell is used to produce the amino acid sequences, NANOBODIES® (V_{HH} sequences) and the polypeptides of the invention, the amino acid sequences, NANOBODIES® (V_{HH} sequences) and polypeptides of the invention can be produced either intracellularly (e.g. in the cytosol, in the periplasma or in inclusion bodies) and then isolated from the host cells and optionally further purified; or can be produced extracellularly (e.g. in the medium in which the host cells are cultured) and then isolated from the culture medium and optionally further purified. Thus, according to one non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is an amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide that has been produced intracellularly and that has been isolated from the host cell, and in particular from a bacterial cell or from an inclusion body in a bacterial cell. According to another non-limiting aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is an amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide that has been produced extracellularly, and that has been isolated from the medium in which the host cell is cultivated.

Some preferred, but non-limiting promoters for use with these host cells include those mentioned on pages 139 and 140 of WO 08/020079.

Some preferred, but non-limiting secretory sequences for use with these host cells include those mentioned on page 140 of WO 08/020079.

Suitable techniques for transforming a host or host cell of the invention will be clear to the skilled person and may depend on the intended host cell/host organism and the genetic construct to be used. Reference is again made to the handbooks and patent applications mentioned above.

After transformation, a step for detecting and selecting those host cells or host organisms that have been successfully transformed with the nucleotide sequence/genetic construct of the invention may be performed. This may for instance be a selection step based on a selectable marker present in the genetic construct of the invention or a step involving the

detection of the amino acid sequence of the invention, e.g. using specific antibodies.

The transformed host cell (which may be in the form or a stable cell line) or host organisms (which may be in the form of a stable mutant line or strain) form further aspects of the present invention.

Preferably, these host cells or host organisms are such that they express, or are (at least) capable of expressing (e.g. under suitable conditions), an amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention (and in case of a host organism: in at least one cell, part, tissue or organ thereof). The invention also includes further generations, progeny and/or offspring of the host cell or host organism of the invention, that may for instance be obtained by cell division or by sexual or asexual reproduction.

To produce/obtain expression of the amino acid sequences of the invention, the transformed host cell or transformed host organism may generally be kept, maintained and/or cultured under conditions such that the (desired) amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention is expressed/produced. Suitable conditions will be clear to the skilled person and will usually depend upon the host cell/host organism used, as well as on the regulatory elements that control the expression of the (relevant) nucleotide sequence of the invention. Again, reference is made to the handbooks and patent applications mentioned above in the paragraphs on the genetic constructs of the invention.

Generally, suitable conditions may include the use of a suitable medium, the presence of a suitable source of food and/or suitable nutrients, the use of a suitable temperature, and optionally the presence of a suitable inducing factor or compound (e.g. when the nucleotide sequences of the invention are under the control of an inducible promoter); all of which may be selected by the skilled person. Again, under such conditions, the amino acid sequences of the invention may be expressed in a constitutive manner, in a transient manner, or only when suitably induced.

It will also be clear to the skilled person that the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention may (first) be generated in an immature form (as mentioned above), which may then be subjected to post-translational modification, depending on the host cell/host organism used. Also, the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention may be glycosylated, again depending on the host cell/host organism used.

The amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention may then be isolated from the host cell/host organism and/or from the medium in which said host cell or host organism was cultivated, using protein isolation and/or purification

techniques known per se, such as (preparative) chromatography and/or electrophoresis techniques, differential precipitation techniques, affinity techniques (e.g. using a specific, cleavable amino acid sequence fused with the amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention) and/or preparative immunological techniques (i.e. using antibodies against the amino acid sequence to be isolated).

Generally, for pharmaceutical use, the polypeptides of the invention may be formulated as a pharmaceutical preparation or compositions comprising at least one polypeptide of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active polypeptides and/or compounds. By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration, for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms—which may be solid, semi-solid or liquid, depending on the manner of administration—as well as methods and carriers for use in the preparation thereof, will be clear to the skilled person, and are further described herein.

Thus, in a further aspect, the invention relates to a pharmaceutical composition that contains at least one amino acid of the invention, at least one NANOBODY® (V_{HH} sequence) of the invention, at least one compound or construct of the invention or at least one polypeptide of the invention and at least one suitable carrier, diluent or excipient (i.e. suitable for pharmaceutical use), and optionally one or more further active substances. Generally, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention can be formulated and administered in any suitable manner known per se, for which reference is for example made to the general background art cited above (and in particular to WO 04/041862, WO 04/041863, WO 04/041865, WO 04/041867 and WO 08/020079) as well as to the standard handbooks, such as Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, USA (1990), Remington, the Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins (2005); or the Handbook of Therapeutic Antibodies (S. Dubel, Ed.), Wiley, Weinheim, 2007 (see for example pages 252-255).

For example, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may be formulated and administered in any manner known per se for conventional antibodies and antibody fragments (including ScFv's and diabodies) and other pharmaceutically active proteins. Such formulations and methods for preparing the same will be clear to the skilled person, and for example include preparations suitable for parenteral administration (for example intravenous, intraperitoneal, subcutaneous, intramuscular, intraluminal, intra-arterial or intrathecal

administration) or for topical (i.e. transdermal or intradermal) administration.

Preparations for parenteral administration may for example be sterile solutions, suspensions, dispersions or emulsions that are suitable for infusion or injection. Suitable carriers or diluents for such preparations for example include, without limitation, those mentioned on page 143 of WO 08/020079. Usually, aqueous solutions or suspensions will be preferred.

The amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention can also be administered using gene therapy methods of delivery. See, e.g., U.S. Pat. No. 5,399,346, which is incorporated by reference in its entirety. Using a gene therapy method of delivery, primary cells transfected with the gene encoding an amino acid sequence, NANOBODY® (V_{HH} sequence) or polypeptide of the invention can additionally be transfected with tissue specific promoters to target specific organs, tissue, grafts, tumors, or cells and can additionally be transfected with signal and stabilization sequences for subcellularly localized expression.

Thus, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs or polypeptide of the invention. Their percentage in the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs or polypeptide of the invention in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain binders, excipients, disintegrating agents, lubricants and sweetening or flavouring agents, for example those mentioned on pages 143-144 of WO 08/020079. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir

may contain the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may be incorporated into sustained-release preparations and devices.

Preparations and formulations for oral administration may also be provided with an enteric coating that will allow the constructs of the invention to resist the gastric environment and pass into the intestines. More generally, preparations and formulations for oral administration may be suitably formulated for delivery into any desired part of the gastrointestinal tract. In addition, suitable suppositories may be used for delivery into the gastrointestinal tract.

The amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may also be administered intravenously or intraperitoneally by infusion or injection, as further described on pages 144 and 145 of WO 08/020079.

For topical administration, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid, as further described on page 145 of WO 08/020079.

Generally, the concentration of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

In a preferred aspect, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention and/or compositions comprising the same are administered to the pulmonary tissue. In the context of the present invention, “pulmonary tissue” is for the purposes of this invention equivalent with lung tissue or lung. The lung comprises 2 distinct zones: a conducting and a respiratory zone, within which the airway and vascular compartments lie (see e.g. “Pulmonary Drug Delivery”, Edited by Karoline Bechtold-Peters and Henrik Luessen, 2007, ISBN 978-3-87193-322-6 pages 16-28).

For pulmonary delivery, the amino acid sequences, NANOBODIES® (V_{HH} sequences),

compounds, constructs and polypeptides of the invention may be applied in pure form, i.e., when they are liquids or a dry powder. However, it will be preferred to administer them to the pulmonary tissue as composition or formulation comprising an amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs and/or polypeptide of the invention and a carrier suitable for pulmonary delivery. Accordingly the present invention also relates to a pharmaceutical composition comprising the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs and/or polypeptide of the invention and a carrier suitable for pulmonary delivery. Carriers suitable for pulmonary delivery are known in the art.

The amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention may also be administered as micro- or nanoparticles of pure drugs with particle sizes and distributions favorable for pulmonary delivery.

Accordingly the present invention also relates to a pharmaceutical device suitable for the pulmonary delivery of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention and suitable in the use of a composition comprising the same. This device may an inhaler for liquids (e.g. a suspension of fine solid particles or droplets) comprising the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs and/or polypeptide of the invention. Preferably this device is an aerosol comprising the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs and/or polypeptide of the invention. The device may also be a dry powder inhaler comprising the amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs and/or polypeptide of the invention in the form of a dry powder.

In a preferred method, the administration to the pulmonary tissue is performed by inhaling the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention and/or the composition comprising the same in an aerosol cloud. According to the invention, inhaling of the aerosol cloud can be performed by an inhaler device. The device should generate from a formulation comprising the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention and/or composition comprising the same an aerosol cloud of the desired particle size (distribution) at the appropriate moment of the mammal's inhalation cycle, containing the right dose of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention ("Pulmonary drug delivery", Bechtold-Peters and Luessen, eds., ISBN 978-3-87193-322-6, page 125).

In the context of the present invention, "aerosol" denotes a suspension of fine solid particles or liquid droplets (or combination thereof) in a gas wherein for the purposes of this invention the particles and/or droplets comprise the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the

invention.

The device should generate from the formulation an aerosol cloud of the desired particle size (distribution) at the appropriate moment of the mammal's inhalation cycle, containing the right dose of amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention. The following 4 requirements (formulation, particle size, time and dose) should be considered ("Pulmonary Drug Delivery", Bechtold-Peters and Luessen, eds., supra, pages 125 and 126):

- The formulations that are used in the devices may vary from aqueous solutions or suspensions used in nebulizers to the propellant-based solutions or suspensions used in metered dose inhaler or even specially engineered powder mixtures for the dry powder inhalers. All these different formulations require different principles for aerosol generation, which emphasizes the mutual dependency of device and formulation;
- Since the site of deposition of aerosol particles depends on their (aerodynamic) size and velocity, the desired particle size of the aerosol cloud varies depending on the desired site of deposition in the lung, which is related to the therapeutic goal of the administration;
- As the aerosol cloud can be tuned to be released at different moments during the inhalation cycle generated by the mammal, it is preferred that for the agents of the invention (to be deposited in the peripheral parts of the lung) the aerosol is released at the start of the inhalation cycle;
- Doses may vary considerably and may e.g. vary e.g. for a human from a few microgram to several hundreds of microgram or even milligrams, e.g. about up to about 10 milligrams.

Various inhalation systems are e.g. described on pages 129 to 148 in the review ("Pulmonary Drug Delivery", Bechtold-Peters and Luessen, eds., supra) and include, but are not limited to, nebulizers, metered dose inhalers, metered dose liquid inhalers, and dry powder inhalers. Devices taking into account optimized and individualized breathing pattern for controlled inhalation maneuvers may also be used (see AKITA® technology on page 157 of "Pulmonary Drug Delivery", Bechtold-Peters and Luessen, eds., supra).

However, not only the device is important to pulmonary delivery of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention but also the right formulation is critical to achieve an effective delivery. This can be in principle achieved by using one of the following approaches:

- Administration of aqueous solutions or suspensions comprising the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention (e.g. nasal drops) into the nasal cavities;

- Nebulisation of aqueous solutions or suspensions comprising the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention;
- Atomization by means of liquefied propellants; and
- Dispersion of dry powders.

Hence formulations of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention have to be adopted and adjusted to the chosen inhalation device. Appropriate formulations, i.e. the excipients in addition to the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and/or polypeptides of the invention, are e.g. described in chapter IV of "Pulmonary Drug Delivery", Bechtold-Peters and Luessen, eds., supra.

The amount of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention required for use in treatment will vary not only with the particular amino acid sequence, NANOBODY® (V_{HH} sequence), compounds, constructs or polypeptide selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. Also the dosage of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds, constructs and polypeptides of the invention varies depending on the target host cell, tumor, tissue, graft, or organ.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

An administration regimen could include long-term, daily treatment. By "long-term" is meant at least two weeks and preferably, several weeks, months, or years of duration. Necessary modifications in this dosage range may be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein. See Remington's Pharmaceutical Sciences (Martin, E. W., ed. 4), Mack Publishing Co., Easton, Pa. The dosage can also be adjusted by the individual physician in the event of any complication.

In another aspect, the invention relates to a method for the prevention and/or treatment of at least one viral disease, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

In the context of the present invention, the term "prevention and/or treatment" not only comprises preventing and/or treating the disease, but also generally comprises preventing the onset of the disease, slowing or reversing the progress of disease, preventing or slowing the onset of one or more symptoms associated with the disease, reducing and/or alleviating one or more symptoms associated with the disease, reducing the severity and/or the duration of the disease and/or of any symptoms associated therewith and/or preventing a further increase in the severity of the disease and/or of any symptoms associated therewith, preventing, reducing or reversing any physiological damage caused by the disease, and generally any pharmacological action that is beneficial to the patient being treated.

The subject to be treated may be any warm-blooded animal, but is in particular a mammal, and more in particular a human being. As will be clear to the skilled person, the subject to be treated will in particular be a person suffering from, or at risk of, the diseases and disorders mentioned herein.

The invention relates to a method for the prevention and/or treatment of at least one disease or disorder that is associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor, with its biological or pharmacological activity, and/or with the viral-mediated biological pathways in which an envelope protein of a virus and/or its viral receptor is involved, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same. In particular, the invention relates to a method for the prevention and/or treatment of at least one disease or disorder that can be treated by modulating and in particular inhibiting and/or preventing the viral-mediated biological pathways in which an envelope protein of a virus and/or a viral receptor are involved, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same. In particular, the invention relates to a method for the prevention and/or treatment of at least one disease or disorder that can be treated by neutralizing a virus (as defined herein) and/or modulating, reducing and/or inhibiting the infectivity of a virus (as defined herein), said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same. Said pharmaceutically effective amount may be an amount that is sufficient to modulate and in particular inhibit and/or prevent the viral-mediated biological

pathways in which an envelope protein of a virus and/or a viral receptor are involved; and/or an amount that provides a level of the amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of compound or construct of the invention in the circulation that is sufficient to modulate and in particular inhibit and/or prevent the viral-mediated biological pathways in which an envelope protein of a virus and/or a viral receptor are involved.

More specifically, said method for the prevention and/or treatment of at least one disease or disorder that may comprise neutralizing a virus (as defined herein) and/or modulating, reducing and/or inhibiting the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place) and/or in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place). Accordingly, said method for the prevention and/or treatment of at least one disease or disorder that may comprise neutralizing a virus (as defined herein) and/or modulating, reducing and/or inhibiting the infectivity of a virus (as defined herein) in the pre-entry phase of viral infection (i.e. before and/or during viral entry in a target host cell has taken place), is said herein to comprise modulating and in particular inhibiting and/or preventing viral entry (as further defined herein) in a target host cell. Furthermore, said method for the prevention and/or treatment of at least one disease or disorder that may comprise neutralizing a virus (as defined herein) and/or modulating, reducing and/or inhibiting the infectivity of a virus (as defined herein) in the post-entry phase of viral infection (i.e. after viral entry in a target host cell has taken place), is said herein to comprise modulating and in particular inhibiting and/or preventing viral replication (as further defined herein) in a target host cell.

Accordingly, the present invention relates to a method for the prevention and/or treatment of at least one disease or disorder that can be treated by modulating and in particular inhibiting and/or preventing viral entry and/or viral replication in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway(s); preferably, the method of the present invention can comprise modulating and in particular inhibiting and/or preventing viral entry in a target host cell by binding to an envelope protein of a virus, such that virion aggregation is induced and/or virion structure is destabilized and/or virion attachment to a target host cell is modulated, inhibited and/or prevented (for instance by modulating and/or inhibiting and/or preventing the interaction between the envelope protein of a virus and a viral receptor on a target host cell or by competing with said envelope protein for binding to said viral receptor) and/or viral fusion with said target host cell is modulated, inhibited and/or prevented (for instance at the target host cell membrane or within an endosomal and/or lysosomal compartment of said target host cell), for example by preventing said envelope protein of a virus from undergoing a conformational change. Alternatively, the method of the present invention can comprise modulating and in particular inhibiting and/or preventing viral replication (as

defined herein) in a target host cell by specifically binding to an envelope protein of a virus at any suitable stage of said biological pathway; preferably, the method of the present invention can comprise modulating and in particular inhibiting and/or preventing viral replication in a target host cell by binding to an envelope protein of a virus, such that transcription and/or translation of the viral genome is affected, inhibited and/or prevented and/or viral packaging and/or the formation of functional virions is affected, inhibited and/or prevented and/or budding of nascent virions from the target host cell membrane is reduced, inhibited and/or prevented.

The invention furthermore relates to a method for the prevention and/or treatment of at least one disease or disorder that can be prevented and/or treated by administering an amino acid sequence of the invention, a NANOBODY® (V_{HH} sequence) of the invention, a compound or construct of the invention or a polypeptide of the invention to a patient, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the invention may relate to a method for the prevention and/or treatment of at least one viral infection, said method comprising administering to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the invention relates to a method for the prevention and/or treatment of at least one disease or disorder chosen from the group consisting of the diseases and disorders listed herein, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, influenza or rabies, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, influenza or rabies, said method comprising administering, to

a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a trivalent amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a bivalent NC41 NANOBODY® (V_{HH} sequence) (such as e.g. SEQ ID NO: 2395). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a trivalent NC41 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2415 and 2989 to 2998).

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for

the prevention and/or treatment of infection by influenza, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a trivalent amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a bivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2423 and 2424). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a trivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2425 and 2426). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza H1N1 (more in particular swine flu H1N1), said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, more particularly a bivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2423 and 2424) or a trivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2425 and 2426).

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a bivalent or biparatopic amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a bivalent

or biparatopic NANOBODY® (V_{HH} sequence) as described in Example 50.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, influenza or rabies, said method comprising administering to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, and/or of a pharmaceutical composition comprising the same.

In another aspect, the invention relates to a method for immunotherapy, and in particular for passive immunotherapy, which method comprises administering, to a subject suffering from or at risk of the diseases and disorders mentioned herein, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

In the above methods, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention and/or the compositions comprising the same can be administered in any suitable manner, depending on the specific pharmaceutical formulation or composition to be used. Thus, the amino acid sequences, NANOBODIES® (V_{HH} sequences) and/or polypeptides of the invention and/or the compositions comprising the same can for example be administered orally, intraperitoneally (e.g. intravenously, subcutaneously, intramuscularly, or via any other route of administration that circumvents the gastrointestinal tract), intranasally, transdermally, topically, by means of a suppository, by inhalation, again depending on the specific pharmaceutical formulation or composition to be used. The clinician will be able to select a suitable route of administration and a suitable pharmaceutical formulation or composition to be used in such administration, depending on the disease or disorder to be prevented or treated and other factors well known to the clinician.

Thus, in general, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and polypeptides according to the invention that are directed against an envelope protein of a virus and/or the compositions comprising the same can be administered in any suitable manner; for example but not limited thereto, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and polypeptides according to the invention and compositions comprising the same that are directed against an envelope protein of a virus (such as e.g. RSV virus, influenza virus or rabies virus) can be administered intranasally and/or by inhalation and/or by any other suitable form of pulmonary delivery; methods for pulmonary delivery and/or intranasal delivery and/or delivery by inhalation of a NANOBODY® (V_{HH} sequence), amino acid sequence, compound or construct and/or polypeptide of the invention will be known to the skilled person and

are e.g. described in the handbook "Drug Delivery: Principles and Applications" (2005) by Binghe Wang, Teruna Siahaan and Richard Soltero (Eds. Wiley Interscience (John Wiley & Sons)); in the International application WO 08/049897 of Ablynx N.V. entitled "Intranasal delivery of polypeptides and proteins"; in "Pharmacology PreTest™ Self-Assessment and Review" (11th Edition) by Rosenfeld G. C., Loose-Mitchell D. S.; and in "Pharmacology" (3rd Edition) by Lippincott Williams & Wilkins, New York; Shlafer M. McGraw-Hill Medical Publishing Division, New York; Yang K. Y., Graff L. R., Caughey A. B. Blueprints Pharmacology, Blackwell Publishing.

Accordingly, the present invention also relates to a method for administering an effective amount of a amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention, directed against an envelope protein of a virus (such as an envelope protein of RSV virus, of influenza virus or of rabies virus) and/or a composition comprising the same, wherein said method comprises the step of administering the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide and/or composition comprising the same to the pulmonary tissue. In such method, the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide and/or a composition comprising the same can be administered by any method know in the art for pulmonary delivery such as e.g. by use of an inhaler or intranasal delivery device or aerosol.

In one aspect of the invention, the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide will bind and/or neutralize virus present in the pulmonary tissue. Viruses that are present in and/or infect the pulmonary tissue are known in the art and include for example, without being limiting influenza virus, RSV, rhinoviruses (see also Fields Virology, Fifth edition, Editors in chief: David-M Knipe, Peter M. Howley, Wolters Kluwer/lipincot Williams & Wilkins, 2007). Preferably in such method for pulmonary delivery at least 5%, preferably at least 10%, 20%, 30%, 40%, more preferably at least 50%, 60%, 70%, and even more preferably at least 80% or more of the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention is stable in the pulmonary tissue for at least 24 hours, preferably at least 48 hours more preferably at least 72 hours.

It has been surprisingly found that the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention have a long lasting stability in the pulmonary tissue. E.g. it has been found that a NANOBODY® (V_{HH} sequence) directed against RSV remains functional in the lung for at least 48 hours (see experimental part). Thus, embodiments of the invention with treatment intervals such as once a day, once every 2nd, 3rd, 4th, 5th, 6th or once every week are thought to be possible taken the estimated long lasting stability of the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention.

Accordingly, the invention relates to a method for delivering an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention to the pulmonary tissue of a subject without being inactivated, said method comprising the step of pulmonary administering said amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention to said subject.

In another aspect of the invention the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide is capable of providing a systemic therapeutic or biological activity. In this aspect, the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide will enter the bloodstream and bind and/or neutralize virus present in the blood, following pulmonar administration of the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide and/or composition comprising the same. Virus that infect non-pulmonary tissues are known in the art and include, for example but without being limiting, Hepatitis, Herpes simplex I and II, Epstein-Barr virus, Cytomegalovirus, West Nile Virus, Rabies virus, Enteroviruses (polioviruses, Coxcackieviruses) (see also Fields Virology, Fifth edition, Editors in chief: David-M. Knipe, Peter M. Howley, Wolters Kluwer/lipincot Williams & Wilkins, 2007). Preferably in such method of pulmonary delivery the bioavailability for the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention is at least 1%, preferably at least 2%, 5%, 10%, 20%, 30%, 40%, more preferably at least 50%, 60%, 70%, and even more preferably at least 80% or more compared to parenteral administration of said NANOBODY® (V_{HH} sequence), polypeptide or protein.

Accordingly, the invention relates to a method for delivering an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention to the bloodstream of a subject without being inactivated, said method comprising the step of pulmonary administering said amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide of the invention to said subject.

The invention also relates to a method for the prevention and/or treatment of at least one viral infection, said method comprising administering to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the invention relates to a method for the prevention and/or treatment of at least one disease or disorder chosen from the group consisting of the diseases and disorders listed herein, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the

invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, influenza or rabies, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence of the invention, of a NANOBODY® (V_{HH} sequence) of the invention, of a polypeptide of the invention, of a compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, influenza or rabies, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same.

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a trivalent amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a bivalent NC41 NANOBODY® (V_{HH} sequence) (such as e.g. SEQ ID NO: 2395). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by RSV, said method comprising

administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a trivalent NC41 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2415 and 2989 to 2998).

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a trivalent amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a bivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2423 and 2424). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a trivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2425 and 2426). More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by influenza H1N1 (more in particular swine flu H1N1), said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, more particularly a bivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2423 and 2424) or a trivalent 202-C8 NANOBODY® (V_{HH} sequence) (such as e.g. one of SEQ ID NO's: 2425 and 2426).

More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to the pulmonary

tissue of a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention and/or of a pharmaceutical composition comprising the same. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a bivalent or biparatopic amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention. More in particular, the present invention may relate to a method for the prevention and/or treatment of infection by rabies, said method comprising administering, to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of a bivalent or biparatopic NANOBODY® (V_{HH} sequence) as described in Example 50.

Also for example but not limited thereto, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs, and polypeptides according to the invention and compositions comprising the same, that are directed against an envelope protein of rabies virus can be administered intramuscularly and/or by any suitable form of delivery to the brain, such as any suitable form of delivery which allows said amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides, compounds or constructs and compositions comprising the same to be transported across the blood-brain-barrier. Such methods for intramuscular delivery and/or any suitable form of delivery to the brain of a NANOBODY® (V_{HH} sequence), amino acid sequence and/or polypeptide of the invention will be known to the skilled person and are e.g. described in the handbook "Drug Delivery: Principles and Applications" (2005) by Binghe Wang, Teruna Siahaan and Richard Soltero (Eds. Wiley Interscience (John Wiley & Sons)); in "Pharmacology PreTest™ Self-Assessment and Review" (11^{th} Edition) by Rosenfeld G. C., Loose-Mitchell D. S.; and in "Pharmacology" (3rd Edition) by Lippincott Williams & Wilkins, New York; Shlafer M. McGraw-Hill Medical Publishing Division, New York; Yang K. Y., Graff L. R., Caughey A. B. Blueprints Pharmacology, Blackwell Publishing.

The amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention and/or the compositions comprising the same are administered according to a regime of treatment that is suitable for preventing and/or treating the disease or disorder to be prevented or treated. The clinician will generally be able to determine a suitable treatment regimen, depending on factors such as the disease or disorder to be prevented or treated, the severity of the disease to be treated and/or the severity of the symptoms thereof, the specific amino acid sequence, NANOBODY® (V_{HH}

sequence), compound or construct or polypeptide of the invention to be used, the specific route of administration and pharmaceutical formulation or composition to be used, the age, gender, weight, diet, general condition of the patient, and similar factors well known to the clinician.

Generally, the treatment regimen will comprise the administration of one or more amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention, or of one or more compositions comprising the same, in one or more pharmaceutically effective amounts or doses. The specific amount(s) or doses to administered can be determined by the clinician, again based on the factors cited above.

Generally, for the prevention and/or treatment of the diseases and disorders mentioned herein and depending on the specific disease or disorder to be treated, the potency of the specific amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and polypeptide of the invention to be used, the specific route of administration and the specific pharmaceutical formulation or composition used, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and polypeptides of the invention will generally be administered in an amount between 1 gram and 0.01 microgram per kg body weight per day, preferably between 0.1 gram and 0.1 microgram per kg body weight per day, such as about 1, 10, 100 or 1000 microgram per kg body weight per day, either continuously (e.g. by infusion), as a single daily dose or as multiple divided doses during the day. The clinician will generally be able to determine a suitable daily dose, depending on the factors mentioned herein. It will also be clear that in specific cases, the clinician may choose to deviate from these amounts, for example on the basis of the factors cited above and his expert judgment. Generally, some guidance on the amounts to be administered can be obtained from the amounts usually administered for comparable conventional antibodies or antibody fragments against the same target administered via essentially the same route, taking into account however differences in affinity/avidity, efficacy, biodistribution, half-life and similar factors well known to the skilled person.

When the amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct and/or polypeptide and/or a composition comprising the same is administered to the pulmonary tissue the treatment regime may be once or twice daily, preferably once daily, or once every 2, 3, 4, 5, 6, or 7 days.

Usually, in the above method, a single amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct, or polypeptide of the invention will be used. It is however within the scope of the invention to use two or more amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs and/or polypeptides of the invention in combination.

The NANOBODIES® (V_{HH} sequences), amino acid sequences, compounds or constructs and polypeptides of the invention may also be used in combination with one or more further

pharmaceutically active compounds or principles, i.e. as a combined treatment regimen, which may or may not lead to a synergistic effect. Again, the clinician will be able to select such further compounds or principles, as well as a suitable combined treatment regimen, based on the factors cited above and his expert judgement.

In particular, the amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs, and polypeptides of the invention may be used in combination with other pharmaceutically active compounds or principles that are or can be used for the prevention and/or treatment of the diseases and disorders cited herein, as a result of which a synergistic effect may or may not be obtained. Examples of such compounds and principles, as well as routes, methods and pharmaceutical formulations or compositions for administering them will be clear to the clinician.

When two or more substances or principles are to be used as part of a combined treatment regimen, they can be administered via the same route of administration or via different routes of administration, at essentially the same time or at different times (e.g. essentially simultaneously, consecutively, or according to an alternating regime). When the substances or principles are to be administered simultaneously via the same route of administration, they may be administered as different pharmaceutical formulations or compositions or part of a combined pharmaceutical formulation or composition, as will be clear to the skilled person.

Also, when two or more active substances or principles are to be used as part of a combined treatment regimen, each of the substances or principles may be administered in the same amount and according to the same regimen as used when the compound or principle is used on its own, and such combined use may or may not lead to a synergistic effect. However, when the combined use of the two or more active substances or principles leads to a synergistic effect, it may also be possible to reduce the amount of one, more or all of the substances or principles to be administered, while still achieving the desired therapeutic action. This may for example be useful for avoiding, limiting or reducing any unwanted side-effects that are associated with the use of one or more of the substances or principles when they are used in their usual amounts, while still obtaining the desired pharmaceutical or therapeutic effect.

The effectiveness of the treatment regimen used according to the invention may be determined and/or followed in any manner known per se for the disease or disorder involved, as will be clear to the clinician. The clinician will also be able, where appropriate and on a case-by-case basis, to change or modify a particular treatment regimen, so as to achieve the desired therapeutic effect, to avoid, limit or reduce unwanted side-effects, and/or to achieve an appropriate balance between achieving the desired therapeutic effect on the one hand and avoiding, limiting or reducing undesired side effects on the other hand.

Generally, the treatment regimen will be followed until the desired therapeutic effect is achieved and/or for as long as the desired therapeutic effect is to be maintained. Again, this can be determined by the clinician.

In another aspect, the invention relates to the use of an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct, or polypeptide of the invention in the preparation of a pharmaceutical composition for prevention and/or treatment of at least one viral disease; and/or for use in one or more of the methods of treatment mentioned herein.

The subject to be treated may be any warm-blooded animal, but is in particular a mammal, and more in particular a human being. As will be clear to the skilled person, the subject to be treated will in particular be a person suffering from, or at risk of, the diseases and disorders mentioned herein.

The invention also relates to the use of an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention in the preparation of a pharmaceutical composition for the prevention and/or treatment of at least one disease or disorder that can be prevented and/or treated by administering an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention to a patient.

More in particular, the invention relates to the use of an amino acid sequence, NANOBODY® (V_{HH} sequence), compound or construct or polypeptide of the invention in the preparation of a pharmaceutical composition for the prevention and/or treatment of viral diseases, and in particular for the prevention and treatment of one or more of the diseases and disorders listed herein.

Again, in such a pharmaceutical composition, the one or more amino acid sequences, NANOBODIES® (V_{HH} sequences), compounds or constructs or polypeptides of the invention may also be suitably combined with one or more other active principles, such as those mentioned herein.

Finally, although the use of the NANOBODIES® (V_{HH} sequences) of the invention (as defined herein) and of the polypeptides of the invention is much preferred, it will be clear that on the basis of the description herein, the skilled person will also be able to design and/or generate, in an analogous manner, other amino acid sequences and in particular (single) domain antibodies against an envelope protein of a virus, as well as polypeptides comprising such (single) domain antibodies.

For example, it will also be clear to the skilled person that it may be possible to “graft” one or more of the CDR's mentioned above for the NANOBODIES® (V_{HH} sequences) of the invention onto such (single) domain antibodies or other protein scaffolds, including but not

limited to human scaffolds or non-immunoglobulin scaffolds. Suitable scaffolds and techniques for such CDR grafting will be clear to the skilled person and are well known in the art, see for example those mentioned in WO 08/020079. For example, techniques known per se for grafting mouse or rat CDR's onto human frameworks and scaffolds can be used in an analogous manner to provide chimeric proteins comprising one or more of the CDR's of the NANOBODIES® (V_{HH} sequences) of the invention and one or more human framework regions or sequences.

It should also be noted that, when the NANOBODIES® (V_{HH} sequences) of the inventions contain one or more other CDR sequences than the preferred CDR sequences mentioned above, these CDR sequences can be obtained in any manner known per se, for example using one or more of the techniques described in WO 08/020079.

Further uses of the amino acid sequences, NANOBODIES® (V_{HH} sequences), polypeptides, nucleic acids, genetic constructs and hosts and host cells of the invention will be clear to the skilled person based on the disclosure herein. For example, and without limitation, the amino acid sequences of the invention can be linked to a suitable carrier or solid support so as to provide a medium than can be used in a manner known per se to purify an envelope protein of a virus from compositions and preparations comprising the same. Derivatives of the amino acid sequences of the invention that comprise a suitable detectable label can also be used as markers to determine (qualitatively or quantitatively) the presence of an envelope protein of a virus in a composition or preparation or as a marker to selectively detect the presence of an envelope protein of a virus on the surface of a cell or tissue (for example, in combination with suitable cell sorting techniques).

The invention will now be further described by means of the following non-limiting preferred aspects, examples and figures:

Preferred Aspects:

- Aspect A-1. Amino acid sequence that is directed against and/or that can specifically bind to an envelope protein of a virus.
- Aspect A-2. Amino acid sequence according to aspect A-1, wherein said amino acid sequence modulates the interaction between said envelope protein and at least one binding partner.
- Aspect A-3. Amino acid sequence according to aspects A-1 or A-2, wherein said amino acid sequence inhibits and/or prevents the interaction between said envelope protein and at least one binding partner.
- Aspect A-4. Amino acid sequence according to any of the preceding aspects, wherein said amino acid sequence competes with said at least one binding partner for binding to said envelope protein.
- Aspect A-5. Amino acid sequence according to aspect A-4, wherein said at least one

binding partner is a viral receptor for an envelope protein of a virus.

- Aspect A-6. Amino acid sequence according to aspect A-5, wherein said viral receptor is chosen from the group consisting of sialic acid, soluble (2,3)-sialic acid, (2,6)-sialic acid, CD4, CCR5, CXCR4, galactosylceramide, ACE2, HveA, CD155, ICAM-1, CAR, αv integrins, heparin sulphate proteoglycans, JAM-1, the Nicotinic Acetylcholine Receptor (AchR), and the Nueral Cell Adhesion Molecule (NCAM).
- Aspect A-7. Amino acid sequence according to aspects A-5 or A-6, wherein said interaction between an envelope protein and a viral receptor is chosen from the group consisting of the interaction of HA of influenza A virus with sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; the interaction of gp120 of HIV-1 virus with CD4; CCR5; CXCR4; and/or galactosylceramide; the interaction of S1 of SARS coronavirus with ACE2; the interaction of gD; gB; and/or gC; the interaction of the heterodimer gH/gL of herpes simplex 1 virus with HveA; the interaction of VP1; VP2; and/or VP3 of poliovirus 1 with CD155; the interaction of VP1; VP2; and/or VP3 of rhinovirus 3 with ICAM-1; the interaction of adenovirus 2 fibre with CAR; the interaction of adenovirus 2 penton base with αv integrins; sialic acid; (2,3) sialic acid; (2,6) sialic acid; and/or heparin sulphate proteoglycans; the interaction of σ1 of reovirus 1 with JAM-1; sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; and the interaction of G-protein of rabies virus with the Nicotinic Acetylcholine Receptor (AchR); and/or the Nueral Cell Adhesion Molecule (NCAM).
- Aspect A-8. Amino acid sequence according to aspect A-4, wherein said at least one binding partner is a monoclonal antibody or an antigen binding part thereof (such as a Fab, Fab_2, Fv, scFv, V_H, V_{HH}, V_L, NANOBODY® (V_{HH} sequence), etc.) that is directed against and/or specifically binds to said envelope protein of a virus.
- Aspect A-9. Amino acid sequence according to aspect A-8, wherein said monoclonal antibody or antigen binding part thereof is selected from Synagis®, 101F Fab, VN04-2, MAb C179 and MAb 8-2.
- Aspect A-10. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a viral-specific protein.
- Aspect A-11. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a membrane protein.
- Aspect A-12. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a non-glycosylated protein.
- Aspect A-13. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a glycoprotein.
- Aspect A-14. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a viral attachment protein.
- Aspect A-15. Amino acid sequence according to aspect A-14, wherein said viral attachment protein is chosen from the group consisting of the G protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein

of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2 and σ1 of Reovirus 1.

- Aspect A-16. Amino acid sequence according to any of aspects A-1 to A-13, wherein said envelope protein is a viral fusion protein.
- Aspect A-17. Amino acid sequence according to aspect A-16, wherein said viral fusion protein is chosen from the group consisting of the F protein of RSV virus, the HA protein of Influenza A virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.
- Aspect A-18. Amino acid sequence according to any of the preceding aspects, wherein said envelope protein is a viral attachment protein and a viral fusion protein.
- Aspect A-19. Amino acid sequence according to aspect A-18, wherein said viral attachment protein and viral fusion protein is chosen from the group consisting of the HA protein of influenza A virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, and the E1 protein of Sindbis virus.
- Aspect A-20. Amino acid sequence according to aspects A-16 or A-18, wherein said viral fusion protein is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state.
- Aspect A-21. Amino acid sequence according to aspect A-20, wherein said viral fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein trimer.
- Aspect A-22. Amino acid sequence according to aspect A-21, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect A-23. Amino acid sequence according to aspects A-21 or A-22, wherein said fusion protein trimer is a six-helix bundle.
- Aspect A-24. Amino acid sequence according to any of aspects A-21 to A-23, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human

parainfluenza virus F protein, Newcastle disease virus F protein, Human respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein, SARS corona virus E2 protein.

- Aspect A-25. Amino acid sequence according to aspect A-24, wherein said fusion protein is Influenza A virus HA protein.
- Aspect A-26. Amino acid sequence according to aspect A-24, wherein said fusion protein is Human respiratory syncytial virus F protein.
- Aspect A-27. Amino acid sequence according to aspect A-20, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a protein dimer.
- Aspect A-28. Amino acid sequence according to aspect A-27, wherein said dimer is a fusion protein homodimer.
- Aspect A-29. Amino acid sequence according to aspect A-27, wherein said dimer is a protein heterodimer.
- Aspect A-30. Amino acid sequence according to aspect A-20, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein monomer.
- Aspect A-31. Amino acid sequence according to any of aspects A-27 to A-30, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect A-32. Amino acid sequence according to aspect A-20, wherein said fusion protein is characterized by a post-fusion conformational state, which is a fusion protein trimer.
- Aspect A-33. Amino acid sequence according to aspect A-32, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect A-34. Amino acid sequence according to aspects A-32 or A-33, wherein said fusion protein trimer is a six-helix bundle.
- Aspect A-35. Amino acid sequence according to aspect A-33, wherein said trimer of hairpins comprises an α-helical coiled coil.
- Aspect A-36. Amino acid sequence according to any of aspects A-32 to A-35, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Respiratory syncytial F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1

gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.

- Aspect A-37. Amino acid sequence according to aspect A-33, wherein said trimer of hairpins comprises β-structures.
- Aspect A-38. Amino acid sequence according to any of aspects A-32 to A-34 and A-37, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect A-39. Amino acid sequence according to any of aspects A-33, A-35 and A-37, wherein said trimer of hairpins comprises an α-helical coiled coil and β-structures.
- Aspect A-40. Amino acid sequence according to aspect A-39, wherein said fusion protein is chosen from the group consisting of vesicular stomatitis virus G protein, Rabies virus G protein and Herpes simplex virus gB protein.
- Aspect A-41. Amino acid sequence according to aspect A-40, wherein said fusion protein is Rabies virus G protein.
- Aspect A-42. Amino acid sequence according to any of aspects A-20 to A-41, wherein said amino acid sequence is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect A-43. Amino acid sequence according to aspect A-42, wherein said amino acid sequence is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state of said fusion protein.
- Aspect A-44. Amino acid sequence according to aspect A-42, wherein said amino acid sequence is directed against and/or can specifically bind to the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect A-45. Amino acid sequence according to aspect A-42, wherein said amino acid sequence is directed against and/or can specifically bind to the pre-fusion conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect A-46. Amino acid sequence according to any of aspects A-21 to A-45, wherein said epitope is located in a cavity or cleft formed by said trimer according to claims A-21 to A-26 and A-32 to A-41 or formed by said dimer according to claims A-27 to A-31.
- Aspect A-47. Amino acid sequence according to any of aspects A-21 to A-46, wherein said epitope is located in the stem region of said fusion protein.
- Aspect A-48. Amino acid sequence according to aspect A-47, wherein said epitope that is located in the stem region of said fusion protein is chosen from the group consisting of an epitope that is located in the region comprising one or more of the

amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA, an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA and an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA.

- Aspect A-49. Amino acid sequence according to any of aspects A-21 to A-46, wherein said epitope is located in the neck region of said fusion protein.
- Aspect A-50. Amino acid sequence according to any of aspects A-21 to A-46, wherein said epitope is located in the globular head region of said fusion protein.
- Aspect A-51. Amino acid sequence according to aspect A-50, wherein said globular head region comprises a β-barrel-type structure.
- Aspect A-52. Amino acid sequence according to aspect A-50, wherein said globular head region comprises an immunoglobulin-type β-sandwich domain and a β-sheet domain.
- Aspect A-53. Amino acid sequence according to any of aspects A-1 to A-52, wherein said epitope is chosen from the group consisting of an epitope that is located in the region comprising the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus, an epitope that is located in the region comprising the Fla site and/or the region comprising amino acid 389 of the F-protein of RSV virus, an epitope that is located in the region comprising amino acids 422 to 438 of the F-protein of RSV virus, an epitope that is located in the region comprising the sialic acid binding site of the H5 HA envelope protein of influenza virus, an epitope that is located in the region comprising the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus, an epitope that is located in the C-terminal region of a fusion protein, an epitope that is located in the N-terminal domain of a fusion protein, an epitope that is located in or comprises the fusion peptide of a fusion protein, an epitope that is located in the transmembrane domain of a fusion protein, an epitope that is located in a α-helical coiled-coil of a fusion protein, an epitope that is located in a β-structure of a fusion protein, an epitope that is located in Domain I of a fusion protein, an epitope that is located in Domain II of a fusion protein and an epitope that is located in Domain III of a fusion protein.
- Aspect A-54. Amino acid sequence according to aspect A-53, wherein said epitope that is located in Domain II of a fusion protein is an epitope that is located in the fusion peptide of Domain II of a fusion protein.
- Aspect A-55. Amino acid sequence according to aspect A-53, wherein said epitope

that is located in Domain III of a fusion protein is chosen from the group consisting of an epitope that is located in the stem region at the C-terminus of Domain III of a fusion protein and an epitope that is located in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.

- Aspect A-56. Amino acid sequence according to any of aspects A-1 to A-55, wherein said virus is chosen from the group consisting of a DNA virus, an RNA virus and a Reverse Transcriptase (RT) virus.
- Aspect A-57. Amino acid sequence according to aspect A-56, wherein said DNA virus is chosen from the group consisting of a ds DNA virus and a ssDNA virus.
- Aspect A-58. Amino acid sequence according to aspect A-56, wherein said RNA virus is chosen from the group consisting of a dsRNA virus, a positive-sense ssRNA virus and a negative-sense ssRNA virus.
- Aspect A-59. Amino acid sequence according to aspect A-56, wherein said Reverse Transcriptase (RT) virus is chosen from the group consisting of a dsDNA-RT virus and a ssRNA-RT virus.
- Aspect A-60. Amino acid sequence according to any of aspects A-1 to A-55, wherein said virus belongs to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae.
- Aspect A-61. Amino acid sequence according to aspect A-60, wherein said virus belongs to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses.
- Aspect A-62. Amino acid sequence according to any of aspects A-1 to A-61, wherein said amino acid sequence neutralizes said virus.
- Aspect A-63. Amino acid sequence according to any of aspects A-1 to A-62, wherein said amino acid sequence modulates the infectivity of said virus.
- Aspect A-64. Amino acid sequence according to aspect A-63, wherein said amino acid sequence inhibits and/or prevents the infectivity of said virus.
- Aspect A-65. Amino acid sequence according to any of aspects A-63 or A-64, wherein said amino acid sequence neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the pre-entry stage.
- Aspect A-66. Amino acid sequence according to aspect A-65, wherein said amino acid sequence modulates, inhibits and/or prevents viral entry in a target host cell.
- Aspect A-67. Amino acid sequence according to any of aspects A-1 to A-66, wherein said amino acid sequence induces virion aggregation of said virus.
- Aspect A-68. Amino acid sequence according to any of aspects A-1 to A-67, wherein said amino acid sequence destabilizes the virion structure of said virus.
- Aspect A-69. Amino acid sequence according to any of aspects A-1 to A-68, wherein said amino acid sequence inhibits virion attachment to a target host cell of said virus.

- Aspect A-70. Amino acid sequence according to aspect A-69, wherein said amino acid sequence inhibits virion attachment to a target host cell of said virus by modulating the interaction between said envelope protein and a viral receptor.
- Aspect A-71. Amino acid sequence according to aspects A-69 or A-70, wherein said amino acid sequence inhibits virion attachment to a target host cell of said virus by inhibiting and/or preventing the interaction between said envelope protein and a viral receptor.
- Aspect A-72. Amino acid sequence according to aspects A-69 to A-71, wherein said amino acid sequence competes with said envelope protein for binding to a viral receptor.
- Aspect A-73. Amino acid sequence according to any of aspects A-1 to A-72, wherein said amino acid sequence inhibits fusion of said virus with a target host cell of said virus.
- Aspect A-74. Amino acid sequence according to aspect A-73, wherein fusion of said virus with a target host cell of said virus taking place at the target host cell membrane is inhibited.
- Aspect A-75. Amino acid sequence according to aspect A-73, wherein fusion of said virus with a target host cell of said virus taking place within an endosomal or lysosomal compartment is inhibited.
- Aspect A-76. Amino acid sequence according to any of aspects A-73 to A-75, wherein said amino acid sequence prevents said envelope protein of a virus from undergoing a conformational change.
- Aspect A-77. Amino acid sequence according to any of aspects A-63 or A-64, wherein said amino acid sequence neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the post-entry stage.
- Aspect A-78. Amino acid sequence according to any of aspects A-1 to A-77, wherein said amino acid sequence modulates, inhibits and/or prevents viral replication in a target host cell.
- Aspect A-79. Amino acid sequence according to any of aspects A-1 to A-78, wherein said amino acid sequence affects, inhibits and/or prevents transcription and/or translation of the viral genome.
- Aspect A-80. Amino acid sequence according to any of aspects A-1 to A-79, wherein said amino acid sequence affects, inhibits and/or prevents viral packaging and/or the formation of functional virions.
- Aspect A-81. Amino acid sequence according to any of aspects A-1 to A-80, wherein said amino acid sequence reduces, inhibits and/or prevents budding or release of nascent virions from a target host cell surface.
- Aspect A-82. Amino acid sequence according to any of aspects A-1 to A-81, wherein said amino acid sequence is directed against and/or can specifically bind to at least two epitopes of at least one envelope protein of a virus.

- Aspect A-83. Amino acid sequence according to aspect A-82, wherein said amino acid sequence is directed against and/or can specifically bind to at least two epitopes of one envelope protein of a virus.
- Aspect A-84. Amino acid sequence according to any of aspects A-1 to A-82, wherein said amino acid sequence is directed against and/or can specifically bind to at least two epitopes of at least two envelope proteins of a virus.
- Aspect A-85. Amino acid sequence according to any of aspects A-1 to A-82 and A-84, wherein said amino acid sequence is directed against and/or can specifically bind to three or more epitopes of an envelope protein of a virus.
- Aspect A-86. Amino acid sequence according to aspect A-85, wherein said amino acid sequence is directed against and/or can specifically bind to three or more epitopes of at least two envelope proteins of a virus.
- Aspect A-87. Amino acid sequence according to any of aspects A-82 to A-86, wherein said at least two or three or more epitopes are the same or are different.
- Aspect A-88. Amino acid sequence according to any of aspects A-84 or A-86, wherein said at least two envelope proteins are the same or are different.
- Aspect A-89. Amino acid sequence according to any of the preceding aspects, that is in essentially isolated form.
- Aspect A-90. Amino acid sequence according to any of the preceding aspects, for administration to a subject, wherein said amino acid sequence does not naturally occur in said subject.
- Aspect A-91. Amino acid sequence according to any of the preceding aspects, that can specifically bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect A-92. Amino acid sequence according to any of the preceding aspects, that can specifically bind to an envelope protein of a virus with a rate of association (k_{on}-rate) of between $10^2\,M^{-1}s^{-1}$ to about $10^7\,M^{-1}s^{-1}$, preferably between $10^3\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, more preferably between $10^4\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, such as between $10^5\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$.
- Aspect A-93. Amino acid sequence according to any of the preceding aspects, that can specifically bind to an envelope protein of a virus with a rate of dissociation (k_{off} rate) between $1\,s^{-1}$ and $10^{-6}\,s^{-1}$, preferably between $10^{-2}\,s^{-1}$ and $10^{-6}\,s^{-1}$, more preferably between $10^{-3}\,s^{-1}$ and $10^{-6}\,s^{-1}$, such as between $10^{-4}\,s^{-1}$ and $10^{-6}\,s^{-1}$.
- Aspect A-94. Amino acid sequence according to any of the preceding aspects, that can specifically bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.
- Aspect A-95. Amino acid sequence according to any of the preceding aspects, that is a naturally occurring amino acid sequence (from any suitable species) or a synthetic or

semi-synthetic amino acid sequence.

- Aspect A-96. Amino acid sequence according to any of the preceding aspects, that comprises an immunoglobulin fold or that under suitable conditions is capable of forming an immunoglobulin fold.
- Aspect A-97. Amino acid sequence according to any of the preceding aspects, that essentially consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively).
- Aspect A-98. Amino acid sequence according to any of the preceding aspects, that is an immunoglobulin sequence.
- Aspect A-99. Amino acid sequence according to any of the preceding aspects, that is a naturally occurring immunoglobulin sequence (from any suitable species) or a synthetic or semi-synthetic immunoglobulin sequence.
- Aspect A-100. Amino acid sequence according to any of the preceding aspects that is a humanized immunoglobulin sequence, a camelized immunoglobulin sequence or an immunoglobulin sequence that has been obtained by techniques such as affinity maturation.
- Aspect A-101. Amino acid sequence according to any of the preceding aspects, that essentially consists of a light chain variable domain sequence (e.g. a V_L-sequence); or of a heavy chain variable domain sequence (e.g. a V_H-sequence).
- Aspect A-102. Amino acid sequence according to any of the preceding aspects, that essentially consists of a heavy chain variable domain sequence that is derived from a conventional four-chain antibody or that essentially consist of a heavy chain variable domain sequence that is derived from heavy chain antibody.
- Aspect A-103. Amino acid sequence according to any of the preceding aspects, that essentially consists of a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), of a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), of a “dAb” (or an amino acid sequence that is suitable for use as a dAb) or of a NANOBODY® (V_{HH} sequence) (including but not limited to a V_{HH} sequence).
- Aspect A-104. Amino acid sequence according to any of the preceding aspects, that essentially consists of a NANOBODY® (V_{HH} sequence).
- Aspect A-105. Amino acid sequence according to any of the preceding aspects, that essentially consists of a NANOBODY® (V_{HH} sequence) that
    - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
    - and in which:
    - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from

the Hallmark residues mentioned in Table B-2.

- Aspect A-106. Amino acid sequence according to any of the preceding aspects, that essentially consists of a NANOBODY® (V_{HH} sequence) that
  - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect A-107. Amino acid sequence according to any of the preceding aspects, that essentially consists of a humanized NANOBODY® (V_{HH} sequence).
- Aspect A-108. Amino acid sequence according to aspect A-107, that essentially consists of a NANOBODY® (V_{HH} sequence) that can bind (as further defined herein) to an envelope protein of a virus and which:
  - i) is a humanized variant of one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1); and/or
  - ii) has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) and/or at least one of the amino acid sequences of SEQ ID NO's: 2999 to 3015 (see Table A-8), in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - iii) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2 below.
- Aspect A-109. Amino acid sequence according to any of the preceding aspects, that in addition to the at least one binding site for binding against an envelope protein of a virus, contains one or more further binding sites for binding against other antigens, proteins or targets.
- Aspect B-1. Amino acid sequence directed against an envelope protein of a virus, that comprises one or more stretches of amino acid residues chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least

one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;

- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- or any suitable combination thereof.

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.

- Aspect B-2. Amino acid sequence according to aspect B-1, in which at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against an envelope protein of a virus.
- Aspect B-3. Amino acid sequence directed against and/or that can specifically bind an envelope protein of a virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109, B-1 or B-2.

- Aspect B-4. Amino acid sequence according to aspect B-3, in which the at least two stretches of amino acid residues forms part of the antigen binding site for binding against an envelope protein of a virus.
- Aspect B-5. Amino acid sequence that is directed against and/or that specifically binds an envelope protein of a virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484,

2590 to 2597, 2754 to 2789 and 3194 to 3258;

- the second stretch of amino acid residues is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- and the third stretch of amino acid residues is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-1 to B-4.

- Aspect B-6. Amino acid sequence according to aspect B-5, in which the at least three stretches of amino acid residues forms part of the antigen binding site for binding against an envelope protein of a virus.
- Aspect B-7. Amino acid sequence that is directed against and/or that can specifically bind an envelope protein of a virus, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-1 to B-6.
- Aspect C-1: Amino acid sequence directed against an envelope protein of a virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 to said envelope protein of a virus. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according

to aspects B-1 to B-7. Also, preferably, such an amino acid sequence is able to specifically bind to an envelope protein of a virus.

- Aspect C-2: Amino acid sequence directed against an envelope protein of a virus that is cross-blocked from binding to said envelope protein of a virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-1 to B-7. Also, preferably, such an amino acid sequence is able to specifically bind to an envelope protein of a virus.
- Aspect C-3: Amino acid sequence according to any of aspects C-1 or C-2 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect C-4: Amino acid sequence according to any of aspects C-1 or C-2 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect B-8: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the F-protein of human RSV virus, that comprises one or more stretches of amino acid residues chosen from the group consisting of:
    - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
    - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
    - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
    - g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
    - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
    - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least

one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;

- or any suitable combination thereof.

Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.

- Aspect B-9: Amino acid sequence according to aspect B-8, in which at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the F-protein of human RSV virus.
- Aspect B-10: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the F-protein of human RSV virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch

of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109, B-8 or B-9.

- Aspect B-11: Amino acid sequence according to aspect B-10, in which the at least two stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the F-protein of human RSV virus.
- Aspect B-12: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the F-protein of human RSV virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - the second stretch of amino acid residues is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - and the third stretch of amino acid residues is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least

one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-8 to B-11.

- Aspect B-13: Amino acid sequence according to aspect B-12, in which the at least three stretches of amino acid residues forms part of the antigen binding site for binding to at least one epitope of the F-protein of human RSV virus.
- Aspect B-14: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the F-protein of human RSV virus, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-8 to B-13.
- Aspect C-5: Amino acid sequence directed against at least one epitope of the F-protein of human RSV virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 to said at least one epitope of the F-protein of human RSV virus. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-8 to B-14. Also, preferably, such an amino acid sequence is able to specifically bind to the F-protein of human RSV virus.
- Aspect C-6: Amino acid sequence directed against at least one epitope of the F-protein of human RSV virus that is cross-blocked from binding to said at least one epitope of the F-protein of human RSV virus by at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-8 to B-14. Also, preferably, such an amino acid sequence is able to specifically bind to the F-protein of human RSV virus.
- Aspect C-7: Amino acid sequence according to any of aspects C-5 or C-6 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect C-8: Amino acid sequence according to any of aspects C-5 or C-6 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect B-15: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the hemagglutinin HA5 protein of influenza virus, that comprises one or more stretches of amino acid residues chosen from the group

consisting of:

- a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- or any suitable combination thereof.
  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.

- Aspect B-16: Amino acid sequence according to aspect B-15, in which at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the hemagglutinin HA5 protein of influenza virus.
- Aspect B-17: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the hemagglutinin HA5 protein of influenza virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483,

2754 to 2755 and 3194 to 3258;

- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109, B-15 or B-16.

- Aspect B-18: Amino acid sequence according to aspect B-17, in which the at least two stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the hemagglutinin HA5 protein of influenza virus.
- Aspect B-19: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the hemagglutinin HA5 protein of influenza virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to

2755 and 3194 to 3258;

- b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- the second stretch of amino acid residues is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- and the third stretch of amino acid residues is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-15 to B-18.

- Aspect B-20: Amino acid sequence according to aspect B-19, in which the at least three stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the hemagglutinin HA5 protein of influenza virus.
- Aspect B-21: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the hemagglutinin HA5 protein of influenza virus, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128.

Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-15 to B-20.

- Aspect C-9: Amino acid sequence directed against at least one epitope of the hemagglutinin HA5 protein of influenza virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 to said at least one epitope of the hemagglutinin HA5 protein of influenza virus. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-15 to B-21. Also, preferably, such an amino acid sequence is able to specifically bind to the hemagglutinin HA5 protein of influenza virus.
- Aspect C-10: Amino acid sequence directed against an epitope of the hemagglutinin HA5 protein of influenza virus that is cross-blocked from binding to said at least one epitope of the hemagglutinin HA5 protein of influenza virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-15 to B-21. Also, preferably, such an amino acid sequence is able to specifically bind to the hemagglutinin HA5 protein of influenza virus.
- Aspect C-11: Amino acid sequence according to any of aspects C-9 or C-10, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect C-12: Amino acid sequence according to any of aspects C-9 or C-10 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect B-22: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the G-protein of rabies virus, that comprises one or more stretches of amino acid residues chosen from the group consisting of:
  - a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;

- g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- or any suitable combination thereof.

  Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.

- Aspect B-23: Amino acid sequence according to aspect B-22, in which at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the G-protein of rabies virus.
- Aspect B-24: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the G-protein of rabies virus, that comprises two or more stretches of amino acid residues chosen from the group consisting of:
  - a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds

to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109, B-22 or B-23.

- Aspect B-25: Amino acid sequence according to aspect B-24, in which the at least two stretches of amino acid residues forms part of the antigen binding site for binding against at least one epitope of the G-protein of rabies virus.
- Aspect B-26: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the G-protein of rabies virus, that comprises three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:
  - a) the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - the second stretch of amino acid residues is chosen from the group consisting of:
  - d) the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - and the third stretch of amino acid residues is chosen from the group consisting of:
  - g) the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

  Such an amino acid sequence may in particular be an amino acid sequence

according to any of the aspects A-1 to A-109 and/or B-22 to B-25.

- Aspect B-27: Amino acid sequence according to aspect B-26, in which the at least three stretches of amino acid residues forms part of the antigen binding site for binding to at least one epitope of the G-protein of rabies virus.
- Aspect B-28: Amino acid sequence that is directed against and/or that can specifically bind at least one epitope of the G-protein of rabies virus, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or B-22 to B-27.
- Aspect C-13: Amino acid sequence directed against at least one epitope of the G-protein of rabies virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717 to said at least one epitope of the G-protein of rabies virus. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-22 to B-28. Also, preferably, such an amino acid sequence is able to specifically bind to the G-protein of rabies virus.
- Aspect C-14: Amino acid sequence directed against at least one epitope of the G-protein of rabies virus that is cross-blocked from binding to said at least one epitope of the G-protein of rabies virus by at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717. Such an amino acid sequence may in particular be an amino acid sequence according to any of the aspects A-1 to A-109 and/or according to aspects B-22 to B-28. Also, preferably, such an amino acid sequence is able to specifically bind to the G-protein of rabies virus.
- Aspect C-15: Amino acid sequence according to any of aspects C-13 or C-14, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect C-16: Amino acid sequence according to any of aspects C-13 or C-14 wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect D-1: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, that is in essentially isolated form.
- Aspect D-2: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1, for administration to a subject, wherein said amino acid sequence does not naturally occur in said subject.
- Aspect D-3: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1 to D-2, that can specifically bind to at least one epitope of an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12}

moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.

- Aspect D-4: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1 to D-3, that can specifically bind to at least one epitope of an envelope protein of a virus with a rate of association (k_{on}-rate) of between $10^2\,M^{-1}s^{-1}$ to about $10^7\,M^{-1}s^{-1}$, preferably between $10^3\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, more preferably between $10^4\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, such as between $10^5\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$.
- Aspect D-5: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1 to D-4, that can specifically bind to at least one epitope of an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and $10^{-6}\,s^{-1}$ preferably between $10^{-2}\,s^{-1}$ and $10^{-6}\,s^{-1}$, more preferably between $10^{-3}\,s^{-1}$ and $10^{-6}\,s^{-1}$, such as between $10^{-4}\,s^{-1}$ and $10^{-6}\,s^{-1}$.
- Aspect D-6: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1 to D-5, that can specifically bind to at least one epitope of an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

  The amino acid sequences according to aspects D-1 to D-6 may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.
- Aspect E-1: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16 and/or D-1 to D-6, that is a naturally occurring amino acid sequence (from any suitable species) or a synthetic or semi-synthetic amino acid sequence.
- Aspect E-2: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1, that comprises an immunoglobulin fold or that under suitable conditions is capable of forming an immunoglobulin fold.
- Aspect E-3: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-2, that is an immunoglobulin sequence.
- Aspect E-4: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-3, that is a naturally occurring immunoglobulin sequence (from any suitable species) or a synthetic or semi-synthetic immunoglobulin sequence.
- Aspect E-5: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-4, that is a humanized immunoglobulin sequence, a camelized immunoglobulin sequence or an immunoglobulin sequence that has been obtained by techniques such as affinity maturation.
- Aspect E-6: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-5, that essentially consists of a light chain variable domain sequence (e.g. a V_L-sequence); or of a heavy chain variable domain sequence (e.g. a V_H-sequence).
- Aspect E-7: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-6, that essentially consists of a heavy chain variable

domain sequence that is derived from a conventional four-chain antibody or that essentially consist of a heavy chain variable domain sequence that is derived from heavy chain antibody.

- Aspect E-8: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-7, that essentially consists of a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), of a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), of a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or of a NANOBODY® (V_{HH} sequence) (including but not limited to a V_{HH} sequence).
- Aspect E-9: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-8, that essentially consists of a NANOBODY® (V_{HH} sequence).
- Aspect E-10: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-9, that essentially consists of a NANOBODY® (V_{HH} sequence) that
  - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect E-11: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-10, that essentially consists of a NANOBODY® (V_{HH} sequence) that
  - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect E-12: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-11, that essentially consists of a humanized NANOBODY® (V_{HH} sequence).
- Aspect E-13: Amino acid sequence according to aspect E-12, that essentially consists

of a humanized NANOBODY® (V_{HH} sequence) which can bind (as further defined herein) to an envelope protein of a virus and which:

- i) is a humanized variant of one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1); and/or
- ii) has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1) and/or at least one of the amino acid sequences of SEQ ID NO's: 2999 to 3015 (see Table A-8), in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
- and in which:
- iii) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2 below.

- Aspect E-14: Amino acid sequence according to any of aspects B-1 to B-28 or C-1 to C-16, D-1 to D-5 and/or E-1 to E-14, that in addition to the at least one binding site for binding formed by the CDR sequences, contains one or more further binding sites for binding against other antigens, proteins or targets.

  The amino acid sequences according to aspects E-1 to E-14 may in particular be an amino acid sequence according to any of the aspects A-1 to A-109.
- Aspect F-1: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - and/or
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- and/or
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

  Such an amino acid sequence is preferably directed against an envelope protein of a virus and/or an amino acid sequence that can specifically bind to an envelope protein of a virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-2: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - and
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;

- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

  Such an amino acid sequence is preferably directed against an envelope protein of a virus and/or an amino acid sequence that can specifically bind to an envelope protein of a virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-3: Amino acid sequence according to any of aspects F-1 or F-2, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.

  Such an amino acid sequence is preferably directed against an envelope protein of a virus and/or an amino acid sequence that can specifically bind to an envelope protein of a virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.
- Aspect F-4: Amino acid sequence directed against an envelope protein of a virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 to an envelope protein of a virus.
- Aspect F-5: Amino acid sequence directed against an envelope protein of a virus that is cross-blocked from binding to an envelope protein of a virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.
- Aspect F-6: Amino acid sequence according to any of aspects F-4 or F-5, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect F-7: Amino acid sequence according to any of aspects F-4 or F-5, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected

in an ELISA assay.

- Aspect F-8: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - and/or
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - and/or
  - CDR3 is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629.

    Such an amino acid sequence is preferably directed against the F protein of RSV virus and/or an amino acid sequence that can specifically bind to the F protein of RSV virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.
- Aspect F-9: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to

CDR3, respectively), in which:

- CDR1 is chosen from the group consisting of:
- a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
- and
- CDR2 is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622-2629.

  Such an amino acid sequence is preferably directed against the F protein of RSV virus and/or an amino acid sequence that can specifically bind to the F protein of RSV virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-10: Amino acid sequence according to any of aspects F-8 or F-9, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of

SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581.

Such an amino acid sequence is preferably directed against the F protein of RSV virus and/or an amino acid sequence that can specifically bind to the F protein of RSV virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-11: Amino acid sequence directed against the F protein of RSV virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 to the F protein of RSV virus.
- Aspect F-12: Amino acid sequence directed against the F protein of RSV virus that is cross-blocked from binding to the F protein of RSV virus by at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581.
- Aspect F-13: Amino acid sequence according to any of aspects F-11 or F-12, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect F-14: Amino acid sequence according to any of aspects F-11 or F-12, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect F-15: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
    - CDR1 is chosen from the group consisting of:
    - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
    - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
    - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
    - and/or
    - CDR2 is chosen from the group consisting of:
    - d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
    - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
    - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;

- and/or
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

  Such an amino acid sequence is preferably directed against the hemagglutinin H5 of influenza virus and/or an amino acid sequence that can specifically bind to the hemagglutinin H5 of influenza virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-16: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - and
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
  - and
  - CDR3 is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898

to 2899 and 3454 to 3518;

- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

Such an amino acid sequence is preferably directed against the hemagglutinin H5 of influenza virus and/or an amino acid sequence that can specifically bind to the hemagglutinin H5 of influenza virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-17: Amino acid sequence according to any of aspects F-15 or F-16, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128. Such an amino acid sequence is preferably directed against the hemagglutinin H5 of influenza virus and/or an amino acid sequence that can specifically bind to the hemagglutinin H5 of influenza virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.
- Aspect F-18: Amino acid sequence directed against the hemagglutinin H5 of influenza virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 to the hemagglutinin H5 of influenza virus.
- Aspect F-19: Amino acid sequence directed against the hemagglutinin H5 of influenza virus that is cross-blocked from binding to the hemagglutinin H5 of influenza virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128.
- Aspect F-20: Amino acid sequence according to any of aspects F-18 or F-19, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect F-21: Amino acid sequence according to any of aspects F-18 or F-19, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect F-22: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

- CDR1 is chosen from the group consisting of:
- a. the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
- and/or
- CDR2 is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- and/or
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

  Such an amino acid sequence is preferably directed against the G envelope protein of rabies virus and/or an amino acid sequence that can specifically bind to the G envelope protein of rabies virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-23: Amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - and
  - CDR2 is chosen from the group consisting of:

- d. the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

  Such an amino acid sequence is preferably directed against the G envelope protein of rabies virus and/or an amino acid sequence that can specifically bind to the G envelope protein of rabies virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.

- Aspect F-24: Amino acid sequence according to any of aspects F-22 or F-23, in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717.
  Such an amino acid sequence is preferably directed against the G envelope protein of rabies virus and/or an amino acid sequence that can specifically bind to the G envelope protein of rabies virus. Also, such an amino acid sequence is preferably an amino acid sequence according to any of the aspects A-1 to A-109, C-1 to C-16, D1 to D-6 and/or E-1 to E-14.
- Aspect F-25: Amino acid sequence directed against the G envelope protein of rabies virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717 to the G envelope protein of rabies virus.
- Aspect F-26: Amino acid sequence directed against the G envelope protein of rabies virus that is cross-blocked from binding to the G envelope protein of rabies virus by at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717.
- Aspect F-27: Amino acid sequence according to any of aspects F-25 or F-26, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is

detected in a Biacore assay.

- Aspect F-28: Amino acid sequence according to any of aspects F-25 or F-26, wherein the ability of said amino acid sequence to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect F-29: Amino acid sequence according to any of aspects F-1 to F-28, that is in essentially isolated form.
- Aspect F-30: Amino acid sequence according to any of aspects F-1 to F-29, for administration to a subject, wherein said amino acid sequence does not naturally occur in said subject.
- Aspect F-31: Amino acid sequence according to any of aspects F-1 to F-30, that can specifically bind to at least one epitope of an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect F-32: Amino acid sequence according to any of aspects F-1 to F-31, that can specifically bind to at least one epitope of an envelope protein of a virus with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$.
- Aspect F-33: Amino acid sequence according to any of aspects F-1 to F-32, that can specifically bind to at least one epitope of an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1} preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.
- Aspect F-34: Amino acid sequence according to any of aspects F-1 to F-33, that can specifically bind to at least one epitope of an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.
- Aspect F-35: Amino acid sequence according to any of aspects F-1 to F-34, that is a naturally occurring amino acid sequence (from any suitable species) or a synthetic or semi-synthetic amino acid sequence.
- Aspect F-36: Amino acid sequence according to any of aspects F-1 to F-35, that comprises an immunoglobulin fold or that under suitable conditions is capable of forming an immunoglobulin fold.
- Aspect F-37: Amino acid sequence according to any of aspects F-1 to F-36, that is an immunoglobulin sequence.
- Aspect F-38: Amino acid sequence according to any of aspects F-1 to F-37, that is a naturally occurring immunoglobulin sequence (from any suitable species) or a synthetic or semi-synthetic immunoglobulin sequence.
- Aspect F-39: Amino acid sequence according to any of aspects F-1 to F-38, that is a humanized immunoglobulin sequence, a camelized immunoglobulin sequence or an

immunoglobulin sequence that has been obtained by techniques such as affinity maturation.

- Aspect F-40: Amino acid sequence according to any of aspects F-1 to F-39, that essentially consists of a light chain variable domain sequence (e.g. a V_L-sequence); or of a heavy chain variable domain sequence (e.g. a V_H-sequence).
- Aspect F-41: Amino acid sequence according to any of aspects F-1 to F-40, that essentially consists of a heavy chain variable domain sequence that is derived from a conventional four-chain antibody or that essentially consist of a heavy chain variable domain sequence that is derived from heavy chain antibody.
- Aspect F-42: Amino acid sequence according to any of aspects F-1 to F-41, that essentially consists of a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), of a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), of a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or of a NANOBODY® (V_{HH} sequence) (including but not limited to a V_{HH} sequence).
- Aspect F-43: Amino acid sequence according to any of aspects F-1 to F-42, that essentially consists of a NANOBODY® (V_{HH} sequence).
- Aspect F-44: Amino acid sequence according to any of aspects F-1 to F-43, that essentially consists of a NANOBODY® (V_{HH} sequence) that
  - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect F-45: Amino acid sequence according to any of aspects F-1 to F-44, that essentially consists of a NANOBODY® (V_{HH} sequence) that:
  - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
  - and in which:
  - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect F-46: Amino acid sequence according to any of aspects F-1 to F-45, that essentially consists of a humanized NANOBODY® (V_{HH} sequence).

- Aspect F-47: Amino acid sequence according to any of aspects F-1 to F-46, that in addition to the at least one binding site for binding formed by the CDR sequences, contains one or more further binding sites for binding against other antigens, proteins or targets.
- Aspect H-1: NANOBODY® (V_{HH} sequence) that is directed against and/or that can specifically bind to an envelope protein of a virus.
- Aspect H-2: NANOBODY® (V_{HH} sequence) according to aspect H-1, wherein said NANOBODY® (V_{HH} sequence) modulates the interaction between said envelope protein and at least one binding partner.
- Aspect H-3: NANOBODY® (V_{HH} sequence) according to aspects H-1 or H-2, wherein said NANOBODY® (V_{HH} sequence) inhibits and/or prevents the interaction between said envelope protein and at least one binding partner.
- Aspect H-4: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-3, wherein said NANOBODY® (V_{HH} sequence) competes with said binding partner for binding to said envelope protein.
- Aspect H-5: NANOBODY® (V_{HH} sequence) according to aspect H-4, wherein said at least one binding partner is a viral receptor for an envelope protein of a virus.
- Aspect H-6: NANOBODY® (V_{HH} sequence) according to aspect H-5, wherein said viral receptor is chosen from the group consisting of sialic acid, soluble (2,3)-sialic acid, (2,6)-sialic acid, CD4, CCR5, CXCR4, galactosylceramide, ACE2, HveA, CD155, ICAM-1, CAR, αv integrins, heparin sulphate proteoglycans, JAM-1, the Nicotinic Acetylcholine Receptor (AchR), and the Nueral Cell Adhesion Molecule (NCAM).
- Aspect H-7: NANOBODY® (V_{HH} sequence) according to aspects H-5 or H-6, wherein said interaction between an envelope protein and a viral receptor is chosen from the group consisting of the interaction of HA of influenza A virus with sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; the interaction of gp120 of HIV-1 virus with CD4; CCR5; CXCR4; and/or galactosylceramide; the interaction of S1 of SARS coronavirus with ACE2; the interaction of gD; gB; and/or gC; the interaction of the heterodimer gH/gL of herpes simplex 1 virus with HveA; the interaction of VP1; VP2; and/or VP3 of poliovirus 1 with CD155; the interaction of VP1; VP2; and/or VP3 of rhinovirus 3 with ICAM-1; the interaction of adenovirus 2 fibre with CAR; the interaction of adenovirus 2 penton base with αv integrins; sialic acid; (2,3) sialic acid; (2,6) sialic acid; and/or heparin sulphate proteoglycans; the interaction of σ1 of reovirus 1 with JAM-1; sialic acid; (2,3) sialic acid; and/or (2,6) sialic acid; and the interaction of G-protein of rabies virus with the Nicotinic Acetylcholine Receptor (AchR); and/or the Nueral Cell Adhesion Molecule (NCAM).
- Aspect H-8: NANOBODY® (V_{HH} sequence) according to aspect H-4, wherein said at least one binding partner is a monoclonal antibody that is directed against and/or specifically binds to said envelope protein of a virus.
- Aspect H-9: NANOBODY® (V_{HH} sequence) according to aspect H-8, wherein said

monoclonal antibody is Synagis®, 101F, VN04-2, MAb C179 or MAb 8-2.

- Aspect H-10: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-9, wherein said envelope protein is a viral-specific protein.
- Aspect H-11: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-9, wherein said envelope protein is a membrane protein.
- Aspect H-12: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-11, wherein said envelope protein is a non-glycosylated protein.
- Aspect H-13: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-11, wherein said envelope protein is a glycoprotein.
- Aspect H-14: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-13, wherein said envelope protein is a viral attachment protein.
- Aspect H-15: NANOBODY® (V_{HH} sequence) according to aspect H-14, wherein said viral attachment protein is chosen from the group consisting of the G protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2 and σ1 of Reovirus 1.
- Aspect H-16: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-13, wherein said envelope protein is a viral fusion protein.
- Aspect H-17: NANOBODY® (V_{HH} sequence) according to aspect H-16, wherein said viral fusion protein is chosen from the group consisting of the F protein of RSV virus, the HA protein of Influenza A virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.
- Aspect H-18: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-17, wherein said envelope protein is a viral attachment protein and a viral fusion protein.
- Aspect H-19: NANOBODY® (V_{HH} sequence) according to aspect H-18, wherein said viral attachment protein and viral fusion protein is chosen from the group consisting of the HA protein of influenza A virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E

protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, and the E1 protein of Sindbis virus.

- Aspect H-20: NANOBODY® (V_{HH} sequence) according to aspects H-16 or H-18, wherein said viral fusion protein is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state.
- Aspect H-21: NANOBODY® (V_{HH} sequence) according to aspect H-20, wherein said viral fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein trimer.
- Aspect H-22: NANOBODY® (V_{HH} sequence) according to aspect H-21, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect H-23: NANOBODY® (V_{HH} sequence) according to aspects H-21 or H-22, wherein said fusion protein trimer is a six-helix bundle.
- Aspect H-24: NANOBODY® (V_{HH} sequence) according to any of aspects H-21 to H-23, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Human respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein, SARS corona virus E2 protein.
- Aspect H-25: NANOBODY® (V_{HH} sequence) according to aspect H-24, wherein said fusion protein is Influenza A virus HA protein.
- Aspect H-26: NANOBODY® (V_{HH} sequence) according to aspect H-24, wherein said fusion protein is Human respiratory syncytial virus F protein.
- Aspect H-27: NANOBODY® (V_{HH} sequence) according to aspect H-20, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a protein dimer.
- Aspect H-28: NANOBODY® (V_{HH} sequence) according to aspect H-27, wherein said dimer is a fusion protein homodimer.
- Aspect H-29: NANOBODY® (V_{HH} sequence) according to aspect H-27, wherein said dimer is a protein heterodimer.
- Aspect H-30: NANOBODY® (V_{HH} sequence) according to aspect 20, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein monomer.
- Aspect H-31: NANOBODY® (V_{HH} sequence) according to any of aspects H-27 to H-30, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein,

West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.

- Aspect H-32: NANOBODY® (V_{HH} sequence) according to aspect 20, wherein said fusion protein is characterized by a post-fusion conformational state, which is a fusion protein trimer.
- Aspect H-33: NANOBODY® (V_{HH} sequence) according to aspect H-32, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect H-34: NANOBODY® (V_{HH} sequence) according to aspects H-32 or H-33, wherein said fusion protein trimer is a six-helix bundle.
- Aspect H-35: NANOBODY® (V_{HH} sequence) according to aspect H-33, wherein said trimer of hairpins comprises an α-helical coiled coil.
- Aspect H-36: NANOBODY® (V_{HH} sequence) according to any of aspects H-32 to H-35, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Respiratory syncytial F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.
- Aspect H-37: NANOBODY® (V_{HH} sequence) according to aspect H-33, wherein said trimer of hairpins comprises β-structures.
- Aspect H-38: NANOBODY® (V_{HH} sequence) according to any of aspects H-32 to H-34 and H-37, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect H-39: NANOBODY® (V_{HH} sequence) according to any of aspects H-33, H-35 and H-37, wherein said trimer of hairpins comprises an α-helical coiled coil and β-structures.
- Aspect H-40: NANOBODY® (V_{HH} sequence) according to aspect H-39, wherein said fusion protein is chosen from the group consisting of vesicular stomatitis virus G protein, Rabies virus G protein and Herpes simplex virus gB protein.
- Aspect H-41: NANOBODY® (V_{HH} sequence) according to aspect H-40, wherein said fusion protein is Rabies virus G protein.
- Aspect H-42: NANOBODY® (V_{HH} sequence) according to any of aspects H-20 to H-41, wherein said amino acid sequence is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect H-43: NANOBODY® (V_{HH} sequence) according to aspect H-42, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to the

pre-fusion conformational state and/or the intermediate conformational state of said fusion protein.

- Aspect H-44: NANOBODY® (V_{HH} sequence) according to aspect H-42, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect H-45: NANOBODY® (V_{HH} sequence) according to aspect H-42, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to the pre-fusion conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect H-46: NANOBODY® (V_{HH} sequence) according to any of aspects H-21 to H-45, wherein said epitope is located in a cavity or cleft formed by said trimer according to aspects H-21 to H-26 and H-32 to H-41 or formed by said dimer according to claims H-27 to H-31.
- Aspect H-47: NANOBODY® (V_{HH} sequence) according to any of aspects H-21 to H-46, wherein said epitope is located in the stem region of said fusion protein.
- Aspect H-48: NANOBODY® (V_{HH} sequence) according to aspect H-47, wherein said epitope that is located in the stem region of said fusion protein is chosen from the group consisting of an epitope that is located in the region comprising one or more of the amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA, an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA and an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA.
- Aspect H-49: NANOBODY® (V_{HH} sequence) according to any of aspects H-21 to H-46, wherein said epitope is located in the neck region of said fusion protein.
- Aspect H-50: NANOBODY® (V_{HH} sequence) according to any of aspects H-21 to H-46, wherein said epitope is located in the globular head region of said fusion protein.
- Aspect H-51: NANOBODY® (V_{HH} sequence) according to aspect H-50, wherein said globular head region comprises a β-barrel-type structure.
- Aspect H-52: NANOBODY® (V_{HH} sequence) according to aspect H-50, wherein said globular head region comprises an immunoglobulin-type β-sandwich domain and a β-sheet domain.
- Aspect H-53: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-52, wherein said epitope is chosen from the group consisting of an epitope that is located in the region comprising the A-antigenic site and/or amino acids 255 to 280 of the

F-protein of RSV virus, an epitope that is located in the region comprising the Fla site and/or the region comprising amino acid 389 of the F-protein of RSV virus, an epitope that is located in the region comprising amino acids 422 to 438 of the F-protein of RSV virus, an epitope that is located in the region comprising the sialic acid binding site of the H5 HA envelope protein of influenza virus, an epitope that is located in the region comprising the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus, an epitope that is located in the C-terminal region of a fusion protein, an epitope that is located in the N-terminal domain of a fusion protein, an epitope that is located in or comprises the fusion peptide of a fusion protein, an epitope that is located in the transmembrane domain of a fusion protein, an epitope that is located in a α-helical coiled-coil of a fusion protein, an epitope that is located in a β-structure of a fusion protein, an epitope that is located in Domain I of a fusion protein, an epitope that is located in Domain II of a fusion protein and an epitope that is located in Domain III of a fusion protein.

- Aspect H-54: NANOBODY® (V_{HH} sequence) according to aspect H-53, wherein said epitope that is located in Domain II of a fusion protein is an epitope that is located in the fusion peptide of Domain II of a fusion protein.
- Aspect H-55: NANOBODY® (V_{HH} sequence) according to aspect H-53, wherein said epitope that is located in Domain III of a fusion protein is chosen from the group consisting of an epitope that is located in the stem region at the C-terminus of Domain III of a fusion protein and an epitope that is located in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.
- Aspect H-56: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-55, wherein said virus is chosen from the group consisting of a DNA virus, an RNA virus and a Reverse Transcriptase (RT) virus.
- Aspect H-57: NANOBODY® (V_{HH} sequence) according to aspect H-56, wherein said DNA virus is chosen from the group consisting of a ds DNA virus and a ssDNA virus.
- Aspect H-58: NANOBODY® (V_{HH} sequence) according to aspect H-56, wherein said RNA virus is chosen from the group consisting of a dsRNA virus, a positive-sense ssRNA virus and a negative-sense ssRNA virus.
- Aspect H-59: NANOBODY® (V_{HH} sequence) according to aspect H-56, wherein said Reverse Transcriptase (RT) virus is chosen from the group consisting of a dsDNA-RT virus and a ssRNA-RT virus.
- Aspect H-60: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-55, wherein said virus belongs to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae.
- Aspect H-61: NANOBODY® (V_{HH} sequence) according to aspect H-60, wherein said

virus belongs to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses.

- Aspect H-62: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-61, wherein said NANOBODY® (V_{HH} sequence) neutralizes said virus.
- Aspect H-63: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-62, wherein said NANOBODY® (V_{HH} sequence) modulates the infectivity of said virus.
- Aspect H-64: NANOBODY® (V_{HH} sequence) according to aspect H-63, wherein said NANOBODY® (V_{HH} sequence) inhibits and/or prevents the infectivity of said virus.
- Aspect H-65: NANOBODY® (V_{HH} sequence) according to any of aspects H-63 or H-64, wherein said NANOBODY® (V_{HH} sequence) neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the pre-entry stage.
- Aspect H-66: NANOBODY® (V_{HH} sequence) according to aspect H-65, wherein said NANOBODY® (V_{HH} sequence) modulates, inhibits and/or prevents viral entry in a target host cell.
- Aspect H-67: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-66, wherein said NANOBODY® (V_{HH} sequence) induces virion aggregation of said virus.
- Aspect H-68: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-67, wherein said NANOBODY® (V_{HH} sequence) destabilizes the virion structure of said virus.
- Aspect H-69: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-68, wherein said NANOBODY® (V_{HH} sequence) inhibits virion attachment to a target host cell of said virus.
- Aspect H-70: NANOBODY® (V_{HH} sequence) according to aspect H-69, wherein said NANOBODY® (V_{HH} sequence) inhibits virion attachment to a target host cell of said virus by modulating the interaction between said envelope protein and a viral receptor.
- Aspect H-71: NANOBODY® (V_{HH} sequence) according to aspects H-69 or H-70, wherein said NANOBODY® (V_{HH} sequence) inhibits virion attachment to a target host cell of said virus by inhibiting and/or preventing the interaction between said envelope protein and a viral receptor.
- Aspect H-72: NANOBODY® (V_{HH} sequence) according to aspects H-69 to H-71, wherein said NANOBODY® (V_{HH} sequence) competes with said envelope protein for binding to a viral receptor.
- Aspect H-73: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-72, wherein said NANOBODY® (V_{HH} sequence) inhibits fusion of said virus with a target host cell of said virus.
- Aspect H-74: NANOBODY® (V_{HH} sequence) according to aspect H-73, wherein fusion of said virus with a target host cell of said virus taking place at the target host cell membrane is inhibited.
- Aspect H-75: NANOBODY® (V_{HH} sequence) according to aspect H-73, wherein fusion

of said virus with a target host cell of said virus taking place within an endosomal or lysosomal compartment is inhibited.

- Aspect H-76: NANOBODY® (V_{HH} sequence) according to any of aspects H-73 to H-75, wherein said NANOBODY® (V_{HH} sequence) prevents said envelope protein of a virus from undergoing a conformational change.
- Aspect H-77: NANOBODY® (V_{HH} sequence) according to any of aspects H-63 or H-64, wherein said NANOBODY® (V_{HH} sequence) neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the post-entry stage.
- Aspect H-78: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-77, wherein said NANOBODY® (V_{HH} sequence) modulates, inhibits and/or prevents viral replication in a target host cell.
- Aspect H-79: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-78, wherein said NANOBODY® (V_{HH} sequence) affects, inhibits and/or prevents transcription and/or translation of the viral genome.
- Aspect H-80: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-79, wherein said NANOBODY® (V_{HH} sequence) affects, inhibits and/or prevents viral packaging and/or the formation of functional virions.
- Aspect H-81: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-80, wherein said NANOBODY® (V_{HH} sequence) reduces, inhibits and/or prevents budding or release of nascent virions from a target host cell surface.
- Aspect H-82: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-81, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to at least two epitopes of an envelope protein of a virus.
- Aspect H-83: NANOBODY® (V_{HH} sequence) according to aspect H-82, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to at least two epitopes of one envelope protein of a virus.
- Aspect H-84: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-82, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to at least two epitopes of at least two envelope proteins of a virus.
- Aspect H-85: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-82 and H-84, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to three or more epitopes of said envelope protein of a virus.
- Aspect H-86: NANOBODY® (V_{HH} sequence) according to aspect H-85, wherein said NANOBODY® (V_{HH} sequence) is directed against and/or can specifically bind to three or more epitopes of at least two envelope proteins of a virus.
- Aspect H-87: NANOBODY® (V_{HH} sequence) according to any of aspects H-82 to H-86, wherein said at least two or three or more epitopes are the same or are different.
- Aspect H-88: NANOBODY® (V_{HH} sequence) according to any of aspects H-84 or H-86, wherein said at least two envelope proteins are the same or are different.
- Aspect H-89: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-88,

that is in essentially isolated form.

- Aspect H-90: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-89, that can specifically bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect H-91: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-90, that can specifically bind to an envelope protein of a virus with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$.
- Aspect H-92: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-91, that can specifically bind to an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1} preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.
- Aspect H-93: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-92, that can specifically bind to an envelope protein of a virus with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.
- Aspect H-94: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-93, that is a naturally occurring NANOBODY® (V_{HH} sequence) (from any suitable species) or a synthetic or semi-synthetic NANOBODY® (V_{HH} sequence).
- Aspect H-95: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-94, that is a V_{HH} sequence, a partially humanized V_{HH} sequence, a fully humanized V_{HH} sequence, a camelized heavy chain variable domain or a NANOBODY® (V_{HH} sequence) that has been obtained by techniques such as affinity maturation.
- Aspect H-96: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-95, that
    - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;
    - and in which:
    - b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.
- Aspect H-97: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-96, that
    - a. has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128, in which for the purposes of determining the degree of

amino acid identity, the amino acid residues that form the CDR sequences are disregarded;

- and in which:
- b. preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.

- Aspect H-98: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-97, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
  - and/or
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
  - and/or
  - CDR3 is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.
- Aspect H-99: NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-98, in which:
  - CDR1 is chosen from the group consisting of:

- a. the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 971, 2467 to 2484, 2590 to 2597, 2754 to 2789 and 3194 to 3258;
- and
- CDR2 is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1535, 2503 to 2520, 2606 to 2613, 2826 to 2861 and 3324 to 3388;
- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 2099, 2539 to 2556, 2622 to 2629, 2898 to 2933 and 3454 to 3518.

- Aspect H-100:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-99, in which the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.
- Aspect H-101:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-100, which is a partially humanized NANOBODY® (V_{HH} sequence).
- Aspect H-102:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-101, which is a fully humanized NANOBODY® (V_{HH} sequence).
- Aspect H-103:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-102 that is chosen from the group consisting of SEQ ID NO's: 126 to 407, 2431 to 2448,

2574 to 2581, 2682 to 2717 and 3064 to 3128 or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.

- Aspect H-104:NANOBODY® (V_{HH} sequence) directed against an envelope protein of a virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 to an envelope protein of a virus.
- Aspect H-105:NANOBODY® (V_{HH} sequence) directed against an envelope protein of a virus that is cross-blocked from binding to an envelope protein of a virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.
- Aspect H-106:NANOBODY® (V_{HH} sequence) according to any of aspects H-104 or H-105, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect H-107:NANOBODY® (V_{HH} sequence) according to any of aspects H-104 or H-105, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect H-108:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-107, in which:
    - CDR1 is chosen from the group consisting of:
    - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
    - and/or
    - CDR2 is chosen from the group consisting of:
    - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
    - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
    - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;

- and/or
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629.

- Aspect H-109:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-108, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 722 to 800, 812 to 971, 2484 and 2590 to 2597;
  - and
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1286 to 1364, 1376 to 1535, 2520 and 2606 to 2613;
  - and
  - CDR3 is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099, 2556 and 2622 to 2629;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1850 to 1928, 1940 to 2099,

2556 and 2622 to 2629.

- Aspect H-110:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-109, in which the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581.
- Aspect H-111:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-110, which is a partially humanized NANOBODY® (V_{HH} sequence).
- Aspect H-112:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-111, which is a fully humanized NANOBODY® (V_{HH} sequence).
- Aspect H-113:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-112, that is chosen from the group consisting of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581.
- Aspect H-114:NANOBODY® (V_{HH} sequence) directed against at least one epitope of the F-protein of human RSV virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581 to at least one epitope of the F-protein of human RSV virus.
- Aspect H-115:NANOBODY® (V_{HH} sequence) directed against at least one epitope of the F-protein of human RSV virus that is cross-blocked from binding to an epitope of the F-protein of human RSV virus by at least one of the amino acid sequences of SEQ ID NO's: 158 to 236, 248 to 407, 2448 and 2574 to 2581.
- Aspect H-116:NANOBODY® (V_{HH} sequence) according to any of aspects H-114 or H-115, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect H-117:NANOBODY® (V_{HH} sequence) according to any of aspects H-114 or H-115, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect H-118:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-117, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;

- c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
- and/or
- CDR2 is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- and/or
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

- Aspect H-119:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-118, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 690 to 721, 2467 to 2483, 2754 to 2755 and 3194 to 3258;
  - and
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519,

2826 to 2827 and 3324 to 3388;

- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1254 to 1285, 2503 to 2519, 2826 to 2827 and 3324 to 3388;
- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1818 to 1849, 2539 to 2555, 2898 to 2899 and 3454 to 3518.

- Aspect H-120:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-119, in which the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128.
- Aspect H-121:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-120, which is a partially humanized NANOBODY® (V_{HH} sequence).
- Aspect H-122:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-121, which is a fully humanized NANOBODY® (V_{HH} sequence).
- Aspect H-123:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-122, that is chosen from the group consisting of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128.
- Aspect H-124:NANOBODY® (V_{HH} sequence) directed against at least one epitope of hemagglutinin H5 protein of influenza virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and 3064 to 3128 to at least one epitope of hemagglutinin H5 protein of influenza virus.
- Aspect H-125:NANOBODY® (V_{HH} sequence) directed against at least one epitope of hemagglutinin H5 protein of influenza virus that is cross-blocked from binding to at least one epitope of hemagglutinin H5 protein of influenza virus by at least one of the amino acid sequences of SEQ ID NO's: 126 to 157, 2431 to 2447, 2682 to 2683 and

3064 to 3128.

- Aspect H-126:NANOBODY® (V_{HH} sequence) according to any of aspects H-124 or H-125, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect H-127:NANOBODY® (V_{HH} sequence) according to any of aspects H-124 or H-125, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect H-128:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-127, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - and/or
  - CDR2 is chosen from the group consisting of:
  - d. the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
  - and/or
  - CDR3 is chosen from the group consisting of:
  - g. the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
  - i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.
- Aspect H-129:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-128, in which:
  - CDR1 is chosen from the group consisting of:
  - a. the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - b. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;
  - c. amino acid sequences that have 3, 2, or 1 amino acid difference with at least

one of the amino acid sequences of SEQ ID NO's: 801 to 811 and 2756 to 2789;

- and
- CDR2 is chosen from the group consisting of:
- d. the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- e. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- f. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1365 to 1375 and 2828 to 2861;
- and
- CDR3 is chosen from the group consisting of:
- g. the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- h. amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933;
- i. amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1929 to 1939 and 2900 to 2933.

- Aspect H-130:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-129, in which the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717.
- Aspect H-131:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-130, which is a partially humanized NANOBODY® (V_{HH} sequence).
- Aspect H-132:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-131, which is a fully humanized NANOBODY® (V_{HH} sequence).
- Aspect H-133:NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-132, that is chosen from the group consisting of SEQ ID NO's: 237 to 247 and 2684 to 2717 or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717.
- Aspect H-134:NANOBODY® (V_{HH} sequence) directed against at least one epitope of the G-protein of rabies virus that cross-blocks the binding of at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717 to at least one epitope of the G-protein of rabies virus.
- Aspect H-135:NANOBODY® (V_{HH} sequence) directed against at least one epitope of

the G-protein of rabies virus that is cross-blocked from binding to at least one epitope of the G-protein of rabies virus by at least one of the amino acid sequences of SEQ ID NO's: 237 to 247 and 2684 to 2717.

- Aspect H-136:NANOBODY® (V_{HH} sequence) according to any of aspects H-134 or H-135, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in a Biacore assay.
- Aspect H-137:NANOBODY® (V_{HH} sequence) according to any of aspects H-134 or H-135, wherein the ability of said NANOBODY® (V_{HH} sequence) to cross-block or to be cross-blocked is detected in an ELISA assay.
- Aspect K-1: Polypeptide that comprises or essentially consists of one or more amino acid sequences according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 and/or one or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137, and optionally further comprises one or more other amino acid binding units, optionally linked via one or more peptidic linkers.
- Aspect K-2: Polypeptide according to aspect K-1, in which said one or more other binding units are immunoglobulin sequences.
- Aspect K-3: Polypeptide according to any of aspects K-1 or K-2, in which said one or more other binding units are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, “dAb”'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).
- Aspect K-4: Polypeptide according to any of aspects K-1 to K-3, in which said one or more amino acid sequences of the invention are immunoglobulin sequences.
- Aspect K-5: Polypeptide according to any of aspects K-1 to K-4, in which said one or more amino acid sequences of the invention are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, “dAb”'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).
- Aspect K-6: Polypeptide according to any of aspects K-1 to K-5, that comprises or essentially consists of one or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 and in which said one or more other binding units are NANOBODIES® (V_{HH} sequences).
- Aspect K-7: Polypeptide according to any of aspects K-1 to K-6, which is a multivalent construct.
- Aspect K-8: Polypeptide according to any of aspects K-1 to K-7, which is a multiparatopic construct.
- Aspect K-9: Polypeptide according to any of aspects K-1 to K-8, which is a

multispecific construct.

- Aspect K-10: Polypeptide according to any of aspects K-1 to K-9, which has an increased half-life, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, respectively.
- Aspect K-11: Polypeptide according to aspect K-10, in which said one or more other binding units provide the polypeptide with increased half-life, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, respectively.
- Aspect K-12: Polypeptide according to aspect K-10 or K-11, in which said one or more other binding units that provide the polypeptide with increased half-life is chosen from the group consisting of serum proteins or fragments thereof, binding units that can bind to serum proteins, an Fc portion, and small proteins or peptides that can bind to serum proteins.
- Aspect K-13: Polypeptide according to aspect K-10 to K-12, in which said one or more other binding units that provide the polypeptide with increased half-life is chosen from the group consisting of human serum albumin or fragments thereof.
- Aspect K-14: Polypeptide according to aspect K-10 to K-13, in which said one or more other binding units that provides the polypeptide with increased half-life are chosen from the group consisting of binding units that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect K-15: Polypeptide according to aspect K-10 to K-14, in which said one or more other binding units that provides the polypeptide with increased half-life are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, “dAb”'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences) that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect K-16: Polypeptide according to aspect K-10 to K-15, in which said one or more other binding units that provides the polypeptide with increased half-life is a NANOBODY® (V_{HH} sequence) that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect K-17: Polypeptide according to any of aspects K-10 to K-16, that has a serum half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY®

(V_{HH} sequence) according to any of aspects H-1 to H-137 per se, respectively.

- Aspect K-18: Polypeptide according to any of aspects K-10 to K-17, that has a serum half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, respectively.
- Aspect K-19: Polypeptide according to any of aspects K-10 to K-18, that has a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more; for example, of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).
- Aspect L-1. Compound or construct, that comprises or essentially consists of one or more amino acid sequences according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 and/or one or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 and/or one or more polypeptides according to any of aspects K-1 to K-19, and optionally further comprises one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers.
- Aspect L-2. Compound or construct according to aspect L-1, in which said one or more other groups, residues, moieties or binding units are amino acid sequences.
- Aspect L-3. Compound or construct according to any of aspects L-1 or L-2, in which said one or more linkers, if present, are one or more amino acid sequences.
- Aspect L-4. Compound or construct according to any of aspects L-1 to L-3, in which said one or more other groups, residues, moieties or binding units are immunoglobulin sequences.
- Aspect L-5. Compound or construct according to any of aspects L-1 to L-4, in which said one or more other groups, residues, moieties or binding units are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, “dAb”'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).
- Aspect L-6. Compound or construct according to any of aspects L-1 to L-5, in which said one or more amino acid sequences of the invention are immunoglobulin sequences.
- Aspect L-7. Compound or construct according to any of aspects L-1 to L-6, in which

said one or more amino acid sequences of the invention are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).

- Aspect L-8. Compound or construct according to any of aspects L-1 to L-7, that comprises or essentially consists of one or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137, and in which said one or more other groups, residues, moieties or binding units are NANOBODIES® (V_{HH} sequences).
- Aspect L-9. Compound or construct according to any of aspects L-1 to L-8, which is a multivalent construct.
- Aspect L-10. Compound or construct according to aspect L-9, which is a bivalent construct.
- Aspect L-11. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the Synagis® binding site on the F protein of RSV.
- Aspect L-12. Compound or construct according to any of aspects L-10 to L11, which comprises two amino acid sequences that are capable of competing with Synagis® for binding to the F protein of RSV.
- Aspect L-13. Compound or construct according to aspect L-11, which comprises two amino acid sequences that are directed against and/or capable of binding antigenic site II of the F protein of RSV.
- Aspect L-14. Compound or construct according to aspect L-11, which comprises two amino acid sequences that are directed against and/or capable of binding amino acid residues 250-275 of the F protein of RSV.
- Aspect L-15. Compound or construct according to any of aspects L-10 to L-14 which can simultaneously bind both binding sites on the F protein of RSV.
- Aspect L-16. Compound or construct according to any of aspects L-10 to L-15 which neutralizes RSV via the same mechanism as Synagis®.
- Aspect L-17. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the 101F binding site on the F protein of RSV.
- Aspect L-18. Compound or construct according to any of aspects L-10 or L-17, which comprises two amino acid sequences that are capable of competing with 101F for binding to the F protein of RSV.
- Aspect L-19. Compound or construct according to aspect L-17, which comprises two amino acid sequences that are directed against and/or capable of binding antigenic site IV-VI of the F protein of RSV.
- Aspect L-20. Compound or construct according to aspect L-17, which comprises two amino acid sequences that are directed against and/or capable of binding amino acid

residues 423-436 of the F protein of RSV.

- Aspect L-21. Compound or construct according to any of aspects L-17 to L-20 which can simultaneously bind both binding sites on the F protein of RSV.
- Aspect L-22. Compound or construct according to any of aspects L-17 to L-21 which neutralizes RSV via the same mechanism as 101F.
- Aspect L-23. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-24. Compound or construct according to any of aspects L-10 or L-23, which comprises two amino acid sequences that are capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-25. Compound or construct according to any of aspects L-23 or L-24, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-26. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-27. Compound or construct according to any of aspects L-10 or L-26, which comprises two amino acid sequences that are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-28. Compound or construct according to any of aspects L-26 or L-27, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-29. Compound or construct according to any of aspects L-26 to L-28 which neutralizes RSV via the same mechanism as VN04-2.
- Aspect L-30. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-31. Compound or construct according to any of aspects L-10 or L-30, which comprises two amino acid sequences that are capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-32. Compound or construct according to any of aspects L-30 or L-31, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-33. Compound or construct according to any of aspects L-30 to L-32 which neutralizes RSV via the same mechanism as MAb C179.
- Aspect L-34. Compound or construct according to aspect L-10, which comprises two amino acid sequences that are directed against and/or capable of binding to the MAb 8-2 binding site on the G envelope protein of rabies virus.
- Aspect L-35. Compound or construct according to any of aspects L-10 or L-34, which

comprises two amino acid sequences that are capable of competing with the MAb 8-2 for binding to the G envelope protein of rabies virus.

- Aspect L-36. Compound or construct according to any of aspects L-34 or L-35, which can simultaneously bind both binding sites on the G envelope protein of rabies virus.
- Aspect L-37. Compound or construct according to any of aspects L-34 to L-36 which neutralizes RSV via the same mechanism as MAb 8-2.
- Aspect L-38. Compound or construct according to aspect L-9, which is a biparatopic construct.
- Aspect L-39. Compound or construct according to any of aspects L-38, which comprises at least one amino acid sequence directed against a first antigenic determinant, epitope, part or domain of an envelope protein of a virus and at least one amino acid sequence directed against a second antigenic determinant, epitope, part or domain of the envelope protein of a virus different from the first antigenic determinant, epitope, part or domain.
- Aspect L-40. Biparatopic compound or construct according to aspect L-39, which is capable of simultaneously binding to said first antigenic determinant, epitope, part or domain of an envelope protein of a virus and to said second antigenic determinant, epitope, part or domain of the envelope protein of a virus.
- Aspect L-41. Compound or construct according to any of aspects L-38 to L-40, which combines two or more different modes of action each mediated by one of its binding units, wherein each binding unit binds at a different binding site of an envelope protein of a virus.
- Aspect L-42. Compound or construct according to any of aspects L-38 to L-41, which comprises at least one amino acid sequence directed against a first antigenic determinant, epitope, part or domain of the F protein of RSV virus and at least one amino acid sequence directed against a second antigenic determinant, epitope, part or domain of the F protein of RSV virus different from the first antigenic determinant, epitope, part or domain.
- Aspect L-43. Biparatopic compound or construct according to aspect L-42, which is capable of simultaneously binding to said first antigenic determinant, epitope, part or domain of the F protein of RSV virus and to said second antigenic determinant, epitope, part or domain of the F protein of RSV virus.
- Aspect L-44. Compound or construct according to any of aspects L-38 to L-43, which combines two or more different modes of action each mediated by one of its binding units, wherein each binding unit binds at a different binding site of the F protein of RSV virus.
- Aspect L-45. Compound or construct according to any of aspects L-42 to L-44 wherein said compound or construct competes with Synagis® for binding to the F protein of RSV virus.
- Aspect L-46. Compound or construct according to aspects L-45, wherein said

compound or construct inhibits and/or blocks binding of Synagis® to the F protein of RSV virus.

- Aspect L-47. Compound or construct according to any of aspects L-45 to L-46, wherein said compound or construct is directed against the Synagis binding site on the F protein of RSV virus.
- Aspect L-48. Compound or construct according to any of aspects L-45 to L-47, wherein said compound or construct specifically binds to antigenic site II of the F protein of RSV.
- Aspect L-49. Compound or construct according to any of aspects L-45 to L-48, wherein said compound or construct specifically binds to at least one of amino acid residues 250-275 of the F protein of RSV.
- Aspect L-50. Compound or construct according to any of aspects L-45 to L-49, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the Synagis® binding site on the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-51. Compound or construct according to any of aspects L-45 to L-50, which comprises at least one amino acid sequence that is capable of competing with Synagis® for binding to the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-52. Compound or construct according to any of aspects L-45 to L-51, which comprises at least one amino acid sequence that is directed against and/or capable of binding antigenic site II of the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-53. Compound or construct according to any of aspects L-45 to L-52, which comprises at least one amino acid sequence that is directed against and/or capable of binding amino acid residues 250-275 of the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-54. Compound or construct according to any of aspects L-45 to L-53, which can simultaneously bind both binding sites on the F protein of RSV.
- Aspect L-55. Compound or construct according to any of aspects L-45 to L-54, which neutralizes RSV via the same mechanism as Synagis®.
- Aspect L-56. Compound or construct according to any of aspects L-42 to L-44 wherein said compound or construct competes with 101F for binding to the F protein of RSV virus.
- Aspect L-57. Compound or construct according to aspect L-56, wherein said compound or construct inhibits and/or blocks binding of 101F to the F protein of RSV

virus.

- Aspect L-58. Compound or construct according to any of aspects L-56 to L-57, wherein said compound or construct is directed against the 101F binding site on the F protein of RSV virus.
- Aspect L-59. Compound or construct according to any of aspects L-56 to L-58, wherein said compound or construct specifically binds to antigenic site IV-VI of the F protein of RSV.
- Aspect L-60. Compound or construct according to any of aspects L-56 to L-59, wherein said compound or construct specifically binds to at least one of amino acid residues 423-436 of the F protein of RSV.
- Aspect L-61. Compound or construct according to any of aspects L-56 to L-60, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the 101F binding site on the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-62. Compound or construct according to any of aspects L-56 to L-61, which comprises at least one amino acid sequence that is capable of competing with 101F for binding to the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-63. Compound or construct according to any of aspects L-56 to L-62, which comprises at least one amino acid sequence that is directed against and/or capable of binding antigenic site IV-VI of the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-64. Compound or construct according to any of aspects L-56 to L-63, which comprises at least one amino acid sequence that is directed against and/or capable of binding amino acid residues 423-436 of the F protein of RSV and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the F protein of RSV.
- Aspect L-65. Compound or construct according to any of aspects L-56 to L-64, which can simultaneously bind both binding sites on the F protein of RSV.
- Aspect L-66. Compound or construct according to any of aspects L-56 to L-65, which neutralizes RSV via the same mechanism as 101F.
- Aspect L-67. Compound or construct according to any of aspects L-38 to L-66, wherein said compound or construct is directed against the Synagis® binding site on the F protein of RSV virus and against the 101F binding site on the F protein of RSV virus.
- Aspect L-68. Compound or construct according to any of aspects L-38 to L-67, wherein said compound or construct competes with Synagis® and 101F for binding

to the F protein of RSV virus.

- Aspect L-69. Compound or construct according to any of aspects L-38 to L-68, wherein said compound or construct inhibits and/or blocks binding of Synagis® and 101F to the F protein of RSV virus.
- Aspect L-70. Compound or construct according to any of aspects L-38 to L-69, which specifically binds the Synagis® binding site on the F protein of RSV virus and to the 101F binding site on the F protein of RSV virus.
- Aspect L-71. Compound or construct according to any of aspects L-38 to L-70, which specifically binds to antigenic site II of the F protein of RSV virus.
- Aspect L-72. Compound or construct according to any of aspects L-38 to L-71, which specifically binds to amino acid residues 250-275 of the F protein of RSV virus.
- Aspect L-73. Compound or construct according to any of aspects L-38 to L-72, which specifically binds to antigenic site IV-VI of the F protein of RSV virus.
- Aspect L-74. Compound or construct according to any of aspects L-38 to L-73, which specifically binds to at least one of amino acid residues 423-436 of the F protein of RSV virus.
- Aspect L-75. Compound or construct according to any of aspects L-38 to L-74, which specifically binds to antigenic site II of the F protein of RSV virus and antigenic site IV-VI of the F protein of RSV virus.
- Aspect L-76. Compound or construct according to any of aspects L-38 to L-75, which specifically binds to amino acid residues 250-275 of the F protein of RSV virus and amino acid residues 423-436 of the F protein of RSV virus.
- Aspect L-77. Compound or construct according to any of aspects L-38 to L-76, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the Synagis® binding site on the F protein of RSV and at least one further amino acid sequence that is directed against the 101F binding site on the F protein of RSV.
- Aspect L-78. Compound or construct according to any of aspects L-38 to L-77, which comprises at least one amino acid sequence that is capable of competing with Synagis® for binding to the F protein of RSV and at least one further amino acid sequence that is capable of competing with 101F for binding to the F protein of RSV.
- Aspect L-79. Compound or construct according to any of aspects L-38 to L-78, which comprises at least one amino acid sequence that is directed against and/or capable of binding antigenic site II of the F protein of RSV and at least one further amino acid sequence that is directed against and/or capable of binding antigenic site IV-VI of the F protein of RSV.
- Aspect L-80. Compound or construct according to any of aspects L-38 to L-79, which comprises at least one amino acid sequence that is directed against and/or capable of binding amino acid residues 250-275 of the F protein of RSV and at least one amino acid sequence that is directed against and/or capable of binding amino acid residues

423-436 of the F protein of RSV.

- Aspect L-81. Biparatopic compound or construct according to any of aspects L-38 to L-80, which can simultaneously bind the Synagis® binding site on the F protein of RSV and to the 101F binding site on the F protein of RSV.
- Aspect L-82. Compound or construct according to any of aspects L-38 to L-81, that neutralizes RSV virus via the same mechanisms of actions as Synagis® and 101F.
- Aspect L-83. Compound or construct according to aspect L-38, wherein both paratopes are directed against the Synagis® binding site on the F protein of RSV.
- Aspect L-84. Compound or construct according to aspect L-83, wherein at least one paratope is directed against antigenic site II of the F protein of RSV.
- Aspect L-85. Compound or construct according to aspect L-83, wherein at least one paratope is directed against amino acid residues 250-275 of the F protein of RSV.
- Aspect L-86. Biparatopic compound or construct according to any of aspects L-83 to L-85, which can simultaneously bind both binding site on the F protein of RSV.
- Aspect L-87. Compound or construct according to aspect L-38, wherein both paratopes are directed against the 101F binding site on the F protein of RSV.
- Aspect L-88. Compound or construct according to aspect L-87, wherein at least one paratope is directed against antigenic site IV-VI of the F protein of RSV.
- Aspect L-89. Compound or construct according to aspect L-87, wherein at least one paratope is directed against amino acid residues 423-436 of the F protein of RSV.
- Aspect L-90. Biparatopic compound or construct according to any of aspects L-87 to L-89, which can simultaneously bind both binding site on the F protein of RSV.
- Aspect L-91. Compound or construct according to any of aspects L-38 to L-41, which comprises at least one amino acid sequence directed against a first antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus and at least one amino acid sequence directed against a second antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus different from the first antigenic determinant, epitope, part or domain.
- Aspect L-92. Biparatopic compound or construct according to aspect L-91, which is capable of simultaneously binding to said first antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus and to said second antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-93. Compound or construct according to any of aspects L-91 to L-92, which combines two or more different modes of action each mediated by one of its binding units, wherein each binding unit binds at a different binding site of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-94. Compound or construct according to any of aspects L-91 to L-93 wherein said compound or construct competes with sialic acid for binding to the

hemagglutinin H5 envelope protein of influenza virus.

- Aspect L-95. Compound or construct according to aspects L-94, wherein said compound or construct inhibits and/or blocks binding of sialic acid to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-96. Compound or construct according to any of aspects L-94 to L-95, wherein said compound or construct is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-97. Compound or construct according to any of aspects L-94 to L-96, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-98. Compound or construct according to any of aspects L-94 to L-97, which comprises at least one amino acid sequence that is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-99. Compound or construct according to any of aspects L-94 to L-98, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-100. Compound or construct according to any of aspects L-91 to L-93 wherein said compound or construct competes with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-101. Compound or construct according to aspects L-100, wherein said compound or construct inhibits and/or blocks binding of VN04-2 to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-102. Compound or construct according to any of aspects L-100 to L-101, wherein said compound or construct is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-103. Compound or construct according to any of aspects L-100 to L-102, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-104. Compound or construct according to any of aspects L-100 to L-103, which comprises at least one amino acid sequence that is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus and

at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.

- Aspect L-105. Compound or construct according to any of aspects L-100 to L-104, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-106. Compound or construct according to any of aspects L-100 to L-105, which neutralizes RSV via the same mechanism as VN04-2.
- Aspect L-107. Compound or construct according to any of aspects L-91 to L-93 wherein said compound or construct competes with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-108. Compound or construct according to aspects L-107, wherein said compound or construct inhibits and/or blocks binding of MAb C179 to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-109. Compound or construct according to any of aspects L-107 to L-108, wherein said compound or construct is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-110. Compound or construct according to any of aspects L-107 to L-109, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-111. Compound or construct according to any of aspects L-107 to L-110, which comprises at least one amino acid sequence that is capable of competing with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-112. Compound or construct according to any of aspects L-107 to L-111, which can simultaneously bind both binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-113. Compound or construct according to any of aspects L-107 to L-112, which neutralizes RSV via the same mechanism as MAb C179.
- Aspect L-114. Compound or construct according to any of aspects L-38 to L-41, which comprises at least one amino acid sequence directed against a first antigenic determinant, epitope, part or domain of the G protein of rabies virus and at least one amino acid sequence directed against a second antigenic determinant, epitope, part or domain of the G protein of rabies virus different from the first antigenic determinant, epitope, part or domain.

- Aspect L-115. Biparatopic compound or construct according to aspect L-114, which is capable of simultaneously binding to said first antigenic determinant, epitope, part or domain of the G protein of rabies virus and to said second antigenic determinant, epitope, part or domain of the G protein of rabies virus.
- Aspect L-116. Compound or construct according to any of aspects L-114 to L-115, which combines two or more different modes of action each mediated by one of its binding units, wherein each binding unit binds at a different binding site of the G protein of rabies virus.
- Aspect L-117. Compound or construct according to any of aspects L-114 to L-116 wherein said compound or construct competes with MAb 8-2 for binding to the G protein of rabies virus.
- Aspect L-118. Compound or construct according to aspects L-117, wherein said compound or construct inhibits and/or blocks binding of MAb 8-2 to the G protein of rabies virus.
- Aspect L-119. Compound or construct according to any of aspects L-117 to L-118, wherein said compound or construct is directed against the MAb 8-2 binding site on the G protein of rabies virus.
- Aspect L-120. Compound or construct according to any of aspects L-117 to L-119, which comprises at least one amino acid sequence that is directed against and/or capable of binding to the MAb 8-2 binding site on the G protein of rabies virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the G protein of rabies virus.
- Aspect L-121. Compound or construct according to any of aspects L-117 to L-120, which comprises at least one amino acid sequence that is capable of competing with MAb 8-2 for binding to the G protein of rabies virus and at least one further amino acid sequence that is capable of binding to at least one other antigenic determinant, epitope, part or domain of the G protein of rabies virus.
- Aspect L-122. Compound or construct according to any of aspects L-117 to L-121, which can simultaneously bind both binding sites on the G protein of rabies virus.
- Aspect L-123. Compound or construct according to any of aspects L-117 to L-122, which neutralizes RSV via the same mechanism as MAb 8-2.
- Aspect L-124. Compound or construct according to aspect L-9, which is a trivalent construct.
- Aspect L-125. Compound or construct according to aspect L-124 that comprises three amino acid sequences that are directed against the same antigenic determinant, epitope, part or domain of the viral envelope protein.
- Aspect L-126. Compound or construct according to aspect L-125, which can simultaneously bind the three antigenic determinants, epitopes, parts or domains of the viral envelope protein.
- Aspect L-127. Compound or construct according to any of aspects L-125 to L-126,

that comprises three amino acid sequences that are directed against and/or specifically bind the F protein of RSV virus.

- Aspect L-128. Compound or construct according to aspect L-127, that comprises three amino acid sequences that are directed against and/or specifically bind the Synagis® binding site on the F protein of RSV virus.
- Aspect L-129. Compound or construct according to any of aspects L-127 to L-128, that comprises three amino acid sequences that compete with Synagis® for binding the F protein of RSV virus.
- Aspect L-130. Compound or construct according to any of aspects L-127 to L-129, that comprises three amino acid sequences that are directed against and/or specifically bind antigenic site II on the F protein of RSV virus.
- Aspect L-131. Compound or construct according to any of aspects L-127 to L-130, that comprises three amino acid sequences that are directed against and/or specifically bind amino acid residues 250-275 of the F protein of RSV virus.
- Aspect L-132. Compound or construct according to any of aspects L-125 to L-131, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-133. Compound or construct according to any of aspects L-127 to L-132, which neutralizes RSV via the same mechanism as Synagis®.
- Aspect L-134. Compound or construct according to aspect L-127, that comprises three amino acid sequences that are directed against and/or specifically bind the 101F binding site on the F protein of RSV virus.
- Aspect L-135. Compound or construct according to any of aspects L-127 and/or L-134, that comprises three amino acid sequences that compete with 101F for binding the F protein of RSV virus.
- Aspect L-136. Compound or construct according to any of aspects L-127 and/or L-134 to L-135, that comprises three amino acid sequences that are directed against and/or specifically bind antigenic site IV-VI on the F protein of RSV virus.
- Aspect L-137. Compound or construct according to any of aspects L-127 and/or L-134 to L-136, that comprises three amino acid sequences that are directed against and/or specifically bind amino acid residues 423-436 of the F protein of RSV virus.
- Aspect L-138. Compound or construct according to any of aspects L-127 and/or L-134 to L-137, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-139. Compound or construct according to any of aspects L-127 and/or L-134 to L-138, which neutralizes RSV via the same mechanism as 101F.
- Aspect L-140. Compound or construct according to any of aspects L-125 to L-126, that comprises three amino acid sequences that are directed against and/or specifically bind the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-141. Compound or construct according to aspect L-140, that comprises three amino acid sequences that are directed against and/or specifically bind the

sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus.

- Aspect L-142. Compound or construct according to any of aspects L-140 to L-141, that comprises three amino acid sequences that compete with sialic acid for binding the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-143. Compound or construct according to any of aspects L-140 to L-142, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-144. Compound or construct according to aspect L-140, that comprises three amino acid sequences that are directed against and/or specifically bind the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-145. Compound or construct according to any of aspects L-140 and/or L-144, that comprises three amino acid sequences that compete with VN04-2 for binding the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-146. Compound or construct according to any of aspects L-140 and/or L-144 to L-145, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-147. Compound or construct according to any of aspects L-140 and/or L-144 to L-146, which neutralizes influenza virus via the same mechanism as VN04-2.
- Aspect L-148. Compound or construct according to aspect L-140, that comprises three amino acid sequences that are directed against and/or specifically bind the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-149. Compound or construct according to any of aspects L-140 and/or L-148, that comprises three amino acid sequences that compete with MAb C179 for binding the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-150. Compound or construct according to any of aspects L-140 and/or L-148 to L-149, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-151. Compound or construct according to any of aspects L-140 and/or L-148 to L-150, which neutralizes influenza virus via the same mechanism as MAb C179.
- Aspect L-152. Compound or construct according to any of aspects L-125 to L-126, that comprises three amino acid sequences that are directed against and/or specifically bind the G envelope protein of rabies virus.
- Aspect L-153. Compound or construct according to aspect L-152, that comprises three amino acid sequences that are directed against and/or specifically bind the MAb 8-2 binding site on the G envelope protein of rabies virus.
- Aspect L-154. Compound or construct according to any of aspects L-152 to L-153, that comprises three amino acid sequences that compete with MAb 8-2 for binding the G envelope protein of rabies virus.
- Aspect L-155. Compound or construct according to any of aspects L-152 to L-154,

which can simultaneously bind all three binding sites on the G envelope protein of rabies virus.

- Aspect L-156. Compound or construct according to any of aspects L-152 to L-155, which neutralizes influenza virus via the same mechanism as MAb 8-2.
- Aspect L-157. Compound or construct according to aspect L-124 that comprises two amino acid sequences that are directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein and one amino acid sequence that is directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein.
- Aspect L-158. Compound or construct according to aspect L-157, which can simultaneously bind the three antigenic determinants, epitopes, parts or domains of the viral envelope protein.
- Aspect L-159. Compound or construct according to any of aspects L-157 to L-158, that comprises two amino acid sequences directed against and or capable of binding a first antigenic determinant, epitope, part or domain on the F protein of RSV virus, and one amino acid sequence directed against another antigenic determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-160. Compound or construct according to aspect L-159, that comprises two amino acid sequences directed against and or capable of binding the Synagis® binding site on the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-161. Compound or construct according to any of aspects L-159 to L-160, that comprises two amino acid sequences that compete with Synagis® for binding the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-162. Compound or construct according to any of aspects L-159 to L-161, that comprises two amino acid sequences that are directed against and/or specifically bind antigenic site II on the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-163. Compound or construct according to any of aspects L-159 to L-162, that comprises two amino acid sequences that are directed against and/or specifically bind amino acid residues 250-275 of the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-164. Compound or construct according to any of aspects L-159 to L-163, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-165. Compound or construct according to any of aspects L-159 to L-164, which neutralizes RSV via the same mechanism as Synagis®.
- Aspect L-166. Compound or construct according to aspect L-159, that comprises two

amino acid sequences directed against and or capable of binding the 101F binding site on the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.

- Aspect L-167. Compound or construct according to any of aspects L-159 and/or L-166, that comprises two amino acid sequences that compete with 101F for binding the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-168. Compound or construct according to any of aspects L-159 and/or L-166 to L-167, that comprises two amino acid sequences that are directed against and/or specifically bind antigenic site IV-VI on the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-169. Compound or construct according to any of aspects L-159 and/or L-166 to L-168, that comprises two amino acid sequences that are directed against and/or specifically bind amino acid residues 423-436 of the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-170. Compound or construct according to any of aspects any of aspects L-159 and/or L-166 to L-169, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-171. Compound or construct according to any of aspects L-159 and/or L-166 to L-170, which neutralizes RSV via the same mechanism as 101F.
- Aspect L-172. Compound or construct according to aspect L-159, that comprises two amino acid sequences directed against and or capable of binding the Synagis® binding site on the F protein of RSV virus, and one amino acid sequence directed against and/or capable of binding the 101F binding site on the F protein of RSV virus.
- Aspect L-173. Compound or construct according to any of aspects L-159 and/or L-172, that comprises two amino acid sequences that compete with Synagis® for binding the F protein of RSV virus, and one amino acid sequence that competes with 101F for binding the F protein of RSV virus.
- Aspect L-174. Compound or construct according to any of aspects L-159 and/or L-172 to L-173, that comprises two amino acid sequences that are directed against and/or specifically bind antigenic site II on the F protein of RSV virus, and one amino acid sequence directed against and/or that can specifically bind antigenic site IV-VI of the F protein of RSV virus.
- Aspect L-175. Compound or construct according to any of aspects L-159 and/or L-172 to L-174, that comprises two amino acid sequences that are directed against and/or specifically bind amino acid residues 250-275 of the F protein of RSV virus, and one amino acid sequence directed against and/or that can specifically bind amino acid residues 423-436 of the F protein of RSV virus.

- Aspect L-176. Compound or construct according to any of aspects L-159, that comprises one amino acid sequence directed against and or capable of binding the Synagis® binding site on the F protein of RSV virus, and two amino acid sequences directed against and/or capable of binding the 101F binding site on the F protein of RSV virus.
- Aspect L-177. Compound or construct according to any of aspects L-159 and/or L-176, that comprises one amino acid sequence that competes with Synagis® for binding the F protein of RSV virus, and two amino acid sequences that compete with 101F for binding the F protein of RSV virus.
- Aspect L-178. Compound or construct according to any of aspects L-159 and/or L-176 to L-177, that comprises one amino acid sequence that is directed against and/or specifically binds antigenic site II on the F protein of RSV virus, and two amino acid sequences directed against and/or that can specifically bind antigenic site IV-VI of the F protein of RSV virus.
- Aspect L-179. Compound or construct according to any of aspects L-159 and/or L-176 to L-178, that comprises one amino acid sequence that is directed against and/or specifically binds amino acid residues 250-275 of the F protein of RSV virus, and two amino acid sequences directed against and/or that can specifically bind amino acid residues 423-436 of the F protein of RSV virus.
- Aspect L-180. Compound or construct according to any of aspects L-159 and/or L-172 to L-179, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-181. Compound or construct according to any of aspects L-159 and/or L-172 to L-180, which neutralizes RSV via the same mechanism as Synagis® and 101F.
- Aspect L-182. Compound or construct according to any of aspects L-157 to L-158, that comprises two amino acid sequences directed against and and/or capable of binding a first antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-183. Compound or construct according to aspect L-182, that comprises two amino acid sequences directed against and and/or capable of binding the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-184. Compound or construct according to any of aspects L-182 to L-183, that comprises two amino acid sequences that compete with sialic acid for binding the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the

hemagglutinin H5 envelope protein of influenza virus.

- Aspect L-185. Compound or construct according to any of aspects any of aspects L-182 to L-184, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-186. Compound or construct according to aspects L-182, that comprises two amino acid sequences directed against and or capable of binding the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-187. Compound or construct according to any of aspects L-182 and/or L-186, that comprises two amino acid sequences that compete with VN04-2 for binding the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-188. Compound or construct according to any of aspects any of aspects L-182 and/or L-186 to L-187, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-189. Compound or construct according to any of aspects L-182 and/or L-186 to L-188, which neutralizes influenza via the same mechanism as VN04-2.
- Aspect L-190. Compound or construct according to aspect L-182 that comprises two amino acid sequences directed against and or capable of binding the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-191. Compound or construct according to any of aspects L-182 and/or L-190, that comprises two amino acid sequences that compete with MAb C179 for binding the hemagglutinin H5 envelope protein of influenza virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-192. Compound or construct according to any of aspects any of aspects L-182 and/or L-190 to L-191, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-193. Compound or construct according to any of aspects L-182 and/or L-190 to L-192, which neutralizes influenza via the same mechanism as MAb C179.
- Aspect L-194. Compound or construct according to any of aspects L-157 to L-158, that comprises two amino acid sequences directed against and or capable of binding a first antigenic determinant, epitope, part or domain on the G envelope protein of rabies virus, and one amino acid sequence directed against another antigenic determinant, epitope, part or domain on the G envelope protein of rabies virus.
- Aspect L-195. Compound or construct according to aspects L-194, that comprises two

amino acid sequences directed against and or capable of binding the MAb 8-2 binding site on the G envelope protein of rabies virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the G envelope protein of rabies virus.

- Aspect L-196. Compound or construct according to any of aspects L-194 to L-195, that comprises two amino acid sequences that compete with MAb 8-2 for binding the G envelope protein of rabies virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the G envelope protein of rabies virus.
- Aspect L-197. Compound or construct according to any of aspects any of aspects L-194 to L-196, which can simultaneously bind all three binding sites on the G envelope protein of rabies virus.
- Aspect L-198. Compound or construct according to any of aspects L-194 to L-197, which neutralizes rabies via the same mechanism as MAb 8-2.
- Aspect L-199. Compound or construct according to aspect L-124, that comprises one amino acid sequence that is directed against a first antigenic determinant, epitope, part or domain of the viral envelope protein, one amino acid sequence that is directed against a second antigenic determinant, epitope, part or domain of the viral envelope protein and one amino acid sequence that is directed against a third antigenic determinant, epitope, part or domain of the viral envelope protein.
- Aspect L-200. Compound or construct according to aspect L-199, which can simultaneously bind the three antigenic determinants, epitopes, parts or domains of the viral envelope protein.
- Aspect L-201. Compound or construct according to any of aspects L-199 or L-200, that comprises one amino acid sequence directed against and or capable of binding one antigenic determinant, epitope, part or domain on the F protein of RSV virus, and two amino acid sequence directed against another antigenic determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-202. Compound or construct according to aspect L-201, that comprises one amino acid sequence directed against and or capable of binding the Synagis® binding site on the F protein of RSV virus, and two amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-203. Compound or construct according to any of aspects L-201 to L-202, that comprises one amino acid sequence that competes with Synagis® for binding the F protein of RSV virus, and two amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-204. Compound or construct according to any of aspects L-201 to L-203, that comprises one amino acid sequence that is directed against and/or specifically binds antigenic site II on the F protein of RSV virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the F protein of RSV

virus.

- Aspect L-205. Compound or construct according to any of aspects L-201 to L-204, that comprises one amino acid sequence that is directed against and/or specifically binds amino acid residues 250-275 of the F protein of RSV virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-206. Compound or construct according to any of aspects L-201 to L-205, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-207. Compound or construct according to any of aspects L-201 to L-206, which neutralizes RSV via the same mechanism as Synagis®.
- Aspect L-208. Compound or construct according to aspect L-201, that comprises one amino acid sequence directed against and or capable of binding the 101F binding site on the F protein of RSV virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-209. Compound or construct according to any of aspects L-201 and/or L-208, that comprises one amino acid sequence that competes with 101F for binding the F protein of RSV virus, and two amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-210. Compound or construct according to any of aspects L-201 and/or L-208 to L-209, that comprises one amino acid sequence that is directed against and/or specifically bind antigenic site IV-VI on the F protein of RSV virus, and two amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-211. Compound or construct according to any of aspects L-201 and/or L-208 to L-210, that comprises one amino acid sequence that is directed against and/or specifically binds amino acid residues 423-436 of the F protein of RSV virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-212. Compound or construct according to any of aspects L-201 and/or L-208 to L-211, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-213. Compound or construct according to any of aspects L-201 and/or L-208 to L-212, which neutralizes RSV via the same mechanism as 101F.
- Aspect L-214. Compound or construct according to aspect L-201, that comprises one amino acid sequence directed against and and/or capable of binding the Synagis® binding site on the F protein of RSV virus, one amino acid sequence directed against and/or capable of binding the 101F binding site on the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-215. Compound or construct according to any of aspects L-201 and/or

L-214, that comprises one amino acid sequence that competes with Synagis® for binding the F protein of RSV virus, one amino acid sequence that competes with 101F for binding the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.

- Aspect L-216. Compound or construct according to any of aspects L-201 and/or L-214 to L-215, that comprises one amino acid sequence that is directed against and/or specifically binds antigenic site II on the F protein of RSV virus, one amino acid sequence directed against and/or that can specifically bind antigenic site IV-VI of the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-217. Compound or construct according to any of aspects L-201 and/or L-214 to L-216, that comprises one amino acid sequence that is directed against and/or specifically binds amino acid residues 250-275 of the F protein of RSV virus, one amino acid sequence directed against and/or that can specifically bind amino acid residues 423-436 of the F protein of RSV virus, and one amino acid sequence directed against another determinant, epitope, part or domain on the F protein of RSV virus.
- Aspect L-218. Compound or construct according to any of aspects L-201 and/or L-214 to L-217, which can simultaneously bind all three binding sites on the F protein of RSV.
- Aspect L-219. Compound or construct according to any of aspects L-201 and/or L-214 to L-218, which neutralizes RSV via the same mechanism as Synagis® and 101F.
- Aspect L-220. Compound or construct according any of aspects L-199 or L-200, that comprises one amino acid sequence directed against and or capable of binding one antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another antigenic determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-221. Compound or construct according aspect L-220, that comprises one amino acid sequence directed against and or capable of binding the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-222. Compound or construct according to any of aspects L-220 to L-221, that comprises one amino acid sequence that competes with sialic acid for binding the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-223. Compound or construct according to any of aspects any of aspects

L-220 to L-222, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.

- Aspect L-224. Compound or construct according to aspects L-220, that comprises one amino acid sequence directed against and or capable of binding the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-225. Compound or construct according to any of aspects L-220 and/or L-224, that comprises one amino acid sequence that competes with VN04-2 for binding the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-226. Compound or construct according to any of aspects L-220 and/or L-224 to L-225, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-227. Compound or construct according to any of aspects L-220 and/or L-224 to L-226, which neutralizes influenza via the same mechanism as VN04-2.
- Aspect L-228. Compound or construct according to aspect L-220, that comprises one amino acid sequence directed against and or capable of binding the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-229. Compound or construct according to any of aspects L-220 and/or L-228, that comprises one amino acid sequence that competes with MAb C179 for binding the hemagglutinin H5 envelope protein of influenza virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-230. Compound or construct according to any of aspects L-220 and/or L-228 to L-229, which can simultaneously bind all three binding sites on the hemagglutinin H5 envelope protein of influenza virus.
- Aspect L-231. Compound or construct according to any of aspects L-220 and/or L-228 to L-230, which neutralizes influenza via the same mechanism as MAb C179.
- Aspect L-232. Compound or construct according to any of aspects L-199 or L-200, that comprises one amino acid sequence directed against and or capable of binding one antigenic determinant, epitope, part or domain on the G envelope protein of rabies virus, and two amino acid sequences directed against another antigenic determinant, epitope, part or domain on the G envelope protein of rabies virus.
- Aspect L-233. Compound or construct according to aspect L-232, that comprises one amino acid sequence directed against and or capable of binding the MAb 8-2 binding site on the G envelope protein of rabies virus, and two amino acid sequences directed

against another determinant, epitope, part or domain on the G envelope protein of rabies virus.

- Aspect L-234. Compound or construct according to any of aspects L-232 or L-233, that comprises one amino acid sequence that competes with MAb 8-2 for binding the G envelope protein of rabies virus, and two amino acid sequences directed against another determinant, epitope, part or domain on the G envelope protein of rabies virus.
- Aspect L-235. Compound or construct according to any of aspects any of aspects L-232 to L-234, which can simultaneously bind all three binding sites on the G envelope protein of rabies virus.
- Aspect L-236. Compound or construct according to any of aspects L-232 to L-236, which neutralizes rabies via the same mechanism as MAb 8-2.
- Aspect L-237. Compound or construct that comprises or that is chosen from the group consisting of SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591 or from the group consisting of from amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 2382 to 2415, 2423 to 2430, 2641 to 2659, 2663 to 2681, 2978 to 2998, 3016 to 3056 and 3584 to 3591.
- Aspect L-238. Compound or construct according to any of aspects L-1 to L-9, which is a multispecific construct.
- Aspect L-239. Compound or construct according to any of aspects L-1 to L-238, which has an increased half-life, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, or polypeptide according to any of aspects K-1 to K-19 per se, respectively.
- Aspect L-240. Compound or construct according to any of aspects L-1 to L-239, in which said one or more other groups, residues, moieties or binding units provide the compound or construct with increased half-life, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, or polypeptide according to any of aspects K-1 to K-19 per se, respectively.
- Aspect L-241. Compound or construct according to aspect L-240, in which said one or more other groups, residues, moieties or binding units that provide the compound or construct with increased half-life is chosen from the group consisting of serum proteins or fragments thereof, binding units that can bind to serum proteins, an Fc portion, and small proteins or peptides that can bind to serum proteins.

- Aspect L-242. Compound or construct according to any of aspects L-240 or L-241, in which said one or more other groups, residues, moieties or binding units that provide the compound or construct with increased half-life is chosen from the group consisting of human serum albumin or fragments thereof.
- Aspect L-243. Compound or construct according to any of aspects L-240 to L-242, in which said one or more other groups, residues, moieties or binding units that provide the compound or construct with increased half-life are chosen from the group consisting of binding units that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect L-244. Compound or construct according to any of aspects L-240 to L-243, in which said one or more other groups, residues, moieties or binding units that provides the compound or construct with increased half-life are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences) that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect L-245. Compound or construct according to any of aspects L-240 to L-244, in which said one or more other groups, residues, moieties or binding units that provides the compound or construct with increased half-life is a NANOBODY® (V_{HH} sequence) that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).
- Aspect L-246. Compound or construct that comprises an Fc portion of an immunoglobulin and two or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137.
- Aspect L-247. Compound or construct that comprises an Fc portion of an immunoglobulin and one or more compounds or constructs according to any of aspects L-10 to L-246.
- Aspect L-248. Compound or construct according to aspects L-246 and L-247, that comprises an Fc portion of an immunoglobulin, one or more NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 and one or more compounds or constructs according to any of aspects L-10 to L-245.
- Aspect L-249. Compound or construct according to any of aspects L-246 or L-248, wherein the Fc portion is derived from an immunoglobulin selected from IgG1, IgG2, IgGA, IgM and IgE.
- Aspect L-250. Compound or construct according to any of aspects L-246 to L-249, wherein the NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 or compounds or constructs according to any of aspects L-10 to L-245 are coupled to the Fc portion via a suitable linker.
- Aspect L-251. Compound or construct according to aspect L-250, wherein the linker

is a hinge linker.

- Aspect L-252. Compound or construct according to any of aspects L-246 to L-251, wherein the NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 or compounds or constructs according to any of aspects L-10 to L-245 are coupled at one side of the Fc portion.
- Aspect L-253. Compound or construct according to any of aspects L-246 to L-252, wherein the NANOBODIES® (V_{HH} sequences) according to any of aspects H-1 to H-137 or compounds or constructs according to any of aspects L-10 to L-245 are coupled at both side of the Fc portion.
- Aspect L-254. Compound or construct according to any of aspects L-246 to L-253, which has a structure as depicted in FIG. 59.
- Aspect L-255. Compound or construct according to any of aspects L-246 to L-253, which has a structure as depicted in FIG. 60.
- Aspect L-256. Compound or construct according to any of aspects L-246 to L-253, which has a structure as depicted in FIG. 61.
- Aspect L-257. Compound or construct according to any of aspects L-246 to L-253, which has a structure as depicted in FIG. 62.
- Aspect L-258. Compound or construct according to any of aspects L-246 to L-253, which has a structure as depicted in FIG. 63.
- Aspect L-259. Compound or construct according to any of aspects L-246 to L-253, that is chosen from the group consisting of SEQ ID NO's: 2641 to 2659 and 2978 to 2988.
- Aspect L-260. Compound or construct according to any of aspects L-239 to L-259, that has a serum half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, or polypeptide according to any of aspects K-1 to K-19 per se, respectively.
- Aspect L-261. Compound or construct according to any of aspects L-239 to L-260, that has a serum half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se or NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, or polypeptide according to any of aspects K-1 to K-19 per se, respectively.
- Aspect L-262. Compound or construct according to any of aspects L-239 to L-261, that has a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or

more; for example, of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

- Aspect G-1: Monovalent construct, comprising or essentially consisting of one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 and/or one NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137.
- Aspect G-2: Monovalent construct according to aspect G-1, in which said amino acid sequence of the invention is chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or NANOBODIES® (V_{HH} sequences).
- Aspect G-3: Monovalent construct, comprising or essentially consisting of one NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137.
- Aspect G-4: Monovalent construct, that is chosen from the group consisting of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 or from the group consisting of amino acid sequences that have more than 80%, preferably more than 90%, more preferably more than 95%, such as 99% or more sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128.
- Aspect G-5: Use of a monovalent construct according to any of aspects G-1 to G-4, in preparing a multivalent compound or construct according to any of aspects L-1 to L-262.
- Aspect G-6: Use of a monovalent construct according to aspect G-5, in preparing a multiparatopic construct such as a bivalent, biparatopic, trivalent, triparatopic construct.
- Aspect G-7: Use of a monovalent construct according to any of aspects G-5 or G-6, wherein the monovalent construct is used as a binding domain or binding unit in preparing a multivalent construct comprising two or more binding units.
- Aspect G-8: Use of a monovalent construct according to any of aspects G-5 to G-7, in preparing a multivalent construct that exhibits intramolecular binding compared to intermolecular binding.
- Aspect G-9: Use of a monovalent construct according to any of aspects G-5 to G-8, as a binding domain or binding unit in preparing a multivalent construct, wherein the binding domains or binding units are linked via a linker such that the multivalent construct preferably exhibits intramolecular binding compared to intermolecular

binding.

- Aspect G-10: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the Synagis® binding site on the F envelope protein of RSV virus and/or is capable of competing with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect G-11: Use of a monovalent construct according to any of aspects G-5 to G-10, wherein the monovalent construct is directed against antigenic site II of the F envelope protein of RSV virus.
- Aspect G-12: Use of a monovalent construct according to any of aspects G-5 to G-11, wherein the monovalent construct is directed against amino acid residues 250-275 of the F envelope protein of RSV virus.
- Aspect G-13: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the 101F binding site on the F envelope protein of RSV virus and/or is capable of competing with 101F for binding to the F envelope protein of RSV virus.
- Aspect G-14: Use of a monovalent construct according to any of aspects G-5 to G-9 and/or G-13, wherein the monovalent construct is directed against antigenic site IV-VI of the F envelope protein of RSV virus.
- Aspect G-15: Use of a monovalent construct according to any of aspects G-5 to G-9 and/or G-13 to G-14, wherein the monovalent construct is directed against amino acid residues 423-436 of the F envelope protein of RSV virus.
- Aspect G-16: Use of two monovalent constructs according to any of aspects G-5 to G-9, wherein a first monovalent construct is directed against the Synagis® binding site on the F envelope protein of RSV virus (and in particular against antigenic site II of the F envelope protein of RSV virus, and more in particular against amino acid residues 250-275 of the F envelope protein of RSV virus) and/or is capable of competing with Synagis® for binding to the F envelope protein of RSV virus and wherein the second monovalent construct is directed against the 101F binding site on the F envelope protein of RSV virus (and in particular against antigenic site IV-VI of the F envelope protein of RSV virus, and more in particular against amino acid residues 423-436 of the F envelope protein of RSV virus) and/or is capable of competing with 101F for binding to the F envelope protein of RSV virus.
- Aspect G-17: Use of two monovalent constructs according to any of aspects G-5 to G-9 for the preparation of a bivalent compound or construct, wherein the monovalent constructs are directed against the Synagis® binding site on the F envelope protein of RSV virus (and in particular against antigenic site II of the F envelope protein of RSV virus, and more in particular against amino acid residues 250-275 of the F envelope protein of RSV virus) and/or capable of competing with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect G-18: Use of three monovalent constructs according to any of aspects G-5 to

G-9 for the preparation of a trivalent compound or construct, wherein the monovalent constructs are directed against the Synagis® binding site on the F envelope protein of RSV virus (and in particular against antigenic site II of the F envelope protein of RSV virus, and more in particular against amino acid residues 250-275 of the F envelope protein of RSV virus) and/or capable of competing with Synagis® for binding to the F envelope protein of RSV virus.

- Aspect G-19: Use of two monovalent constructs according to any of aspects G-5 to G-9 for the preparation of a bivalent compound or construct, wherein the monovalent constructs are directed against the 101F binding site on the F envelope protein of RSV virus (and in particular against antigenic site IV-VI of the F envelope protein of RSV virus, and more in particular against amino acid residues 423-436 of the F envelope protein of RSV virus) and/or capable of competing with 101F for binding to the F envelope protein of RSV virus.
- Aspect G-20: Use of three monovalent constructs according to any of aspects G-5 to G-9 for the preparation of a trivalent compound or construct, wherein the monovalent constructs are directed against the 101F binding site on the F envelope protein of RSV virus (and in particular against antigenic site IV-VI of the F envelope protein of RSV virus, and more in particular against amino acid residues 423-436 of the F envelope protein of RSV virus) and/or capable of competing with 101F for binding to the F envelope protein of RSV virus.
- Aspect G-21: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-22: Use of two monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a bivalent compound or construct, wherein the monovalent constructs are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or is capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-23: Use of three monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a trivalent compound or construct, wherein the monovalent constructs are directed against the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or are capable of competing with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-24: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or is capable of competing

with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.

- Aspect G-25: Use of two monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a bivalent compound or construct, wherein the monovalent constructs are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-26: Use of three monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a trivalent compound or construct, wherein the monovalent constructs are directed against the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-27: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or is capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-28: Use of two monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a bivalent compound or construct, wherein the monovalent constructs are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-29: Use of three monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a trivalent compound or construct, wherein the monovalent constructs are directed against the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or are capable of competing with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect G-30: Use of a monovalent construct according to any of aspects G-5 to G-9, wherein the monovalent construct is directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or is capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.
- Aspect G-31: Use of two monovalent constructs according to any of aspects G-5 to G-9, for the preparation of a bivalent construct, wherein the monovalent constructs are directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or are capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.
- Aspect G-32: Use of three monovalent constructs according to any of aspects G-5 to

G-9, for the preparation of a trivalent construct, wherein the monovalent constructs are directed against the MAb 8-2 binding site on the G envelope protein of rabies virus and/or are capable of competing with MAb 8-2 for binding to the G envelope protein of rabies virus.

- Aspect M-1: Nucleic acid or nucleotide sequence, that encodes an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, or a monovalent construct according to any of aspects G-1 to G-32.
- Aspect M-2: Nucleic acid or nucleotide sequence according to aspect M-1, that is in the form of a genetic construct.
- Aspect M-3: Use of a nucleic acid or nucleotide sequence according to aspect M-1, that encodes a monovalent construct according to any of aspects G-1 to G-32, for the preparation of a genetic construct that encodes a multivalent construct according to any of aspects L-1 to L-262.
- Aspect M-4: Use of a nucleic acid or nucleotide sequence according to aspect M-2, wherein the genetic construct encodes a multiparatopic (such as a biparatopic) construct.
- Aspect N-1: Host or host cell that expresses, or that under suitable circumstances is capable of expressing, an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, or a monovalent construct according to any of aspects G-1 to G-32; and/or that comprises a nucleic acid or nucleotide sequence according to aspects M-1 or M-2.
- Aspect O-1: Composition, comprising at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, monovalent construct according to any of aspects G-1 to G-32, or nucleic acid or nucleotide sequence according to aspects M-1 or M-2.
- Aspect O-2: Composition according to aspect O-1, which is a pharmaceutical composition.
- Aspect O-3: Composition according to aspects O-1 or O-2, which is a pharmaceutical composition, that further comprises at least one pharmaceutically acceptable carrier,

diluent or excipient and/or adjuvant, and that optionally comprises one or more further pharmaceutically active polypeptides and/or compounds.

- Aspect P-1: Method for producing an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, a monovalent construct according to any of aspects G-1 to G-32, or a composition according to any of aspects O-1 to O-3, said method at least comprising the steps of:
  - a. expressing, in a suitable host cell or host organism or in another suitable expression system, a nucleic acid or nucleotide sequence according to aspects M-1 or M-2,
  - optionally followed by:
  - b. isolating and/or purifying the amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, the polypeptide according to any of aspects K-1 to K-19, the compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, or the monovalent construct according to any of aspects G-1 to G-32 thus obtained.
- Aspect P-2: Method for producing an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, a monovalent construct according to any of aspects G-1 to G-32, or a composition according to any of aspects O-1 to O-3, said method at least comprising the steps of:
  - a. cultivating and/or maintaining a host or host cell according to aspect N-1 under conditions that are such that said host or host cell expresses and/or produces at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, a monovalent construct according to any of aspects G-1 to G-32, or composition according to any of aspects O-1 to O-3,

- optionally followed by:
- b. isolating and/or purifying the amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, the polypeptide according to any of aspects K-1 to K-19, the compound or construct according to any of aspects L-1 to L-262, that is such that it can be obtained by expression of a nucleic acid or nucleotide sequence encoding the same, or a monovalent construct according to any of aspects G-1 to G-32, or the composition according to aspects O-1 to O-3, thus obtained.

- Aspect P-3: Method for preparing and/or generating a multiparatopic (such as e.g. biparatopic, triparatopic, etc.) construct according to any of aspects L-38 to L-123 and/or L-157 to L-236, said method comprising at least the steps of:
  - a. providing a nucleic acid sequence according to aspect M-1, encoding a first viral envelope protein binding amino acid sequence, fused to a set, collection or library of nucleic acid sequences encoding amino acid sequences;
  - b. screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode a second amino acid sequence that can bind to and/or has affinity for an antigenic determinant on the viral envelope protein different from the antigenic determinant recognized by the first viral envelope protein binding amino acid sequence;
  - and
  - c. isolating the nucleic acid sequence encoding a the viral envelope protein binding amino acid sequence fused to the nucleic acid sequence obtained in b), followed by expressing the encoded construct.
- Aspect P-4: Method for preparing and/or generating a biparatopic or triparatopic construct according to any of aspects L-38 to L-123 or L-157 to L-236, said method comprising at least the steps of:
  - a. providing a set, collection or library of nucleic acid sequences, in which each nucleic acid sequence in said set, collection or library encodes a fusion protein that comprises a first amino acid sequence that can bind to and/or has affinity for a first antigenic determinant, part, domain or epitope on a viral envelope protein that is fused (optionally via a linker sequence) to a second amino acid sequence, in which essentially each second amino acid sequence (or most of these) is a different member of a set, collection or library of different amino acid sequences;
  - b. screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for a second antigenic determinant, part, domain or epitope on the viral envelope protein different from the first antigenic determinant, part, domain or epitope on the viral envelope protein;

- and
- c. isolating the nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for a second antigenic determinant, part, domain or epitope on the viral envelope protein different from the first antigenic determinant, part, domain or epitope on the viral envelope protein, obtained in b), optionally followed by expressing the encoded amino acid sequence.

- Aspect P-5: Method according to aspect P-4, wherein the first amino acid is also encoded by a set, collection or library of nucleic acid sequences and wherein, in step b), said set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for the first antigenic determinant, part, domain or epitope on the viral envelope protein.
- Aspect P-6: Method according to aspect P-5, wherein the screening in step b) is performed in a single step.
- Aspect P-7: Method according to aspect P-5, wherein the screening in step b) is performed in subsequent steps.
- Aspect P-8: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or (ii) it competes with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect P-9: Method according to any of aspects P-4 to P-8, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode (i) an amino acid sequence that can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or (ii) an amino acid sequence that can compete with 101F for binding to the F envelope protein of RSV virus.
- Aspect P-10: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or (ii) it competes with 101F for binding to the F envelope protein of RSV virus.
- Aspect P-11: Method according to any of aspects P-4 to P-7 and P-10, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode (i) an amino acid sequence that can bind to and/or has affinity

for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or (ii) an amino acid sequence that can compete with Synagis® for binding to the F envelope protein of RSV virus.

- Aspect P-12: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) it competes with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-13: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) it competes with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-14: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) it competes with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-15: Method according to any of aspects P-4 to P-7, wherein the first amino acid sequence used in step a) is preferably such that (i) it can bind to and/or has affinity for the MAb 8-2 binding site on the G envelope protein of rabies virus and/or (ii) it competes with MAb 8-2 for binding to the G envelope protein of rabies virus.
- Aspect P-16: Method according to any of aspects P-4 to P-15, wherein the screening in step b) is performed in a single step.
- Aspect P-17: Method according to any of aspects P-4 to P-15, wherein the screening in step b) is performed in subsequent steps.
- Aspect P-18: Method according to any of aspects P-4 to P-17, wherein the screening in step b) is performed in the presence of Synagis®, 101F, sialic acid, VN04-2, MAb C179 and/or MAb 8-2.
- Aspect P-19: Method for screen for suitable and/or optimal linker lengths for linking a first and a second amino acid sequence in a biparatopic or triparatopic construct according to any of aspects L-38 to L-123 or L-157 to L-236, wherein said method comprises at least the steps of:
    - a. providing a set, collection or library of nucleic acid sequences, in which each nucleic acid sequence in said set, collection or library encodes a fusion protein that comprises a first amino acid sequence that can bind to and/or has affinity for a first antigenic determinant, part, domain or epitope on a viral envelope protein that is fused via a linker sequence to a second amino acid sequence that

has can bind to and/or has affinity for a second antigenic determinant, part, domain or epitope on the viral envelope protein (which may be the same or different as the first antigenic determinant, part, domain or epitope on the viral envelope protein), in which essentially each nucleic acid sequence (or most of these) encodes a fusion protein with a different linker sequence so as to provide a set, collection or library encoding different fusion proteins;

- b. screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for the first and second antigenic determinant, part, domain or epitope on the viral envelope protein;
- and
- c. isolating the nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for the first and second antigenic determinant, part, domain or epitope on the viral envelope protein, optionally followed by expressing the encoded amino acid sequence.

- Aspect P-20: Method according to aspect P-19, wherein the first amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or that can compete with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect P-21: Method according to aspect P-20, wherein the second amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or that can compete with 101F for binding to the F envelope protein of RSV virus.
- Aspect P-22: Method according to aspect P-19, wherein the first amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or that can compete with 101F for binding to the F envelope protein of RSV virus.
- Aspect P-23: Method according to aspect P-22, wherein the second amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or that can compete with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect P-24: Method according to aspect P-19, wherein the first amino acid sequence

is an amino acid sequence that can bind to and/or has affinity for the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that can compete with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.

- Aspect P-25: Method according to aspect P-19, wherein the first amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that can compete with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-26: Method according to aspect P-19, wherein the first amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or that can compete with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-27: Method according to aspect P-19, wherein the first amino acid sequence is an amino acid sequence that can bind to and/or has affinity for the MAb 8-2 binding site on the G envelope protein of rabies virus and/or that can compete with MAb 8-2 for binding to the G envelope protein of rabies virus.
- Aspect P-28: Method according to any of aspects P-19 to P-27, wherein the screening in step b) is performed in a single step.
- Aspect P-29: Method according to any of aspects P-19 to P-27, wherein the screening in step b) is performed in subsequent steps.
- Aspect P-30: Method according to any of aspects P-19 to P-29, wherein the screening in step b) is performed in the presence of Synagis®, 101F, sialic acid, VN04-2, MAb C179 and/or MAb 8-2.
- Aspect P-31: Method for preparing and/or generating biparatopic or triparatopic constructs according to any of aspects L-38 to L-123 or L-157 to L-236, said method comprising at least the steps of:
    - a. providing a set, collection or library of nucleic acid sequences encoding amino acid sequences;
    - b. screening said set, collection or library of nucleic acid sequences for a set, collection or library of nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for a viral envelope protein;
    - c. ligating said set, collection or library of nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for the viral envelope protein to another nucleic acid sequence that encodes an amino acid sequence that can bind to and/or has affinity for the viral envelope protein (e.g. a nucleic acid sequence that encodes an amino acid sequence that competes with Synagis® for binding the viral envelope protein);
    - and

- d. from the set, collection or library of nucleic acid sequences obtained in c), isolating the nucleic acid sequences encoding a biparatopic amino acid sequence that can bind to and/or has affinity for the viral envelope protein (and e.g. further selecting for nucleic acid sequences that encode a biparatopic amino acid sequence that antagonizes with higher potency compared to the monovalent amino acid sequences), followed by expressing the encoded amino acid sequence.

- Aspect P-32: Method for preparing and/or generating biparatopic or triparatopic constructs according to any of aspects L-38 to L-123 or L-157 to L-236, said method comprising at least the steps of:
  - a. providing a first set, collection or library of nucleic acid sequences encoding amino acid sequences;
  - b. screening said first set, collection or library of nucleic acid sequences for a nucleic acid sequence that encodes an amino acid sequence that can bind to and/or has affinity for a first antigenic determinant, part, domain or epitope on a viral envelope protein;
  - c. ligating the nucleic acid sequence encoding said amino acid sequence that can bind to and/or has affinity for a first antigenic determinant, part, domain or epitope on the viral envelope protein obtained in b) to another set, collection or library of nucleic acid sequences encoding amino acid sequences to obtain a set, collection or library of nucleic acid sequences that encode fusion proteins;
  - d. screening said set, collection or library of nucleic acid sequences obtained in step c) for a nucleic acid sequence that encodes an amino acid sequence that can bind to and has affinity for a second antigenic determinant, part, domain or epitope on the viral envelope protein which is the same or different from the first antigenic determinant, part, domain or epitope on the viral envelope protein;
  - and
  - e. isolating the nucleic acid sequence that encodes an amino acid sequence that can bind to and/or has affinity for the first and second antigenic determinant, part, domain or epitope on the viral envelope protein, optionally followed by expressing the encoded amino acid sequence.
- Aspect P-33: Method according to aspect P-32, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or (ii) competes with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect P-34: Method according to any of aspects P-32 and/or P-33 wherein in step d),

the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a second amino acid sequence that (i) can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or (ii) competes with 101F for binding to the F envelope protein of RSV virus.

- Aspect P-35: Method according to aspect P-32, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the 101F binding site on the F envelope protein of RSV virus (and in particular antigenic site IV-VI of the F envelope protein of RSV virus, more in particular at least amino acid residues 423-436 of the F envelope protein of RSV virus) and/or (ii) competes with 101F for binding to the F envelope protein of RSV virus.
- Aspect P-36: Method according to any of aspects P-32 and/or P-35, wherein in step d), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a second amino acid sequence that (i) can bind to and/or has affinity for the Synagis® binding site on the F envelope protein of RSV virus (and in particular antigenic site II of the F envelope protein of RSV virus, more in particular at least amino acid residues 250-275 of the F envelope protein of RSV virus) and/or (ii) competes with Synagis® for binding to the F envelope protein of RSV virus.
- Aspect P-37: Method according to aspect P-32, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the sialic acid binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) competes with sialic acid for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-38: Method according to aspect P-32, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the VN04-2 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) competes with VN04-2 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-39: Method according to aspect P-32, wherein in step b), the set, collection or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the MAb C179 binding site on the hemagglutinin H5 envelope protein of influenza virus and/or (ii) competes with MAb C179 for binding to the hemagglutinin H5 envelope protein of influenza virus.
- Aspect P-40: Method according to aspect P-32, wherein in step b), the set, collection

or library of nucleic acid sequences is screened for nucleic acid sequences that encode a first amino acid sequence that (i) can bind to and/or has affinity for the MAb 8-2 binding site on the G envelope protein of rabies virus and/or (ii) competes with MAb 8-2 for binding to the G envelope protein of rabies virus.

- Aspect P-41: Method according to any of aspects P-32 to P-40, wherein the screening in steps b) and/or d) is performed in the presence of Synagis®, 101F, sialic acid, VN04-2, MAb C179 and/or MAb 8-2.
- Aspect P-42: Method for preparing and/or generating a bivalent or trivalent construct according to any of aspects L-38 to L-123 or L-157 to L-236, said method comprising at least the steps of linking two or more monovalent amino acid sequences or monovalent construct according to any of aspects G-1 to G-32 and for example one or more linkers.
- Aspect P-43: Method according to aspect P-42, comprising the steps of:
  - a. linking two or more nucleic acid sequences according to aspect M-1, encoding a monovalent construct according to any of aspects G-1 to G-32 (and also for example nucleic acids encoding one or more linkers and further one or more further elements of genetic constructs known per se) to obtain a genetic construct according to aspect M-2;
  - b. expressing, in a suitable host cell or host organism or in another suitable expression system, the genetic construct obtained in a)
  - optionally followed by:
  - c. isolating and/or purifying the biparatopic or triparatopic construct according to any of aspects L-38 to L-123 or L-157 to L-236 thus obtained.
- Aspect Q-1: Method for screening amino acid sequences directed against an envelope protein of a virus, said method comprising at least the steps of:
  - a. providing a set, collection or library of nucleic acid sequences encoding amino acid sequences;
  - b. screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for an envelope protein of a virus and that is cross-blocked or is cross blocking a NANOBODY® (V_{HH} sequence) of the invention, e.g. one of SEQ ID NO: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (Table A-1), or a humanized variant of a NANOBODY® (V_{HH} sequence) of the invention, e.g. a humanized variant of one of SEQ ID NO: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (Table A-1), or a polypeptide or construct comprising at least one NANOBODY® (V_{HH} sequence) of the invention, e.g. a polypeptide or construct comprising at least one of SEQ ID NO: 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 (see Table A-1); and
  - c. isolating said nucleic acid sequence, followed by expressing said amino acid

sequence.

- Aspect R-1: Method for the prevention and/or treatment of at least one viral disease, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, monovalent construct according to any of aspects G-1 to G-32 and/or composition according to aspects O-1 to O-3.
- Aspect R-2: Method for the prevention and/or treatment of at least one disease or disorder that is associated with viral entry and/or viral replication and/or mediated by an envelope protein of a virus and/or its viral receptor, with its biological or pharmacological activity, and/or with the viral-mediated biological pathways in which an envelope protein of a virus and/or its viral receptor is involved, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, monovalent construct according to any of aspects G-1 to G-32 and/or composition according to aspects O-1 to O-3.
- Aspect R-3: Method for the prevention and/or treatment of at least one disease or disorder that can be prevented and/or treated by administering, to a subject in need thereof, an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, a monovalent construct according to any of aspects G-1 to G-32 and/or a composition according to aspects O-1 to O-3, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, monovalent construct according to any of aspects G-1 to G-32 and/or composition according to aspects O-1 to O-3.
- Aspect R-4: Method for immunotherapy, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of at least one amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, NANOBODY® (V_{HH} sequence) according to any of

aspects H-1 to H-137, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262, monovalent construct according to any of aspects G-1 to G-32 and/or composition according to aspects O-1 to O-3.

- Aspect R-5: Use of an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137, a polypeptide according to any of aspects K-1 to K-19, a compound or construct according to any of aspects L-1 to L-262, a monovalent construct according to any of aspects G-1 to G-32 and/or a composition according to aspects O-1 to O-3 in the preparation of a pharmaceutical composition for prevention and/or treatment of at least one viral disease; and/or for use in one or more of the methods according to aspects R-1 to R-4.
- Aspect S-1: Part or fragment of an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 or of a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137.
- Aspect S-2: Part or fragment according to aspect S-1, that can specifically bind to an envelope protein of a virus.
- Aspect S-3: Part or fragment according to aspect S-2, wherein said part or fragment modulates the interaction between said envelope protein and at least one binding partner.
- Aspect S-4: Part or fragment according to aspects S-2 or S-3, wherein said part or fragment inhibits and/or prevents the interaction between said envelope protein and at least one binding partner.
- Aspect S-5: Part or fragment according to any of aspects S-2 to S-4, wherein said part or fragment competes with said binding partner for binding to said envelope protein.
- Aspect S-6: Part or fragment according to aspect S-4, wherein said at least one binding partner is a viral receptor for an envelope protein of a virus.
- Aspect S-7: Part or fragment according to aspect S-6, wherein said viral receptor is chosen from the group consisting of sialic acid, soluble (2,3)-sialic acid, (2,6)-sialic acid, CD4, CCR5, CXCR4, galactosylceramide, ACE2, HveA, CD155, ICAM-1, CAR, αv integrins, heparin sulphate proteoglycans, JAM-1, the Nicotinic Acetylcholine Receptor (AchR), and the Nueral Cell Adhesion Molecule (NCAM).
- Aspect S-8: Part or fragment according to aspects S-6 or S-7, wherein said interaction between an envelope protein and a viral receptor is chosen from the group consisting of the interaction between HA of influenza A virus and sialic acid and/or (2,3) sialic acid and/or (2,6) sialic acid; the interaction between gp120 of HIV-1 virus and CD4 and/or CCR5 and/or CXCR4 and/or galactosylceramide; the interaction between S1 of SARS coronavirus and ACE2; the interaction between gD and/or gB and/or gC and/or the heterodimer gH/gL of herpes simplex 1 virus and HveA; the interaction between VP1 and/or VP2 and/or VP3 of poliovirus 1 with CD155; the interaction

between VP1 and/or VP2 and/or VP3 of rhinovirus 3 with ICAM-1; the interaction of adenovirus 2 fibre with CAR; the interaction of adenovirus 2 penton base with αv integrins and/or sialic acid and/or (2,3) sialic acid and/or (2,6) sialic acid and/or heparin sulphate proteoglycans, the interaction between σ1 of reovirus 1 and JAM-1 and/or sialic acid and/or (2,3) sialic acid and/or (2,6) sialic acid, the interaction between G-protein of rabies virus and the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM).

- Aspect S-9: Part or fragment according to aspect S-4, wherein said at least one binding partner is a monoclonal antibody that is directed against and/or specifically binds to said envelope protein of a virus.
- Aspect S-10: Part or fragment according to aspect S-9, wherein said monoclonal antibody is Synagis®, 101F, VN04-2, MAb C179 or MAb 8-2.
- Aspect S-11: Part or fragment according to any of aspects S-2 to S-10, wherein said envelope protein is a viral-specific protein.
- Aspect S-12: Part or fragment according to any of aspects S-2 to S-11, wherein said envelope protein is a membrane protein.
- Aspect S-13: Part or fragment according to any of aspects S-2 to S-12, wherein said envelope protein is a non-glycosylated protein.
- Aspect S-14: Part or fragment according to any of aspects S-2 to S-12, wherein said envelope protein is a glycoprotein.
- Aspect S-15: Part or fragment according to any of aspects S-2 to S-14, wherein said envelope protein is a viral attachment protein.
- Aspect S-16: Part or fragment according to aspect S-15, wherein said viral attachment protein is chosen from the group consisting of the G protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2 and σ1 of Reovirus 1.
- Aspect S-17: Part or fragment according to any of aspects S-2 to S-16, wherein said envelope protein is a viral fusion protein.
- Aspect S-18: Part or fragment according to aspect S-17, wherein said viral fusion protein is chosen from the group consisting of the F protein of RSV virus, the HA protein of Influenza A virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne

encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

- Aspect S-19: Part or fragment according to any of aspects S-2 to S-18, wherein said envelope protein is a viral attachment protein and a viral fusion protein.
- Aspect S-20: Part or fragment according to aspect S-19, wherein said viral attachment protein and viral fusion protein is chosen from the group consisting of the HA protein of influenza A virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, and the E1 protein of Sindbis virus.
- Aspect S-21: Part or fragment according to any of aspects S-17 to S-20, wherein said viral fusion protein is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state.
- Aspect S-22: Part or fragment according to aspect S-21, wherein said viral fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein trimer.
- Aspect S-23: Part or fragment according to aspect S-22, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect S-24: Part or fragment according to aspects S-22 or S-23, wherein said fusion protein trimer is a six-helix bundle.
- Aspect S-25: Part or fragment according to any of aspects S-22 to S-24, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Human respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein, SARS corona virus E2 protein.
- Aspect S-26: Part or fragment according to aspect S-25, wherein said fusion protein is Influenza A virus HA protein.
- Aspect S-27: Part or fragment according to aspect S-25, wherein said fusion protein is Human respiratory syncytial virus F protein.
- Aspect S-28: Part or fragment according to aspect S-21, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a protein dimer.
- Aspect S-29: Part or fragment according to aspect S-28, wherein said dimer is a fusion protein homodimer.
- Aspect S-30: Part or fragment according to aspect S-28, wherein said dimer is a

protein heterodimer.

- Aspect S-31: Part or fragment according to aspect S-21, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein monomer.
- Aspect S-32: Part or fragment according to any of aspects S-28 to S-31, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect S-33: Part or fragment according to aspect S-21, wherein said fusion protein is characterized by a post-fusion conformational state, which is a fusion protein trimer.
- Aspect S-34: Part or fragment according to aspect S-33, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect S-35: Part or fragment according to aspects S-33 or S-34, wherein said fusion protein trimer is a six-helix bundle.
- Aspect S-36: Part or fragment according to aspect S-34, wherein said trimer of hairpins comprises an α-helical coiled coil.
- Aspect S-37: Part or fragment according to any of aspects S-33 to S-36, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Respiratory syncytial F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.
- Aspect S-38: Part or fragment according to aspect S-34, wherein said trimer of hairpins comprises β-structures.
- Aspect S-39: Part or fragment according to any of aspects S-33 to S-35 and S-38, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect S-40: Part or fragment according to any of aspects S-34, S-36 and S-38, wherein said trimer of hairpins comprises an α-helical coiled coil and β-structures.
- Aspect S-41: Part or fragment according to aspect S-40, wherein said fusion protein is chosen from the group consisting of vesicular stomatitis virus G protein, Rabies virus G protein and Herpes simplex virus gB protein.
- Aspect S-42: Part or fragment according to aspect S-41, wherein said fusion protein is Rabies virus G protein.
- Aspect S-43: Part or fragment according to any of aspects S-21 to S-42, wherein said part or fragment is directed against and/or can specifically bind to the pre-fusion

conformational state and/or the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.

- Aspect S-44: Part or fragment according to aspect S-43, wherein said part or fragment is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state of said fusion protein.
- Aspect S-45: Part or fragment according to aspect S-43, wherein said part or fragment is directed against and/or can specifically bind to the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect S-46: Part or fragment according to aspect S-43, wherein said part or fragment is directed against and/or can specifically bind to the pre-fusion conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect S-47: Part or fragment according to any of aspects S-21 to S-46, wherein said epitope is located in a cavity or cleft formed by said trimer according to claims S-22 to S-27 and S-33 to S-42 or formed by said dimer according to aspects S-28 to S-32.
- Aspect S-48: Part or fragment according to any of aspects S-21 to S-47, wherein said epitope is located in the stem region of said fusion protein.
- Aspect S-49: Part or fragment according to aspect S-48, wherein said epitope that is located in the stem region of said fusion protein is chosen from the group consisting of an epitope that is located in the region comprising one or more of the amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA, an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA and an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA.
- Aspect S-50: Part or fragment according to any of aspects S-21 to S-47, wherein said epitope is located in the neck region of said fusion protein.
- Aspect S-51: Part or fragment according to any of aspects S-21 to S-47, wherein said epitope is located in the globular head region of said fusion protein.
- Aspect S-52: Part or fragment according to aspect S-51, wherein said globular head region comprises a β-barrel-type structure.
- Aspect S-53: Part or fragment according to aspect S-51, wherein said globular head region comprises an immunoglobulin-type β-sandwich domain and a β-sheet domain.
- Aspect S-54: Part or fragment according to any of aspects S-2 to S-53, wherein said epitope is chosen from the group consisting of an epitope that is located in the region comprising the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus, an epitope that is located in the region comprising the Fla site and/or the

region comprising amino acid 389 of the F-protein of RSV virus, an epitope that is located in the region comprising amino acids 422 to 438 of the F-protein of RSV virus, an epitope that is located in the region comprising the sialic acid binding site of the H5 HA envelope protein of influenza virus, an epitope that is located in the region comprising the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus, an epitope that is located in the C-terminal region of a fusion protein, an epitope that is located in the N-terminal domain of a fusion protein, an epitope that is located in or comprises the fusion peptide of a fusion protein, an epitope that is located in the transmembrane domain of a fusion protein, an epitope that is located in a α-helical coiled-coil of a fusion protein, an epitope that is located in a β-structure of a fusion protein, an epitope that is located in Domain I of a fusion protein, an epitope that is located in Domain II of a fusion protein and an epitope that is located in Domain III of a fusion protein.

- Aspect S-55: Part or fragment according to aspect S-54, wherein said epitope that is located in Domain II of a fusion protein is an epitope that is located in the fusion peptide of Domain II of a fusion protein.
- Aspect S-56: Part or fragment according to aspect S-54, wherein said epitope that is located in Domain III of a fusion protein is chosen from the group consisting of an epitope that is located in the stem region at the C-terminus of Domain III of a fusion protein and an epitope that is located in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.
- Aspect S-57: Part or fragment according to any of aspects S-2 to S-56, wherein said virus is chosen from the group consisting of a DNA virus, an RNA virus and a Reverse Transcriptase (RT) virus.
- Aspect S-58: Part or fragment according to aspect S-57, wherein said DNA virus is chosen from the group consisting of a ds DNA virus and a ssDNA virus.
- Aspect S-59: Part or fragment according to aspect S-57, wherein said RNA virus is chosen from the group consisting of a dsRNA virus, a positive-sense ssRNA virus and a negative-sense ssRNA virus.
- Aspect S-60: Part or fragment according to aspect S-57, wherein said Reverse Transcriptase (RT) virus is chosen from the group consisting of a dsDNA-RT virus and a ssRNA-RT virus.
- Aspect S-61: Part or fragment according to any of aspects S-2 to S-60, wherein said virus belongs to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae.
- Aspect S-62: Part or fragment according to aspect S-61, wherein said virus belongs to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses.

- Aspect S-63: Part or fragment according to any of aspects S-2 to S-62, wherein said part or fragment neutralizes said virus.
- Aspect S-64: Part or fragment according to any of aspects S-2 to S-63, wherein said part or fragment modulates the infectivity of said virus.
- Aspect S-65: Part or fragment according to aspect S-64, wherein said part or fragment inhibits and/or prevents the infectivity of said virus.
- Aspect S-66: Part or fragment according to any of aspects S-64 or S-65, wherein said part or fragment neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the pre-entry stage.
- Aspect S-67: Part or fragment according to aspect S-66, wherein said part or fragment modulates, inhibits and/or prevents viral entry in a target host cell.
- Aspect S-68: Part or fragment according to any of aspects S-2 to S-67, wherein said part or fragment induces virion aggregation of said virus.
- Aspect S-69: Part or fragment according to any of aspects S-2 to S-68, wherein said part or fragment destabilizes the virion structure of said virus.
- Aspect S-70: Part or fragment according to any of aspects S-2 to S-69, wherein said part or fragment inhibits virion attachment to a target host cell of said virus.
- Aspect S-71: Part or fragment according to aspect S-70, wherein said part or fragment inhibits virion attachment to a target host cell of said virus by modulating the interaction between said envelope protein and a viral receptor.
- Aspect S-72: Part or fragment according to aspects S-70 or S-71, wherein said part or fragment inhibits virion attachment to a target host cell of said virus by inhibiting and/or preventing the interaction between said envelope protein and a viral receptor.
- Aspect S-73: Part or fragment according to aspects S-70 or S-72, wherein said part or fragment competes with said envelope protein for binding to a viral receptor.
- Aspect S-74: Part or fragment according to any of aspects S-2 to S-73, wherein said part or fragment inhibits fusion of said virus with a target host cell of said virus.
- Aspect S-75: Part or fragment according to aspect S-74, wherein fusion of said virus with a target host cell of said virus taking place at the target host cell membrane is inhibited.
- Aspect S-76: Part or fragment according to aspect S-74, wherein fusion of said virus with a target host cell of said virus taking place within an endosomal or lysosomal compartment is inhibited.
- Aspect S-77: Part or fragment according to any of aspects S-74 to S-76, wherein said part or fragment prevents said envelope protein of a virus from undergoing a conformational change.
- Aspect S-78: Part or fragment according to any of aspects S-64 to S-65, wherein said part or fragment neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the post-entry stage.
- Aspect S-79: Part or fragment according to any of aspects S-2 to S-78, wherein said

part or fragment modulates, inhibits and/or prevents viral replication in a target host cell.

- Aspect S-80: Part or fragment according to any of aspects S-2 to S-79, wherein said part or fragment affects, inhibits and/or prevents transcription and/or translation of the viral genome.
- Aspect S-81: Part or fragment according to any of aspects S-2 to S-80, wherein said part or fragment affects, inhibits and/or prevents viral packaging and/or the formation of functional virions.
- Aspect S-82: Part or fragment according to any of aspects S-2 to S-81, wherein said part or fragment reduces, inhibits and/or prevents budding or release of nascent virions from a target host cell surface.
- Aspect S-83: Part or fragment according to any of aspects S-2 to S-82, wherein said part or fragment is directed against and/or can specifically bind to at least two epitopes of an envelope protein of a virus.
- Aspect S-84: Part or fragment according to aspect S-83, wherein said part or fragment is directed against and/or can specifically bind to at least two epitopes of one envelope protein of a virus.
- Aspect S-85: Part or fragment according to any of aspects S-2 to S-83, wherein said part or fragment is directed against and/or can specifically bind to at least two epitopes of at least two envelope proteins of a virus.
- Aspect S-86: Part or fragment according to any of aspects S-2 to S-83 and S-85, wherein said part or fragment is directed against and/or can specifically bind to three or more epitopes of said envelope protein of a virus.
- Aspect S-87: Part or fragment according to aspect S-85, wherein said part or fragment is directed against and/or can specifically bind to three or more epitopes of at least two envelope proteins of a virus.
- Aspect S-88: Part or fragment according to any of aspects S-83 to S-87, wherein said at least two or three or more epitopes are the same or are different.
- Aspect S-89: Part or fragment according to any of aspects S-85 or S-87, wherein said at least two envelope proteins are the same or are different.
- Aspect S-90: Part of fragment according to any of aspects S-2 to S-89, that can specifically bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect S-91: Part or fragment according to any of aspects S-2 to S-90, that can specifically bind to an envelope protein of a virus with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$.
- Aspect S-92: Part or fragment according to any of aspects S-2 to S-91, that can

specifically bind to an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1} preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

- Aspect S-93: Compound or construct, that comprises or essentially consists of one or more parts or fragments according to any of aspects S-1 to S-92, and optionally further comprises one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers.
- Aspect S-94: Compound or construct according to aspect S-93, in which said one or more other groups, residues, moieties or binding units are amino acid sequences.
- Aspect S-95: Compound or construct according to aspects S-93 or S-94, in which said one or more linkers, if present, are one or more amino acid sequences.
- Aspect S-96: Nucleic acid or nucleotide sequence, that encodes a part or fragment according to any of aspects S-1 to S-92 or a compound or construct according to any of aspects S-93 to S-95.
- Aspect S-97: Composition, comprising at least one part or fragment according to any of aspects S-1 to S-92, compound or construct according to any of aspects S-93 to S-95, or nucleic acid or nucleotide sequence according to aspect S-96.
- Aspect T-1: Derivative of an amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, or of a NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137.
- Aspect T-2: Derivative according to aspect T-1, that can specifically bind to an envelope protein of a virus.
- Aspect T-3: Derivative according to aspects T-1 or T-2, wherein said derivative modulates the interaction between said envelope protein and at least one binding partner.
- Aspect T-4: Derivative according to any of aspects T-1 to T-3, wherein said derivative inhibits and/or prevents the interaction between said envelope protein and at least one binding partner.
- Aspect T-5: Derivative according to any of aspects T-1 to T-4, wherein said derivative competes with said binding partner for binding to said envelope protein.
- Aspect T-6: Derivative according to aspect T-5, wherein said at least one binding partner is a viral receptor for an envelope protein of a virus.
- Aspect T-7: Derivative according to aspect T-6, wherein said viral receptor is chosen from the group consisting of sialic acid, soluble (2,3)-sialic acid, (2,6)-sialic acid, CD4, CCR5, CXCR4, galactosylceramide, ACE2, HveA, CD155, ICAM-1, CAR, αv integrins, heparin sulphate proteoglycans, JAM-1, the Nicotinic Acetylcholine Receptor (AchR), and the Nueral Cell Adhesion Molecule (NCAM).
- Aspect T-8: Derivative according to any of aspects T-6 or T-7, wherein said interaction between an envelope protein and a viral receptor is chosen from the group consisting of the interaction between HA of influenza A virus and sialic acid

and/or (2,3) sialic acid and/or (2,6) sialic acid; the interaction between gp120 of HIV-1 virus and CD4 and/or CCR5 and/or CXCR4 and/or galactosylceramide; the interaction between S1 of SARS coronavirus and ACE2; the interaction between gD and/or gB and/or gC and/or the heterodimer gH/gL of herpes simplex 1 virus and HveA; the interaction between VP1 and/or VP2 and/or VP3 of poliovirus 1 with CD155; the interaction between VP1 and/or VP2 and/or VP3 of rhinovirus 3 with ICAM-1; the interaction of adenovirus 2 fibre with CAR; the interaction of adenovirus 2 penton base with αv integrins and/or sialic acid and/or (2,3) sialic acid and/or (2,6) sialic acid and/or heparin sulphate proteoglycans, the interaction between σ1 of reovirus 1 and JAM-1 and/or sialic acid and/or (2,3) sialic acid and/or (2,6) sialic acid, the interaction between G-protein of rabies virus and the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM).

- Aspect T-9: Derivative according to any of aspect T-4 or T-5, wherein said at least one binding partner is a monoclonal antibody that is directed against and/or specifically binds to said envelope protein of a virus.
- Aspect T-10: Derivative according to aspect T-9, wherein said monoclonal antibody is Synagis®, 101F, VN04-2, MAb C179 and/or MAb 8-2.
- Aspect T-11: Derivative according to any of aspects T-2 to T-10, wherein said envelope protein is a viral-specific protein.
- Aspect T-12: Derivative according to any of aspects T-2 to T-10, wherein said envelope protein is a membrane protein.
- Aspect T-13: Derivative according to any of aspects T-2 to T-12, wherein said envelope protein is a non-glycosylated protein.
- Aspect T-14: Derivative according to any of aspects T-2 to T-12, wherein said envelope protein is a glycoprotein.
- Aspect T-15: Derivative according to any of aspects T-2 to T-14, wherein said envelope protein is a viral attachment protein.
- Aspect T-16: Derivative according to aspect T-15, wherein said viral attachment protein is chosen from the group consisting of the G protein of RSV virus, the HA protein of influenza A virus, the gp120 protein of HIV-1 virus, the S1 protein of SARS Corona virus, the gD protein of Herpes simplex 1 virus, the VP1 and/or VP2 and/or VP3 proteins of Poliovirus 1, the VP1 and/or VP2 and/or VP3 proteins of Rhinovirus 3, fibre and/or penton base of Adenovirus 2 and al of Reovirus 1.
- Aspect T-17: Derivative according to any of aspects T-2 to T-14, wherein said envelope protein is a viral fusion protein.
- Aspect T-18: Derivative according to aspect T-17, wherein said viral fusion protein is chosen from the group consisting of the F protein of RSV virus, the HA protein of Influenza A virus, the HEF protein of influenza C virus, the 5 F protein of Simian parainfluenza virus, the F protein of Human parainfluenza virus, the F protein of Newcastle disease virus, the F2 protein of measles, the F2 protein of Sendai virus, the

gp2 protein of Ebola virus, the TM protein of Moloney murine leukemia virus, the gp41 protein of Human immunodeficiency virus 1, the gp41 protein of Simian immunodeficiency virus, the gp21 protein of Human T cell leukemia virus 1, the TM protein of Human syncytin-2, the TM protein of Visna virus, the S2 protein of Mouse hepatitis virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, the E1 protein of Sindbis virus, the G protein of Rabies virus, the G protein of Vesicular stomatitis virus and the gB protein of Herpes simplex virus.

- Aspect T-19: Derivative according to any of aspects T-2 to T-18, wherein said envelope protein is a viral attachment protein and a viral fusion protein.
- Aspect T-20: Derivative according to aspect T-19, wherein said viral attachment protein and viral fusion protein is chosen from the group consisting of the HA protein of influenza A virus, the E2 protein of SARS corona virus, the E protein of Tick-borne encephalitis virus, the E2 protein of Dengue 2 and 3 virus, the E protein of Yellow Fever virus, the E protein of West Nile virus, the E1 protein of Semliki forest virus, and the E1 protein of Sindbis virus.
- Aspect T-21: Derivative according to aspects T-17 to T-20, wherein said viral fusion protein is characterized by a pre-fusion conformational state and/or an intermediate conformational state and/or a post-fusion conformational state.
- Aspect T-22: Derivative according to aspect T-21, wherein said viral fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein trimer.
- Aspect T-23: Derivative according to aspect T-22, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect T-24: Derivative according to aspects T-22 or T-23, wherein said fusion protein trimer is a six-helix bundle.
- Aspect T-25: Derivative according to any of aspects T-22 to T-24, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Human respiratory syncytial virus F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein, SARS corona virus E2 protein.
- Aspect T-26: Derivative according to aspect T-25, wherein said fusion protein is Influenza A virus HA protein.
- Aspect T-27: Derivative according to aspect T-25, wherein said fusion protein is Human respiratory syncytial virus F protein.
- Aspect T-28: Derivative according to aspect T-21, wherein said fusion protein is

characterized by a pre-fusion conformational state, which is a protein dimer.

- Aspect T-29: Derivative according to aspect T-28, wherein said dimer is a fusion protein homodimer.
- Aspect T-30: Derivative according to aspect T-28, wherein said dimer is a protein heterodimer.
- Aspect T-31: Derivative according to aspect T-21, wherein said fusion protein is characterized by a pre-fusion conformational state, which is a fusion protein monomer.
- Aspect T-32: Derivative according to any of aspects T-28 to T-31, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect T-33: Derivative according to aspect T-21, wherein said fusion protein is characterized by a post-fusion conformational state, which is a fusion protein trimer.
- Aspect T-34: Derivative according to aspect T-33, wherein said fusion protein trimer is a trimer of hairpins.
- Aspect T-35: Derivative according to aspects T-33 or T-34, wherein said fusion protein trimer is a six-helix bundle.
- Aspect T-36: Derivative according to aspect T-34, wherein said trimer of hairpins comprises an α-helical coiled coil.
- Aspect T-37: Derivative according to any of aspects T-33 to T-36, wherein said fusion protein is chosen from the group consisting of Influenza A virus HA protein, Influenza C virus HEF protein, Simian parainfluenza virus 5 F protein, Human parainfluenza virus F protein, Newcastle disease virus F protein, Respiratory syncytial F protein, Measles F2 protein, Sendai F2 protein, Ebola virus gp2 protein, Moloney murine leukemia virus TM protein, Human immunodeficiency virus 1 gp41 protein, Simian immunodeficiency virus gp41 protein, Human T cell leukemia virus 1 gp21 protein, Human syncytin-2 TM protein, Visna virus TM protein, Mouse hepatitis virus S2 protein and SARS corona virus E2 protein.
- Aspect T-38: Derivative according to aspect T-34, wherein said trimer of hairpins comprises β-structures.
- Aspect T-39: Derivative according to any of aspects T-33 to T-35 and T-38, wherein said fusion protein is chosen from the group consisting of Tick-borne encephalitis virus E protein, Dengue 2 and 3 virus E2 protein, yellow fever E protein, West Nile virus E protein, Semliki forest virus E1 protein and Sindbis E1 protein.
- Aspect T-40: Derivative according to any of aspects T-34, T-36 and T-38, wherein said trimer of hairpins comprises an α-helical coiled coil and β-structures.
- Aspect T-41: Derivative according to aspect T-40, wherein said fusion protein is chosen from the group consisting of vesicular stomatitis virus G protein, Rabies virus G protein and Herpes simplex virus gB protein.

- Aspect T-42: Derivative according to aspect T-41, wherein said fusion protein is Rabies virus G protein.
- Aspect T-43: Derivative according to any of aspects T-21 to T-42, wherein said derivative is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect T-44: Derivative according to aspect T-43, wherein said derivative is directed against and/or can specifically bind to the pre-fusion conformational state and/or the intermediate conformational state of said fusion protein.
- Aspect T-45: Derivative according to aspect T-43, wherein said derivative is directed against and/or can specifically bind to the intermediate conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect T-46: Derivative according to aspect T-43, wherein said derivative is directed against and/or can specifically bind to the pre-fusion conformational state and/or the post-fusion conformational state of said fusion protein.
- Aspect T-47: Derivative according to any of aspects T-22 to T-46, wherein said epitope is located in a cavity or cleft formed by said trimer according to claims T-22 to T-27 and T-33 to T-42 or formed by said dimer according to aspects T-28 to T-32.
- Aspect T-48: Derivative according to any of aspects T-22 to T-47, wherein said epitope is located in the stem region of said fusion protein.
- Aspect T-49: Derivative according to aspect T-48, wherein said epitope that is located in the stem region of said fusion protein is chosen from the group consisting of an epitope that is located in the region comprising one or more of the amino acids 318 to 322 of the HA1 subunit of influenza HA and/or the region comprising one or more of the amino acids 47 to 58 of the HA2 subunit of influenza HA, an epitope that is located in the N-terminal region comprising one or more of the amino acids 1 to 38 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 38 to 112 of the HA2 subunit of influenza HA, an epitope that is located in the region comprising one or more of the amino acids 125 to 175 of the HA2 subunit of influenza HA and an epitope that is located in the region comprising one or more of the amino acids 176 to 185 of the HA2 subunit of influenza HA.
- Aspect T-50: Derivative according to any of aspects T-22 to T-47, wherein said epitope is located in the neck region of said fusion protein.
- Aspect T-51: Derivative according to any of aspects T-22 to T-47, wherein said epitope is located in the globular head region of said fusion protein.
- Aspect T-52: Derivative according to aspect T-51, wherein said globular head region comprises a β-barrel-type structure.
- Aspect T-53: Derivative according to aspect T-51, wherein said globular head region comprises an immunoglobulin-type β-sandwich domain and a β-sheet domain.

- Aspect T-54: Derivative according to any of aspects T-2 to T-53, wherein said epitope is chosen from the group consisting of an epitope that is located in the region comprising the A-antigenic site and/or amino acids 255 to 280 of the F-protein of RSV virus, an epitope that is located in the region comprising the Fla site and/or the region comprising amino acid 389 of the F-protein of RSV virus, an epitope that is located in the region comprising amino acids 422 to 438 of the F-protein of RSV virus, an epitope that is located in the region comprising the sialic acid binding site of the H5 HA envelope protein of influenza virus, an epitope that is located in the region comprising the Nicotinic Acetylcholine Receptor (AchR) and/or the Nueral Cell Adhesion Molecule (NCAM) binding site of the G-protein of rabies virus, an epitope that is located in the C-terminal region of a fusion protein, an epitope that is located in the N-terminal domain of a fusion protein, an epitope that is located in or comprises the fusion peptide of a fusion protein, an epitope that is located in the transmembrane domain of a fusion protein, an epitope that is located in a α-helical coiled-coil of a fusion protein, an epitope that is located in a β-structure of a fusion protein, an epitope that is located in Domain I of a fusion protein, an epitope that is located in Domain II of a fusion protein and an epitope that is located in Domain III of a fusion protein.
- Aspect T-55: Derivative according to aspect T-54, wherein said epitope that is located in Domain II of a fusion protein is an epitope that is located in the fusion peptide of Domain II of a fusion protein.
- Aspect T-56: Derivative according to aspect T-54, wherein said epitope that is located in Domain III of a fusion protein is chosen from the group consisting of an epitope that is located in the stem region at the C-terminus of Domain III of a fusion protein and an epitope that is located in the transmembrane anchor at the C-terminus of Domain III of a fusion protein.
- Aspect T-57: Derivative according to any of aspects T-2 to T-56, wherein said virus is chosen from the group consisting of a DNA virus, an RNA virus and a Reverse Transcriptase (RT) virus.
- Aspect T-58: Derivative according to aspect T-57, wherein said DNA virus is chosen from the group consisting of a ds DNA virus and a ssDNA virus.
- Aspect T-59: Derivative according to aspect T-57, wherein said RNA virus is chosen from the group consisting of a dsRNA virus, a positive-sense ssRNA virus and a negative-sense ssRNA virus.
- Aspect T-60: Derivative according to aspect T-57, wherein said Reverse Transcriptase (RT) virus is chosen from the group consisting of a dsDNA-RT virus and a ssRNA-RT virus.
- Aspect T-61: Derivative according to any of aspects T-2 to T-60, wherein said virus belongs to a viral family chosen from the group consisting of Orthomyxoviridae, Paramyxoviridae, Filoviridae, Retroviridae, Coronaviridae, Togaviridae and

Flaviviridae, Rhabdoviridae, Herpesviridae, Arenaviridae, Bornaviridae, Bunyaviridae, Hepadnaviridae and Poxviridae.

- Aspect T-62: Derivative according to aspect T-61, wherein said virus belongs to a viral genus chosen from the group consisting of Alphaviruses and Flaviviruses.
- Aspect T-63: Derivative according to any of aspects T-2 to T-62, wherein said derivative neutralizes said virus.
- Aspect T-64: Derivative according to any of aspects T-2 to T-63, wherein said derivative modulates the infectivity of said virus.
- Aspect T-65: Derivative according to aspect T-64, wherein said derivative inhibits and/or prevents the infectivity of said virus.
- Aspect T-66: Derivative according to any of aspects T-64 or T-65, wherein said derivative neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the pre-entry stage.
- Aspect T-67: Derivative according to aspect T-66, wherein said derivative modulates, inhibits and/or prevents viral entry in a target host cell.
- Aspect T-68: Derivative according to any of aspects T-2 to T-67, wherein said derivative induces virion aggregation of said virus.
- Aspect T-69: Derivative according to any of aspects T-2 to T-68, wherein said derivative destabilizes the virion structure of said virus.
- Aspect T-70: Derivative according to any of aspects T-2 to T-69, wherein said derivative inhibits virion attachment to a target host cell of said virus.
- Aspect T-71: Derivative according to aspect T-70 wherein said derivative inhibits virion attachment to a target host cell of said virus by modulating the interaction between said envelope protein and a viral receptor.
- Aspect T-72: Derivative according to aspects T-70 or T-71, wherein said derivative inhibits virion attachment to a target host cell of said virus by inhibiting and/or preventing the interaction between said envelope protein and a viral receptor.
- Aspect T-73: Derivative according to aspects T-70 to T-72, wherein said derivative competes with said envelope protein for binding to a viral receptor.
- Aspect T-74: Derivative according to any of aspects T-2 to T-73, wherein said derivative inhibits fusion of said virus with a target host cell of said virus.
- Aspect T-75: Derivative according to aspect T-74, wherein fusion of said virus with a target host cell of said virus taking place at the target host cell membrane is inhibited.
- Aspect T-76: Derivative according to aspect T-74, wherein fusion of said virus with a target host cell of said virus taking place within an endosomal or lysosomal compartment is inhibited.
- Aspect T-77: Derivative according to any of aspects T-74 to T-76, wherein said derivative prevents said envelope protein of a virus from undergoing a conformational change.
- Aspect T-78: Derivative according to any of aspects T-64 or T-65, wherein said

derivative neutralizes said virus and/or modulates, inhibits and/or prevents the infectivity of said virus in the post-entry stage.

- Aspect T-79: Derivative according to any of aspects T-2 to T-78, wherein said derivative modulates, inhibits and/or prevents viral replication in a target host cell.
- Aspect T-80: Derivative according to any of aspects T-2 to T-79, wherein said derivative affects, inhibits and/or prevents transcription and/or translation of the viral genome.
- Aspect T-81: Derivative according to any of aspects T-2 to T-80, wherein said derivative affects, inhibits and/or prevents viral packaging and/or the formation of functional virions.
- Aspect T-82: Derivative according to any of aspects T-2 to T-81, wherein said derivative reduces, inhibits and/or prevents budding or release of nascent virions from a target host cell surface.
- Aspect T-83: Derivative according to any of aspects T-2 to T-82, wherein said derivative is directed against and/or can specifically bind to at least two epitopes of an envelope protein of a virus.
- Aspect T-84: Derivative according to aspect T-83, wherein said derivative is directed against and/or can specifically bind to at least two epitopes of one envelope protein of a virus.
- Aspect T-85: Derivative according to any of aspects T-2 to T-83, wherein said derivative is directed against and/or can specifically bind to at least two epitopes of at least two envelope proteins of a virus.
- Aspect T-86: Derivative according to any of aspects T-2 to T-83 and T-85, wherein said derivative is directed against and/or can specifically bind to three or more epitopes of said envelope protein of a virus.
- Aspect T-87: Derivative according to aspect T-86, wherein said derivative is directed against and/or can specifically bind to three or more epitopes of at least two envelope proteins of a virus.
- Aspect T-88: Derivative according to any of aspects T-83 to T-87, wherein said at least two or three or more epitopes are the same or are different.
- Aspect T-89: Derivative according to any of aspects T-85 or T-87, wherein said at least two envelope proteins are the same or are different.
- Aspect T-90: Derivative according to any of aspects T-2 to T-89, that can specifically bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect T-91: Derivative according to any of aspects T-2 to T-90, that can specifically bind to an envelope protein of a virus with a rate of association (k_{on}-rate) of between $10^2\,M^{-1}s^{-1}$ to about $10^7\,M^{-1}s^{-1}$, preferably between $10^3\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, more preferably between $10^4\,M^{-1}s^{-1}$ and $10^7\,M^{-1}s^{-1}$, such as between $10^5\,M^{-1}s^{-1}$ and 10^7

$M^{-1}s^{-1}$.

- Aspect T-92: Derivative according to any of aspects T-2 to T-91, that can specifically bind to an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1} preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.
- Aspect T-93: Derivative of a compound or construct according to any of aspects L-1 to L-262 or a polypeptide according to any of aspects K-1 to K-19.
- Aspect T-94: Derivative according to aspect T-93, that can specifically bind to an envelope protein of a virus.
- Aspect T-95: Derivative according to any of aspects T-93 to T-94, that can specifically bind to an envelope protein of a virus with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter.
- Aspect T-96: Derivative according to any of aspects T-93 to T-95, that can specifically bind to an envelope protein of a virus with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$.
- Aspect T-97: Derivative according to any of aspects T-93 to T-96, that can specifically bind to an envelope protein of a virus with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1} preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.
- Aspect T-98: Derivative according to any of aspects T-1 to T-97, that has a serum half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262 per se, or monovalent construct according to any of aspects G-1 to G-32 per se, respectively.
- Aspect T-99: Derivative according to any of aspects T-1 to T-98, that has a serum half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence according to any of aspects A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47 per se, NANOBODY® (V_{HH} sequence) according to any of aspects H-1 to H-137 per se, polypeptide according to any of aspects K-1 to K-19, compound or construct according to any of aspects L-1 to L-262 per se, or monovalent construct according to any of aspects G-1 to G-32 per se, respectively.

- Aspect T-100: Derivative according to any of aspects T-1 to T-99, that has a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more; for example, at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).
- Aspect T-101: Derivative according to any of aspects T-1 to T-100, that is a pegylated derivative.
- Aspect T-102: Compound or construct, that comprises or essentially consists of one or more derivatives according to any of aspects T-1 to T-101, and optionally further comprises one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers.
- Aspect T-103: Compound or construct according to aspect T-102, in which said one or more other groups, residues, moieties or binding units are amino acid sequences.
- Aspect T-104: Compound or construct according to aspects T-102 or T-103, in which said one or more linkers, if present, are one or more amino acid sequences.
- Aspect T-105: Nucleic acid or nucleotide sequence, that encodes a derivative according to any of aspects T-1 to T-101 or a compound or construct according to any of aspects T-102 to T-104.
- Aspect T-106: Composition, comprising at least one derivative according to any of aspects T-1 to T-101, compound or construct according to any of aspects T-102 to T-104, or nucleic acid or nucleotide sequence according to aspect T-105.
- Aspect U-1: A method for administering an effective amount of an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32, directed against an envelope protein of a virus (such as an envelope protein of RSV virus, an envelope protein of influenza virus and/or an envelope protein of rabies virus) and/or a composition comprising the same, wherein said method comprises the step of administering the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262, the monovalent construct according to any of claims G-1 to G-32 and/or the composition comprising the same to the pulmonary tissue.
- Aspect U-2: The method according to aspect U-1, wherein the amino acid sequence

according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262, the monovalent construct according to any of claims G-1 to G-32 and/or the composition comprising the same is administered by use of an inhaler or intranasal delivery device or aerosol.

- Aspect U-3: Method according to any of aspects U-1 or U-2, wherein at least 5%, preferably at least 10%, 20%, 30%, 40%, more preferably at least 50%, 60%, 70%, and even more preferably at least 80% or more of the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262, the monovalent construct according to any of claims G-1 to G-32 and/or the composition comprising the same is stable in the pulmonary tissue for at least 24 hours, preferably at least 48 hours more preferably at least 72 hours.
- Aspect U-4: Method according to any of aspects U-1 to U-3, wherein the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262, the monovalent construct according to any of claims G-1 to G-32 and/or the composition comprising the same are applied in pure form, i.e., when they are liquids or a dry powder.
- Aspect U-5: Method according to any of aspects U-1 to U-3, wherein the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262, the monovalent construct according to any of claims G-1 to G-32 and/or the composition comprising the same are administered to the pulmonary tissue as composition or formulation comprising an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32 and a carrier suitable for pulmonary delivery.
- Aspect U-6: Pharmaceutical composition comprising an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or

construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32 and a carrier suitable for pulmonary delivery.

- Aspect U-7: Pharmaceutical device suitable for the pulmonary delivery of an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32 and/or suitable in the use of a composition comprising the same.
- Aspect U-8: Pharmaceutical device according to aspect U-7 that is an inhaler for liquids (e.g. a suspension of fine solid particles or droplets) comprising the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262 and/or the monovalent construct according to any of claims G-1 to G-32.
- Aspect U-9: Pharmaceutical device according to aspect U-7 that is an aerosol comprising the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262 and/or the monovalent construct according to any of claims G-1 to G-32.
- Aspect U-10: Pharmaceutical device according to aspect U-7 that is a dry powder inhaler comprising the amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, the NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, the polypeptide according to any of claims K-1 to K-19, the compound or construct according to any of claims L-1 to L-262 and/or the monovalent construct according to any of claims G-1 to G-32 in the form of a dry powder.
- Aspect U-11: Method for the prevention and/or treatment of at least one viral disease, said method comprising administering to the pulmonary tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32 and/or of a pharmaceutical composition comprising the same.
- Aspect U-12: Method for the prevention and/or treatment of infection by RSV, influenza and/or rabies, said method comprising administering to the pulmonary

tissue of a subject in need thereof, a pharmaceutically active amount of an amino acid sequence according to any of claims A-1 to A-109, B-1 to B-28, C-1 to C-16, D-1 to D-6, E-1 to E-14 and/or F-1 to F-47, a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, a polypeptide according to any of claims K-1 to K-19, a compound or construct according to any of claims L-1 to L-262 and/or a monovalent construct according to any of claims G-1 to G-32, and/or of a pharmaceutical composition comprising the same.

- Aspect V-1: Method for the prevention and/or treatment of viral infection (such as e.g. infection by RSV, influenza or rabies), said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the same.
- Aspect V-2: Use of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the same for binding and/or neutralization of virus.
- Aspect V-3: Use of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the same for binding and/or neutralization different genotypes of a virus.
- Aspect V-4: Use of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the

same for binding and/or neutralization of different subtypes of a virus.

- Aspect V-5: Use of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the same for binding and/or neutralization of different strains of a virus.
- Aspect V-6: Use of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) amino acid sequence of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) NANOBODY® (V_{HH} sequence) of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) polypeptide of the invention, of a multivalent (e.g. trivalent, bivalent, triparatopic, biparatopic, trivalent biparatopic) compound or construct of the invention, and/or of a pharmaceutical composition comprising the same for binding and/or neutralization of one or more escape mutants of a virus.
- Aspect V-7: Method or use according to any of aspects V-1 to V-6, wherein the multivalent amino acid sequence, the multivalent NANOBODY® (V_{HH} sequence), the multivalent polypeptide, and/or the multivalent compound or construct is bivalent.
- Aspect V-8: Method or use according to any of aspects V-1 to V-7, wherein the multivalent amino acid sequence, the multivalent NANOBODY® (V_{HH} sequence), the multivalent polypeptide, and/or the multivalent compound or construct is biparatopic.
- Aspect V-9: Method or use according to any of aspects V-1 to V-6, wherein the multivalent amino acid sequence, the multivalent NANOBODY® (V_{HH} sequence), the multivalent polypeptide, and/or the multivalent compound or construct is trivalent.
- Aspect V-10: Method or use according to any of aspects V-1 to V-6 and/or V-9, wherein the multivalent amino acid sequence, the multivalent NANOBODY® (V_{HH} sequence), the multivalent polypeptide, and/or the multivalent compound or construct is triparatopic.
- Aspect V-11: Method or use according to any of aspects V-1 to V-10, wherein said multivalent amino acid sequence, multivalent NANOBODY® (V_{HH} sequence), multivalent polypeptide, multivalent compound or construct and/or pharmaceutical composition comprising the same is administered according to any of the methods of claims U-1 to U-5 and/or U-11 to U-12.
- Aspect V-12: Method for the prevention and/or treatment of infection by RSV virus, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent compound or construct according to any of aspects L-9 to L-262 and/or of a pharmaceutical composition comprising the

same.

- Aspect V-13: Method according to aspect V-12 wherein the multivalent compound or construct is selected from Table A-2 (SEQ ID NO's: 2382 to 2415 and 3584 to 3587) Table A-5 (SEQ ID NO's: 2641 to 2659 and 2978 to 2988), Table A-9 (SEQ ID NO's: 2996 to 2998) or Table A-10 (SEQ ID NO's: 3016 to 3056 and 3588 to 3591).
- Aspect V-14: Method according to any of aspects V-12 or V-13, wherein infection by one or more RSV escape mutants is treated.
- Aspect V-15: Method according to aspect V-14, wherein the escape mutant is an escape mutant specific for antigenic site II.
- Aspect V-16: Method according to aspect V-14, wherein the escape mutant is an escape mutant specific for antigenic site IV-VI.
- Aspect V-17: Method according to aspect V-14, wherein the escape mutant is an escape mutant specific for antigenic site II and for antigenic site IV-VI.
- Aspect V-18: Use of a multivalent compound or construct according to any of aspects L-9 to L-262, and/or of a pharmaceutical composition comprising the same for binding and/or neutralization one or more different escape mutants of RSV.
- Aspect V-19: Use according to claim V-18 wherein the escape mutant is an escape mutant specific for antigenic site II.
- Aspect V-20: Use according to claim V-18 wherein the escape mutant is an escape mutant specific for antigenic site IV-VI.
- Aspect V-21: Use according to claim V-18 wherein the escape mutant is an escape mutant specific for antigenic site II and antigenic site IV-VI.
- Aspect V-22: Method according to any of aspects V-12 or V-13, wherein infection by one or more strains of RSV is treated.
- Aspect V-23: Method according to aspect V-22, wherein the RSV strain is Long.
- Aspect V-24: Method according to aspect V-22, wherein the RSV strain is A-2.
- Aspect V-25: Method according to aspect V-22, wherein the RSV strain is B-1.
- Aspect V-26: Method according to any of aspects V-12 to V-13, wherein the multivalent compound or constructs binds and/or neutralizes RSV strain Long and A-2.
- Aspect V-27: Method according to any of aspects V-12 to V-13, wherein the multivalent compound or constructs binds and/or neutralizes RSV strain Long and B-1.
- Aspect V-28: Method according to any of aspects V-12 to V-13, wherein the multivalent compound or constructs binds and/or neutralizes RSV strain B-1 and A-2.
- Aspect V-29: Method according to any of aspects V-12 to V-13, wherein the multivalent compound or constructs binds and/or neutralizes RSV strain Long, A-2 and B-1.
- Aspect V-30: Use of a multivalent compound or construct according to any of aspects L-9 to L-262, and/or of a pharmaceutical composition comprising the same for

binding and/or neutralization different strains of RSV.

- Aspect V-31: Use according to aspect V-30, wherein the strains of RSV are Long and A-2.
- Aspect V-32: Use according to aspect V-30, wherein the strains of RSV are Long and B-1.
- Aspect V-33: Use according to aspect V-30, wherein the strains of RSV are A-1 and B-1.
- Aspect V-34: Use according to aspect V-30, wherein the strains of RSV are Long, A-2 and B-1.
- Aspect V-35: Method for the prevention and/or treatment of infection by influenza, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a NANOBODY® (V_{HH} sequence) according to any of claims H-1 to H-137, or a multivalent compound or construct according to any of aspects L-9 to L-262, and/or of a pharmaceutical composition comprising the same.
- Aspect V-36: Method according to aspect V-35, wherein the multivalent compound or construct is selected from Table A-4 (SEQ ID NO's: 2423 to 2426 and 2428 to 2430).
- Aspect V-37: Method according to any of aspects V-35 or V-36, wherein said NANOBODY® (V_{HH} sequence) is 202-C8 (SEQ ID NO: 138).
- Aspect V-38: Method according to any of aspects V-35 or V-36, wherein said compound or construct is bivalent.
- Aspect V-39: Method according to aspect V-38, wherein said compound or construct is a bivalent 202-C8 NANOBODY® (V_{HH} sequence).
- Aspect V-40: Method according to aspect V-39, wherein said compound or construct is selected from SEQ ID NO's: 2423 and 2424.
- Aspect V-41: Method according to any of aspects V-35 or V-36, wherein said compound or construct is trivalent.
- Aspect V-42: Method according to aspect V-41, wherein said compound or construct is a trivalent 202-C8 NANOBODY® (V_{HH} sequence).
- Aspect V-43: Method according to aspect V-42, wherein said compound or construct is selected from SEQ ID NO's: 2425 and 2426.
- Aspect V-44: Method according to any of aspects V-35 or V-36, wherein said compound or construct is biparatopic.
- Aspect V-45: Method according to any of aspects V-35 or V-36, wherein said compound or construct is trivalent biparatopic.
- Aspect V-46: Method according to any of aspects V-35 or V-36, wherein said compound or construct is triparatopic.
- Aspect V-47: Method according to any of aspects V-35 or V-36, wherein said compound or construct is trivalent triparatopic.
- Aspect V-48: Method according to any of aspects V-35 or V-36, wherein infection by one or more influenza subtypes is treated.

- Aspect V-49: Method according to aspect V-48, wherein the influenza subtype is H5N1.
- Aspect V-50: Method according to aspect V-48, wherein the influenza subtype is H1N1.
- Aspect V-51: Method according to aspect V-50, wherein the influenza subtype causes swine flu (also referred to as Mexican flu).
- Aspect V-52: Method according to aspect V-48, wherein the influenza subtype is H3N2.
- Aspect V-53: Method according to any of aspects V-35 to V-52, wherein the multivalent compound or constructs binds and/or neutralizes H5N1 and H1N1.
- Aspect V-54: Method according to any of aspects V-35 to V-52, wherein the multivalent compound or constructs binds and/or neutralizes H5N1 and H3N2.
- Aspect V-55: Method according to any of aspects V-35 to V-52, wherein the multivalent compound or constructs binds and/or neutralizes H1N1 and H3N2.
- Aspect V-56: Method according to any of aspects V-35 to V-52, wherein the multivalent compound or constructs binds and/or neutralizes H5N1, H1N1 and H3N2.
- Aspect V-57: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing different subtypes of influenza virus.
- Aspect V-58: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing influenza subtype H5N1 as well as influenza subtype H1N1.
- Aspect V-59: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing influenza subtype H5N1 as well as influenza subtype H3N2.
- Aspect V-60: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing influenza subtype H3N2 as well as influenza subtype H1N1.
- Aspect V-61: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing influenza subtype H5N1, influenza subtype H3N2 as well as influenza subtype H1N1.
- Aspect V-62: Method for the prevention and/or treatment of infection by rabies, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a multivalent compound or construct according to any of aspects L-9 to L-262, and/or of a pharmaceutical composition comprising the same.
- Aspect V-63: Method according to aspect V-62, wherein the multivalent compound or construct is selected from Table A-6 (SEQ ID NO's: 2427 and 2663 to 2681).
- Aspect V-64: Method according to any of aspects V-62 or V-63, wherein infection by one or more rabies genotypes is treated.
- Aspect V-65: Method according to aspect V-64, wherein rabies genotype 1 is treated.

- Aspect V-66: Method according to aspect V-64, wherein rabies genotype 5 is treated.
- Aspect V-67: Method according to any of aspects V-62 to V-66, wherein the multivalent compound or constructs binds and/or neutralizes rabies genotypes 1 and 5.
- Aspect V-68: Use of a multivalent compound or constructs according to any of aspects L-9 to L-262 for binding and/or neutralizing different genotypes of rabies virus.
- Aspect V-69: Use according to claim V-68, wherein the rabies virus genotypes are 1 and 5.
- Aspect W-1: Compound or construct that comprises an Fc portion of an immunoglobulin and one or more NANOBODIES® (V_{HH} sequences) coupled at each side of the Fc portion.
- Aspect W-2: Compound or construct according to aspect W-1, wherein one NANOBODY® (V_{HH} sequence) is coupled at each side of the Fc portion.
- Aspect W-3: Compound or construct according to aspect W-1, wherein two NANOBODIES® (V_{HH} sequences) are coupled at each side of the Fc portion.
- Aspect W-4: Compound or construct according to aspect W-1, wherein one NANOBODY® (V_{HH} sequence) is coupled at one side of the Fc portion and two NANOBODIES® (V_{HH} sequences) are coupled at the other side of the Fc portion.
- Aspect W-5: Compound or construct according to any of aspects W-1 to W-4, wherein the Fc portion is derived from an immunoglobulin selected from IgG1, IgG2, IgGA, IgM and IgE.
- Aspect W-6: Compound or construct according to any of aspects W-1 to W-5, wherein the NANOBODIES® (V_{HH} sequences) are coupled to the Fc portion via a suitable linker.
- Aspect W-7: Compound or construct according to aspect W-6, wherein the linker is a hinge linker.
- Aspect W-8: Compound or construct according to any of aspects W-1 to W-7, which has a structure as depicted in FIG. 59.
- Aspect W-9: Polypeptide chain construct comprising two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a “first” NANOBODY® (V_{HH} sequence) (5) and a “second” NANOBODY® (V_{HH} sequence) (6), wherein the first NANOBODY® (V_{HH} sequence) (5) is linked, optionally via a suitable linker or hinge region (7) to the constant domain (3) and wherein the second NANOBODY® (V_{HH} sequence) (6) is linked, optionally via a suitable linker or hinge region (8) to the constant domain (4).
- Aspect W-10: Construct according to any of aspects W-8 or W-9, wherein the NANOBODIES® (V_{HH} sequences) in each polypeptide chain are directed against the same target, antigen, antigenic determinant or epitope.
- Aspect W-11: Construct according to any of aspects W-8 or W-9, wherein the NANOBODIES® (V_{HH} sequences) in each polypeptide chain are directed against a

different target, antigen, antigenic determinant or epitope.

- Aspect W-12: Compound or construct according to any of aspects W-1 to W-7, which has a structure as depicted in FIG. 62.
- Aspect W-13: Polypeptide chain construct comprising two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" NANOBODY® (V_{HH} sequence) (5), a "second" NANOBODY® (V_{HH} sequence) (6), a "third" NANOBODY® (V_{HH} sequence) (10) and a "fourth" single NANOBODY® (V_{HH} sequence) (13), wherein the first NANOBODY® (V_{HH} sequence) (5) is linked, optionally via a suitable linker (7), to the second NANOBODY® (V_{HH} sequence) (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8); and wherein the third NANOBODY® (V_{HH} sequence) (10) is linked, optionally via a suitable linker (12), to the fourth NANOBODY® (V_{HH} sequence) (13), and is also linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14).
- Aspect W-14: Construct according to any of aspects W-12 or W-13, wherein the NANOBODIES® (V_{HH} sequences) in each polypeptide chain are directed against the same target, antigen, antigenic determinant or epitope.
- Aspect W-15: Construct according to any of aspects W-12 or W-13, wherein the NANOBODIES® (V_{HH} sequences) at one side of each polypeptide chain are directed against the same target, antigen, antigenic determinant or epitope and the NANOBODIES® (V_{HH} sequences) at the other side of each polypeptide chain are directed against another target, antigen, antigenic determinant or epitope.
- Aspect W-16: Construct according to any of aspects W-12 or W-13, wherein the NANOBODIES® (V_{HH} sequences) at one side of each polypeptide chain are directed against two different targets, antigens, antigenic determinants or epitopes and the NANOBODIES® (V_{HH} sequences) at the other side of each polypeptide chain are directed against the same two different targets, antigens, antigenic determinants or epitopes.
- Aspect W-17: Compound or construct according to any of aspects W-1 to W-7, which has a structure as depicted in FIG. 63.
- Aspect W-18: Polypeptide chain construct comprising two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" NANOBODY® (V_{HH} sequence) (5), a "second" NANOBODY® (V_{HH} sequence) (6) and a "third" NANOBODY® (V_{HH} sequence) (10), wherein the first NANOBODY® (V_{HH} sequence) (5) is linked, optionally via a suitable linker (7), to the second NANOBODY® (V_{HH} sequence) (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8); and wherein the third NANOBODY® (V_{HH} sequence) (10) is linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14).
- Aspect W-19: Construct according to any of aspects W-17 or W-18, wherein the

NANOBODIES® (V_{HH} sequences) in each polypeptide chain are directed against the same target, antigen, antigenic determinant or epitope.

- Aspect W-20: Construct according to any of aspects W-17 or W-18, wherein the NANOBODIES® (V_{HH} sequences) at one side of each polypeptide chain are directed against the same target, antigen, antigenic determinant or epitope and the NANOBODY® (V_{HH} sequence) at the other side of each polypeptide chain is directed against another target, antigen, antigenic determinant or epitope.
- Aspect W-21: Construct according to any of aspects W-17 or W-18, wherein the NANOBODIES® (V_{HH} sequences) at one side of each polypeptide chain are directed against two different targets, antigens, antigenic determinants or epitopes and the NANOBODY® (V_{HH} sequence) at the other side of each polypeptide chain is directed against another different target, antigen, antigenic determinant or epitope.
- Aspect W-22: Construct according to any of aspects W-17 or W-18, wherein the NANOBODIES® (V_{HH} sequences) at one side of each polypeptide chain are directed against two different targets, antigens, antigenic determinants or epitopes and the NANOBODY® (V_{HH} sequence) at the other side of each polypeptide chain is directed against one of these two targets, antigens, antigenic determinants or epitopes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Competition of NANOBODIES® (V_{HH} sequences) of the invention with Synagis® for binding to the F-protein of hRSV. 20 μl periplasmic fractions binding hRSV F_{TM-} were incubated with 100 ng/ml Synagis®, as described in Example 7. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (Synagis®+ahFcHRP).

FIG. 2: Competition of NANOBODIES® (V_{HH} sequences) of the invention with VN04-2 for binding to the hemagglutinin of influenza H5N1. 20 μl periplasmic fractions were incubated with 100 ng/ml VN04-2, as described in Example 7. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (VN04-2).

FIG. 3: Competition of NANOBODIES® (V_{HH} sequences) of the invention with IgG2a for binding to the G-protein of rabies. Dilution of periplasmic fractions binding rabies G protein were incubated with mouse IgG2a monoclonal (mab) (dilution $1/10^6$), as described in Example 7. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (Mab+DAMPO).

FIG. 4: Binding assay with a dilution series of purified anti-hRSV F protein NANOBODIES® (V_{HH} sequences).

FIG. 5: Binding assay with a dilution series of purified anti-H5 HA Nanobodies.

FIG. 6: Competition of purified NANOBODIES® (V_{HH} sequences) of the invention with Synagis® for binding to the F-protein of hRSV. Dilution series of NANOBODIES® (V_{HH} sequences) binding 1.4 nM hRSV F_{TM-} compete with 0.67 nM Synagis®, as described in Example 8. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (Synagis®). Bars indicate Standard Deviation from duplicates.

FIG. 7: Competition of purified NANOBODIES® (V_{HH} sequences) of the invention with VN04-2 for binding to the hemagglutinin of influenza H5N1. Dilution series of NANOBODIES® (V_{HH} sequences) binding H5 HA competing with 0.67 nM VN04-2, as described in Example 8. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (VN04-2+DAMPO).

FIG. 8: hRSV F_{TM-} protein with Site II (binding site Synagis®; residues 255-280) and Site IV-VI (binding site 101F; residues 422-438).

FIG. 9: Competition of NANOBODIES® (V_{HH} sequences) of the invention with 9C5 for binding to the F-protein of hRSV. 20 ul periplasmic fractions binding hRSV F_{TM}-compete with 100 ng/ml 9C5, as described in Example 11. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (9C5+Rampo).

FIG. 10: Competition of NANOBODIES® (V_{HH} sequences) of the invention with 101F Fab for binding to the F-protein of hRSV. NANOBODIES® (V_{HH} sequences) binding hRSV F_{TM}-compete with 3 nM 101F Fab, as described in Example 11. 101 Fab was detected using an anti-HA-HRP. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence).

FIG. 11: Competition of NANOBODIES® (V_{HH} sequences) of the invention with fetuin for binding to the hemagglutinin of influenza H5N1. 10 μl periplasmic fractions compete with fetuin for binding to 0.7 μg/ml HA-bio, as described in Example 13. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (HA-bio+strep).

FIG. 12: Dendrogram of isolated hRSV binding NANOBODIES® (V_{HH} sequences). Nine families of hRSV binding NANOBODIES® (V_{HH} sequences) could be distinguished:

Family 1 comprises the following NANOBODIES® (V_{HH} sequences): 192-C10, 206-11H, 206-12F

Family 2 comprises the following NANOBODIES® (V_{HH} sequences): 192-A8, 206-10F,

206-11D, 206-7E, 207-9G

Family 3 comprises the following NANOBODIES® (V_{HH} sequences): 192-C4, 206-6A, 206-5A, 206-3A, 206-3D, 206-4G, 192-F2, 206-4D, 192-C6, 192-H2, 206-5E, 206-2A, 207-5D, 206-3E, 206-2G, 206-2H, 206-3C, 191-D3, 206-2F, 207-6B, 206-3F, 207-1D

Family 4 comprises the following NANOBODIES® (V_{HH} sequences): 191-B9, 207-9A, 207-9B, 207-9H, 206-10C, 206-10D, 192-D3, 206-10B, 207-9D, 207-11D, 207-11E, 206-10E, 191-E4, 207-1C, 207-1F, 207-5C, 207-1E, 207-4D, 206-2E, 206-7H, 207-11F, 207-9F, 207-11H, 192-B1, 206-3B, 207-11B, 207-4H, 192-H1, 206-6D, 206-7B, 207-11A, 207-11A, 207-5B, 207-4A, 207-4B, 207-6A, 207-6D, 207-1B, 207-5A, 207-6C, 207-5E, 207-6E, 207-6F, 207-11G
Family 5 comprises the following NANOBODIES® (V_{HH} sequences): 207-9C
Family 6 comprises the following NANOBODIES® (V_{HH} sequences): 206-7G
Family 7 comprises the following NANOBODIES® (V_{HH} sequences): 207-9E
Family 8 comprises the following NANOBODIES® (V_{HH} sequences): 206-2C
Family 9 comprises the following NANOBODIES® (V_{HH} sequences): 206-7C

FIG. 13: Dendrogram of CDR3 sequences of isolated hRSV binding NANOBODIES® (V_{HH} sequences).

FIG. 14: Dendrogram of isolated H5 binding NANOBODIES® (V_{HH} sequences). Seven families of H5 binding NANOBODIES® (V_{HH} sequences) could be distinguished:

Family 1 comprises the following NANOBODIES® (V_{HH} sequences): 202-B8

Family 2 comprises the following NANOBODIES® (V_{HH} sequences): 202-D5

Family 3 comprises the following NANOBODIES® (V_{HH} sequences): 202-A10, 202-A12, 202-E6, 202-F8

Family 4 comprises the following NANOBODIES® (V_{HH} sequences): 202-G3

Family 5 comprises the following NANOBODIES® (V_{HH} sequences): 202-C8

Family 6 comprises the following NANOBODIES® (V_{HH} sequences): 202-A5, 202-C2, 202-F3, 202-F4, 202-C1, 202-E5, 202-H2

Family 7 comprises the following NANOBODIES® (V_{HH} sequences): 202-B10, 202-D8, 202-E11, 202-B7, 202-A9, 202-H8, 202-C11, 202-B9, 202-G8, 202-D7, 202-F10, 202-C9, 202-E7, 202-G11, 202-F12, 202-C7

FIG. 15: Dendrogram of CDR3 sequences of isolated H5 binding NANOBODIES® (V_{HH} sequences).

FIG. 16: Dendrogram of isolated rabies binding NANOBODIES® (V_{HH} sequences). Seven families of rabies binding NANOBODIES® (V_{HH} sequences) could be distinguished:

Family 1 comprises the following NANOBODIES® (V_{HH} sequences): 213-B7, 213-D7

Family 2 comprises the following NANOBODIES® (V_{HH} sequences): 213-E6

Family 3 comprises the following NANOBODIES® (V_{HH} sequences): 213-H7

Family 4 comprises the following NANOBODIES® (V_{HH} sequences): 2113-D6, 214-C10

Family 5 comprises the following NANOBODIES® (V_{HH} sequences): 214-A8, 214-E8, 214-H10

Family 6 comprises the following NANOBODIES® (V_{HH} sequences): 214-D10

Family 7 comprises the following NANOBODIES® (V_{HH} sequences): 214-F8

FIG. 17: Dendrogram of CDR3 sequences of isolated rabies binding NANOBODIES® (V_{HH} sequences).

FIG. 18: Microneutralization of RSV Long LM-2 by monovalent NANOBODIES® (V_{HH} sequences) and control Fabs (IC50 values are given in μM) as described in Example 15.

FIG. 19: Competition ELISA: Synagis® Fab competes with purified RSV binding NANOBODIES® (V_{HH} sequences) for binding to F_{TM}- protein as described in Example 22.

FIG. 20: Binding of monovalent, bivalent and trivalent NANOBODIES® (V_{HH} sequences) to F_{TM}- protein as described in Example 24.

FIGS. 21A and B: Potency of monovalent, bivalent and trivalent constructs to neutralize Long and B-1 RSV strains as described in Example 25.

FIG. 22: Neutralization of RSV Long by bivalent 191D3 NANOBODIES® (V_{HH} sequences) with different linker lengths as described in Example 25.

FIG. 23: Neutralization of RSV Long by biparatopic NANOBODIES® (V_{HH} sequences) of 191D3 (antigenic site II) and 191E4 (antigenic site IV-VI) as described in Example 26: effect of orientation and linker lengths.

FIG. 24: Neutralization of virus in vivo by NANOBODY® (V_{HH} sequence) RSV101. Bivalent NANOBODY® (V_{HH} sequence) 191-D3 (RSV101), bivalent NANOBODY® (V_{HH} sequence) 12D2biv, palivisumab and PBS only were inoculated intranasally into mice and 4 hours later challenged with RSV A2 strain as described in Example 29. Infectious virus (pfu/lung) present in lung homogenates 3 (FIG. 24A) and 5 (FIG. 24B) days after viral challenge and

the mean (FIG. 24C) infectious virus (pfu/lung) for the 5 mice are given.

FIG. 25: Presence of NANOBODY® (V_{HH} sequence) RSV101 3 (FIG. 25A) and 5 (FIG. 25B) days following intranasal inoculation in mice. Lung homogenates of PBS treated mice were pre-incubated with lung homogenate from RSV101 treated mice, 12D2biv treated mice and palivisumab treated mice as described in Example 30.

FIGS. 26A and B: Virus neutralizing titers of llama serum after immunization with hemaglutinin as described in Example 33.

FIG. 27A: Binding assay with a dilution series of purified anti-H5 HA NANOBODIES® (V_{HH} sequences).

FIG. 27B: Competition of purified NANOBODIES® (V_{HH} sequences) with fetuin for binding to hemaglutinin as described in Example 13.

FIG. 28: Neutralization of HA pseudotyped virus by a single 10 fold dilution of different NANOBODIES® (V_{HH} sequences) as described in Example 34.

FIG. 29: Neutralization of HA pseudotyped virus by NANOBODY® (V_{HH} sequence) 203-B12 and 203-H9 as described in Example 34.

FIG. 30: Neutralization of HA pseudotyped virus by combinations of NANOBODIES® (V_{HH} sequences) 202-C8, 203-H9 and 203-B12 as described in Example 35.

FIG. 31: Potency of monovalent, bivalent and trivalent NANOBODY® (V_{HH} sequence) constructs to neutralize HA pseudotyped virus as described in Example 36.

FIG. 32: Intranasal delivery of NANOBODY® (V_{HH} sequence) 202-C8 protects against infection and replication of mouse-adapted NIBRG-14 virus as described in Example 38.

FIG. 33: Kinetic sensogram showing the binding capacity for the neutralizing NANOBODIES® (V_{HH} sequences) 202-C8, 203-B12 and 203-H9.

FIG. 34: Binding assay (ELISA) with a dilution series of purified multivalent anti-H5 HA NANOBODIES® (V_{HH} sequences) as described in Example 40.

FIG. 35: Competition of purified multivalent NANOBODIES® (V_{HH} sequences) with fetuin for binding to the hemagglutinin (H5) as described in Example 41.

FIG. 36: Individual observed plasma concentration-time plot of RSV NB2, ALX-0081, and RANKL008a after a single i.v. bolus dose of RSV NB2 (4 mg/kg), ALX-0081 (5 mg/kg) and RANKL008a (5 mg/kg), respectively to male Wistar rats.

FIG. 37: Individual (i.v.) and mean (i.t.) observed plasma concentration-time plot of RSV

NB2 (i.v. 4 mg/kg; i.t. 3.6 mg/kg and adjustment to 4 mg/kg).

FIG. 38: Individual (i.v.) and mean (i.t.) observed plasma concentration-time plot of ALX-0081 (i.v. 5 mg/kg; i.t. 3.1 mg/kg and adjustment to 5 mg/kg).

FIG. 39: Individual (i.v.) and mean (i.t.) observed plasma concentration-time plot of RANKL008a (i.v. 5 mg/kg; i.t. 3.2 mg/kg and adjustment to 5 mg/kg).

FIG. 40: Mean (+SD) observed BALF concentration-time profiles of RSV NB2, ALX-0081, and RANKL008a after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008a (3.2 mg/kg) to male rats.

FIG. 41: Pulmonary delivered NANOBODIES® (V_{HH} sequences) are stable in the lung for at least 24 hrs post-administration.

FIG. 42: Bioavailability in plasma of pulmonary administered vs i.v. administered NANOBODIES® (V_{HH} sequences).

FIG. 43: Kaplan Meier curve showing the survival proportion of mice inoculated with a mix of virus and monovalent anti-rabies NANOBODY® (V_{HH} sequence) (212-C12 and 213-E6). Control mice were inoculated with a mix of virus and PBS, mab 8-2 or irrelevant NANOBODY® (V_{HH} sequence) (191-G2=anti-human respiratory syncytial virus).

FIG. 44: Kaplan Meier curve showing the survival proportion of mice inoculated with a mix of virus and bivalent/biparatopic NANOBODY® (V_{HH} sequence). Control mice were inoculated with a mix of virus and mab 8-2 or an irrelevant NANOBODY® (V_{HH} sequence) (191-G2=anti-human respiratory syncytial virus).

FIG. 45: Kaplan Meier curve showing the survival proportion of mice after intranasal administration with NANOBODIES® (V_{HH} sequences) followed by intranasal inoculation of the virulent CVS-11 strain one day later.

FIG. 46: Non-limiting examples of NANOBODY® (V_{HH} sequence) constructs.

FIG. 47A-C: Kaplan Meier curve showing the survival proportion of mice inoculated intranasally with a mix of CVS-11 and 1 IU of NANOBODY® (V_{HH} sequence) or antibody. A dose of 10^3 $TCID_{50}$ was used in the experiment of graph A and a dose of 10^2 $TCID_{50}$ in the experiments of graph B and C.

FIG. 48: Kaplan Meier curve showing the survival proportion of mice inoculated with a mixture of virus and bivalent/biparatopic NANOBODY® (V_{HH} sequence). Control mice were inoculated with a mix of virus and Mab 8-2 or an irrelevant NANOBODY® (V_{HH} sequence) (RSV115; SEQ ID NO: 2367).

FIG. 49: Western blot of lung homogenates of mice after intranasal administration of bivalent NANOBODY® (V_{HH} sequence) RSV101 as described in Example 55. M: Marker; 1: pos control (100 ng NB2biv); 2-6: mice inoculated with NB2biv NANOBODY® (V_{HH} sequence).

FIG. 50: Neutralization assay of RSV Long and the escape mutants R7C2/1; R7C2/11 and R7.936/4 by the monovalent NANOBODIES® (V_{HH} sequences) 7B2 (A), 15H8, (B) NC41 (C) at a concentration range from about 2 μM to 6 nM and the trivalent NANOBODIES® (V_{HH} sequences) RSV 400 (D), RSV404 (E), RSV 407 (F) and RSV 403 (G) at a concentration range of about 20 nM to 100 pM. Curve fitting was only done for data of monovalent NANOBODIES® (V_{HH} sequences).

FIG. 51: Immunofluorescence staining of acetone-fixed brain smears of mice inoculated with $10^{1.5}$ $TCID_{50}$ CVS-11 mixed with an anti-rabies NANOBODY® (V_{HH} sequence) (1 IU 213-E6). Staining was done with an FITC-conjugated anti-nucleoprotein antibody (FAT). A: brain of mouse at 7 DPI with $10^{1.5}$ $TCID_{50}$ CVS-11 mixed with an irrelevant NANOBODY® (V_{HH} sequence) (192-G2); B: brain of mouse at 7 DPI with 10^{15} $TCID_{50}$ CVS-11 mixed with an anti-rabies NANOBODY® (V_{HH} sequence) (1 IU 213-E6).

FIG. 52: Kaplan Meier curve showing the survival proportion of mice inoculated with a mix of 10^2 $TCID_{50}$ virus and the biparatopic NANOBODY® (V_{HH} sequence) 213E6-15GS-213H7 as described in Example 50.4. Control mice were inoculated with a mix of virus and mab RV1C5 or PBS.

FIG. 53: Kaplan Meier curve showing the survival proportion of mice upon intranasal or intracerebral inoculation of 10^2 $TCID_{50}$ CVS-11 mixed with 1 IU 212-C12.

FIG. 54: Demonstration of presence of functional virus-neutralizing NANOBODIES® (V_{HH} sequences) in the lung homogenates of mice as described in Example 30. A: 8 μl lung homogenate; B: 2 μl lung homogenate; C: 0.5 μl lung homogenate; D: 0.125 μl lung homogenate; E: 0.03125 μl lung homogenate; F: 0.0078 μl lung homogenate; G: 0.00019 lung homogenate; H: 0 μl lung homogenate (dilution in PBS). LGB1 is the RSV101 NANOBODY® (V_{HH} sequence) construct. LGB2 is the 12B2biv control NANOBODY® (V_{HH} sequence) construct.

FIG. 55: Western blots of lung homogenates of mice inoculated with NANOBODY® (V_{HH} sequence) RSV101 (A-C) or 12B2biv (D-E). The Western blots were scanned with an Odyssey Infrared Imaging system (Licor Biosciences) and the analyses (determinations of concentrations) were done with the Odyssey v3.0 software. Standards: 50 ng, 20 ng, 10 ng and 5 ng of the same NANOBODY® (V_{HH} sequence) in homogenization buffer; D3: three days after infection; D5: five days after infection; m1-m5: mouse 1-5.

FIG. 56: Screening for NANOBODIES® (V_{HH} sequences) that compete with the monoclonal antibody C179 for binding hemaglutinin H5 of influenza virus as described in Example 57.

FIG. 57A-K: Neutralization of different H5 variants by different multivalent constructs of NANOBODY® (V_{HH} sequence) 202-C8, tested in the lentiviral pseudotyped neutralization assay as described in Example 36. C8 refers to NANOBODY® (V_{HH} sequence) 202-C8; C8Bi(9) refers to the bivalent 202-C8 NANOBODY® (V_{HH} sequence) with a 9GS linker (SEQ ID NO: 2423); C8Bi(15) refers to the bivalent 202-C8 NANOBODY® (V_{HH} sequence) with a 15GS linker (SEQ ID NO: 2424); C8Tri(10) refers to the trivalent 202-C8 NANOBODY® (V_{HH} sequence) with a 10GS linker (SEQ ID NO: 2425); C8Tri(20) refers to the trivalent 202-C8 NANOBODY® (V_{HH} sequence) with a 20GS linker (SEQ ID NO: 2426).

FIG. 58A-K: Neutralization of different H5 variants by different multivalent constructs of NANOBODY® (V_{HH} sequence) 203-H9, tested in the lentiviral pseudotyped neutralization assay as described in Example 36. H9 refers to NANOBODY® (V_{HH} sequence) 203-H9; H9Bi(5) refers to the bivalent 203-H9 NANOBODY® (V_{HH} sequence) with a 5GS linker (SEQ ID NO: 2429); H9Bi(25) refers to the bivalent 203-H9 NANOBODY® (V_{HH} sequence) with a 25GS linker (SEQ ID NO: 2430).

FIG. 59: Polypeptide construct with four single variable domains and four constant domains. The polypeptide chain construct comprises two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a “first” single variable domain (5) and a “second” single variable domain (6). The first single variable domain (5) is linked, optionally via a suitable linker or hinge region (7) to the constant domain (3). The second single variable domain (6) is linked, optionally via a suitable linker or hinge region (8) to the constant domain (4). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 60: Polypeptide construct with four single variable domains and four constant domains. The polypeptide chain construct comprises two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a “first” single variable domain (5) and a “second” single variable domain (6). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domains, optionally (and usually) via a suitable linker or hinge region (8). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 61: Polypeptide construct with six single variable domains and four constant domains. The polypeptide chain construct comprises two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a “first” single variable domain (5), a “second”

single variable domain (6) and a "third" single variable domain (10). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domains, optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (11) is linked, optionally via a suitable linker (12), to the second single variable domain (6). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 62: Polypeptide chain construct with eight single variable domains and four constant domains. The polypeptide chain construct comprises two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5), a "second" single variable domain (6), a "third" single variable domain (10) and a "fourth" single variable domain (13). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (10) is linked, optionally via a suitable linker (12), to the fourth single variable domain (13), and is also linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 63: Polypeptide chain construct with six single variable domains and four constant domains. The polypeptide chain construct comprises two polypeptide chains (1) and (2), which each comprise two constant domains (3) and (4), a "first" single variable domain (5), a "second" single variable domain (6) and a "third" single variable domain (10). The first single variable domain (5) is linked, optionally via a suitable linker (7), to the second single variable domain (6), and is also linked to the constant domain (3), optionally (and usually) via a suitable linker or hinge region (8). The third single variable domain (10) is linked to the constant domain (4), optionally (and usually) via a suitable linker or hinge region (14). The constant domains (3) and (4) of the polypeptide chain (1) and the corresponding constant domains (3) and (4) of the polypeptide chain (2) together form the Fc portion (9).

FIG. 64A-B: Neutralization of RSV Long and RSV B-1 strains by trivalent NC41 NANOBODY® (V_{HH} sequence) with different linker lengths as described in Example 58.

FIG. 65: Schematic overview of the humanized residues introduced in selected NC41 variants. Dots indicate the presence of the wildtype residue; letters correspond to the humanized residue. Numbering is according to Kabat.

FIG. 66: Binding of yeast-produced NANOBODIES® (V_{HH} sequences) to authentic antigens of different influenza strains (see Table C-57). Clones in panel A and B were selected for binding to H5 strains whereas clones in panel C and D were selected for binding to H7

strains. ELISA plates coated with 5 μg/ml influenza antigens were incubated with 10 μg/ml NANOBODY® (V_{HH} sequence) that was subsequently detected using an anti-his6 peroxidase conjugate.

FIG. 67: Neutralization of hRSV Long strain and B-1 strain by monovalent and trivalent humanized NC41 variants.

EXAMPLES

Example 1

Immunizations

Two llamas (156 and 157) were immunized according to standard protocols with 6 boosts of hRSV F_{TM-} (membrane anchorless form of the fusion protein, 70 kDa; Conan T. et al. 2007, BMC Biotechnol. 7: 17). Blood was collected from these animals 7 days after boost 6 and 10 days after boost 6.

Two llamas (140 and 163) were immunized according to standard protocols with 6 boosts of H5 Hemagglutinin (HA, A/Vietnam/1203/2004 (H5), Protein Sciences Cat. No. 3006). Blood was collected from these animals 10 days after boost 6.

Two llamas (183 and 196) were immunized according to standard protocols with 6 boosts of Rabies vaccine (inactivated rabies virus; Sanofi Pasteur MSD). Blood was collected from these animals 7 days after boost 6, 17 days after boost 6 and 21 days after boost 6.

Example 2

Library Construction

Peripheral blood mononuclear cells were prepared from blood samples using Ficoll-Hypaque according to the manufacturer's instructions. Next, total RNA was extracted from these cells as well as from the lymph node bow cells and used as starting material for RT-PCR to amplify NANOBODY® (V_{HH} sequence) encoding gene fragments. These fragments were cloned into phagemid vector derived from pUC119 which contains the LacZ promoter, a coliphage pIII protein coding sequence, a resistance gene for ampicillin or carbenicillin, a multicloning site and the gen3 leader sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector codes for a C-terminal c-myc tag and a (His)6 tag. Phage was prepared according to standard methods and stored at 4° C. for further use, making phage libraries 156, 157, 140b, 163b, 183 and 196b.

Example 3

Selections Against hRSV

hRSV is a member of the Paramyxoviridae family and is an enveloped virus with two main surface glycoproteins that make the spikes of the virus particle. One of these glycoproteins (protein G) is the attachment protein that mediates binding of the virus to the cell surface. The other glycoprotein (protein F or fusion) mediates fusion of the viral and cell membranes, allowing the entry of the viral nucleocapsid into the cell cytoplasm Inhibition of the steps mediated by either G or F glycoproteins blocks the initial stages of the infectious cycle and neutralizes virus infectivity. Therefore, antibodies directed against either G or F, and which inhibit their respective activities, neutralize virus infectivity and may protect against a hRSV infection. The F protein is highly conserved and forms trimeric spikes that undergo conformational changes upon activation.

Human respiratory syncytial virus (hRSV) is the leading cause of severe lower respiratory tract infections (bronchiolitis and pneumonia) in infants and very young children and causes annual epidemics during the winter months. The virus also causes a substantial disease burden among the elderly and adults with underlying cardiopulmonary disorders and/or immunosuppressive conditions are also at risk of severe hRSV disease. The immune response does not prevent reinfections.

There is no vaccine available to prevent hRSV infections. The only drug product available in the market is a humanized monoclonal antibody (Synagis®) directed against one of the viral glycoproteins (protein F) which is used prophylactically in children that are at a very high risk of suffering a severe hRSV infection. The restricted use of Synagis® is due, at least in part, to the high cost of this product.

To identify NANOBODIES® (V_{HH} sequences) recognizing the F_{TM}- (membrane anchorless form of the fusion protein, 70 kDa, Corrall T. et al. 2007, BMC Biotechnol. 7: 17), libraries 156 and 157 were used. The same antigen was used for selections as for immunizations. The F_{TM}- protein (25 ng/well) was immobilized on Nunc Maxisorp ELISA plates. A control was included with 0 μg/ml F_{TM}-. Bound phages were eluted from the F_{TM}-using trypsin and Synagis® (Palivizumab, MedImmune, humanized monoclonal antibody, described in Zhao & Sullender 2005, J. Virol. 79: 3962) in the first and second round of selections. Remicade (Infliximab, anti-TNF; Centorcor) was used as a control for Synagis®. A 100 molar excess of Synagis® was used in order to identify NANOBODIES® (V_{HH} sequences) binding specifically at the binding site on RSV. Outputs from the first round selections, eluted with Synagis® were used for second round selections.

Outputs of both rounds of selections were analyzed for enrichment factor (phage present in

eluate relative to controls). Based on these parameters the best selections were chosen for further analysis. Individual colonies were picked and grown in 96 deep well plates (1 ml volume) and induced by adding IPTG for NANOBODY® (V_{HH} sequence) expression. Periplasmic extracts (volume: ˜80 μl) were prepared according to standard methods.

Example 4

Selections Against H5N1

Influenza is an enveloped virus with two main surface antigens, the hemagglutinin (HA) and the neuraminidase (NA). The influenza HA is responsible for virus attachment to target host cells via recognition and binding to sialic acid receptors on membrane-bound proteins of the host cell.

By analysis using monoclonal antibody-resistant mutants it has been shown that neutralizing antibody binding sites map to regions on the surface of the globular membrane distal domains of the HA. Bi- or multispecific NANOBODIES® (V_{HH} sequences) can exhibit enhanced neutralizing potency and can reduce the incidence of escape mutants in comparison to monospecific NANOBODIES® (V_{HH} sequences), or currently used monoclonals.

Human infections with avian influenza H5N1 virus were first observed during large scale poultry outbreaks in Hong Kong in 1997. Since its re-emergence in Asia in 2003, 277 laboratory-confirmed human H5N1 cases have been reported from Asia, Europe and Africa of whom 167 have died (WHO, 1st March 2007). In general, humans who catch a humanized Influenza A virus (a human flu virus of type A) usually have symptoms that include fever, cough, sore throat, muscle aches, conjunctivitis and, in severe cases, breathing problems, pneumonia, fever, chills, vomiting and headache. Tissue damage associated with pathogenic flu virus infection can ultimately result in death. The inflammatory cascade triggered by H5N1 has been called a 'cytokine storm' by some, because of what seems to be a positive feedback process of damage to the body resulting from immune system stimulation. H5N1 induces higher levels of cytokines than the more common flu virus types. The mortality rate of highly pathogenic H5N1 avian influenza in a human is high; WHO data indicates that 60% of cases classified as H5N1 resulted in death. Influenza virus entry inhibitors may have potential uses as antivirals, prophylactics and as topical treatments (i.e. nasal sprays). These inhibitors may also serve as useful tools in H5N1 vaccine and antiviral research by elucidating novel epitopes involved in protective immune responses against the virus.

To identify NANOBODIES® (V_{HH} sequences) recognizing the hemagglutinin (HA) of Influenza H5N1, libraries 140b and 163b were used. The same antigen was used for selections as for immunizations. The H5N1 recombinant HA (A/Vietnam/1203/2004

(H5N1), Protein Sciences Cat. No. 3006) was immobilized on Nunc Maxisorp ELISA plates. A control was included with 0 μg/ml HA. Bound phages were eluted from the HA using trypsin in the first and trypsin and VN04-2 (Mouse Monoclonal Anti-H5 Hemagglutinin of A/Vietnam/1203/04 Influenza Virus, Rocklnad Inc. Cat. No. 200-301-975) in the second round of selections. Mouse IgG was used as an antibody control. A 100 molar excess of the antibody was used in order to identify NANOBODIES® (V_{HH} sequences) binding specifically at the binding site on influenza HA. Outputs from the first round selections were used for second round selections.

Outputs of both rounds of selections were analyzed for enrichment factor (phage present in eluate relative to controls). Based on these parameters the best selections were chosen for further analysis. Individual colonies were picked and grown in 96 deep well plates (1 ml volume) and induced by adding IPTG for NANOBODY® (V_{HH} sequence) expression. Periplasmic extracts (volume: ˜80 μl) were prepared according to standard methods.

Example 5

Selections Against Rabies

Rabies is a neurotropic virus that belongs to one of the largest families (Rhabdoviridae) of viruses. It is surrounded by an envelope in which glycoprotein G is embedded. Glycoprotein G is responsible for the induction of protective immunity and contains different motifs that define virulence and pathogenicity.

Glycoprotein G consists of 505 amino-acids and a typical rabies virion contains about 1800 of these proteins. Glycoprotein G binds to the cellular receptor, leading to endocytosis of the virus-receptor complex. Glycoprotein G is the immunodominant antigen of the virus and antibodies are typically directed against 1 of 8 antigenic sites on glycoprotein G, some of which are highly conserved between different strains and genotypes. Neutralizing antibodies prevent binding and entry into the target host cell by blocking binding of viral proteins to the target host cell.

Rabies continues to be a serious worldwide health problem. Each year, an estimated 55,000 people die from rabies and 10 million people are treated after contact with suspected animals.

Rabies virus causes encephalitis in man and animal. The virus is excreted in saliva and transmitted by close contact with infected animals through bites, scratches or licks. Once introduced in a wound, it replicates locally in the muscle cells. After an incubation period of a few days up to several years, the virus crawls up in the peripheral nerves and reaches the brain via retrograde axonal transport. This is followed by extensive replication in the

cytoplasm of neurons, brain dysfunction and death. Once symptoms of the disease develop, rabies is fatal.

There is no cure for rabies and once the virus reaches the central nervous system, the patient will die. The present treatment is post-exposure with vaccinations with inactivated virus. Two sources of antibodies are available for passive immunization: human rabies immunoglobulins (HRIG: Imogam, Aventis Pasteur) and equine rabies immunoglobulins (ERIG). These are purified from pooled sera of vaccinated people or horses and administered directly after the bite. Due to technical and economical limitations, the supply of rabies immunoglobulins is limited and there is a worldwide shortage. Immunoglobulins can trigger allergic reactions ranging form skin erythema, fever to anaphylactic shock (as described in the patient information leaflet). The possibility of contamination with blood-borne infectious agents can not be excluded. The WHO strongly recommends that more cost-efficient and safer alternatives should be developed.

To identify NANOBODIES® (V_{HH} sequences) recognizing the Rabies G protein, libraries 183 and 196b were used. The Rabies virus (rabies inactivated HDCV vaccine; Sanofi Pasteur MSD) was immobilized on Nunc Maxisorp ELISA plates. A control was included with 0 μg/ml. Precoated 8 well strips (Platelia II Rabies plates, BioRad cat no 355-1180) were also used for selections in both first and second round. Phages were preincubated with 100 mg/ml BSA, because the rabies vaccine contained 50 mg/ml HSA. Bound phages were eluted from the virus using trypsin in the first and second round. Bound phages were eluted from the G protein with trypsin or a mouse monoclonal MAb 8-2m or Ab 8-2, a mouse IgG2a (Montaño-Hirose et al. 1993, Vaccine 11: 1259-1266) in the first and second round of selections. A mouse IgG2a was used as an antibody control. A 100 molar excess of the antibody was used in order to identify NANOBODIES® (V_{HH} sequences) binding specifically at the binding site on rabies virus. Outputs from the first round selections were used for second round selections.

Outputs of both rounds of selections were analyzed for enrichment factor (phage present in eluate relative to controls). Based on these parameters the best selections were chosen for further analysis. Individual colonies were picked and grown in 96 deep well plates (1 ml volume) and induced by adding IPTG for NANOBODY® (V_{HH} sequence) expression. Periplasmic extracts (volume: ˜80 μl) were prepared according to standard methods.

Example 6

Screening for Binding

In order to determine binding specificity to the viral envelope proteins, the clones were tested in an ELISA binding assay setup. In short, 2 μg/ml of F_{TM}- or 5 μg/ml H5N1 HA were

immobilized directly on Maxisorp microtiter plates (Nunc). Rabies G protein precoated plates from BioRad were used (Cat. No. 355-1180). Free binding sites were blocked using 4% Marvel in PBS. Next, 10 μl of periplasmic extract containing NANOBODY® (V_{HH} sequence) or monoclonal phages of the different clones in 100 μl 2% Marvel PBST were allowed to bind to the immobilized antigen. After incubation and a wash step, NANOBODY® (V_{HH} sequence) binding was revealed using a rabbit-anti-VHH secondary antibody (for the periplasmic fractions) or an anti-M13 antibody against the phages gene3. After a wash step the NANOBODIES® (V_{HH} sequences) in the periplasmic fractions were detected with a HRP-conjugated goat-anti-rabbit antibody. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence).

(a) hRSV

Phage binding ELISA showed binders for both library 156 (61%) and 157 (59%) after the first round of selections and Synagis® elutions.

Phage binding ELISA showed binders for both library 156 (85%) and 157 (50%) after the first round of selections and trypsin elutions.

Periplasmic fraction binding ELISA showed binders for both library 156 (83%) and 157 (78%) after the second round of selections and trypsin elutions.

Periplasmic fraction binding ELISA showed binders for both library 156 (87%) and 157 (68%) after the second round of selections and Synagis® elutions.

(b) H5N1

Periplasmic fraction binding ELISA showed binders for both library 140b (35%) and 163b (24%) after the second round of selections and monoclonal antibody elutions.

Periplasmic fraction binding ELISA showed binders for both library 140b (37%) and 163b (33%) after the second round of selections and trypsins elutions.

(c) Rabies

Periplasmic fraction binding ELISA showed binders for the rabies virus from both library 183 (67%) and 196 (48%) after the second round of selections on virus and trypsin elutions. No binders for the G protein from the virus selected periplasmic fractions. No binders for HSA control.

Periplasmic fraction binding ELISA showed binders for G protein from both library 183 (50%) and 196 (75%) after the second round of selections and trypsins elutions.

Periplasmic fraction binding ELISA showed binders for G protein from library 196 (37%) after the second round of selections and monoclonal antibody elutions.

Sequences of the obtained NANOBODIES® (V_{HH} sequences) are given in Table A-1.

Clustering of the obtained NANOBODIES® (V_{HH} sequences) is shown in FIGS. 12 to 17.

Example 7

Screening for Competition

Competition assays were set up with the NANOBODIES® (V_{HH} sequences) competing with monoclonal, neutralizing antibodies, Synagis® for hRSV, VN04-2 (as described in Hanson et al. 2006, Respiratory Research 7: 126) for H5N1 and a mouse IgG2a monoclonal (as described in Montaño-Hirose et al. 1993, Vaccine 11: 1259-1266) against Rabies. A chessboard ELISA was run to determine the best coating concentration of antigen and the concentration of antibody that gave IC_{50}.

In short, the antigen was immobilized on Maxisorp microtiter plates (Nunc) and free binding sites were blocked using 4% Marvel in PBS. Next, 100 ng/ml of Synagis®, VN04-2 or mouse IgG2a monoclonal (mab) (dilution $1/10^6$) was preincubated with 20 μl of periplasmic extract containing NANOBODY® (V_{HH} sequence) of the different clones. Control periplasmic fractions selected against other viral coat proteins were included. The competing antibody was allowed to bind to the immobilized antigen with or without NANOBODY® (V_{HH} sequence). After incubation and a wash step, antibody binding was revealed using a HRP-conjugated goat anti-human Fc antibody (ahFcHRP; Synagis®) or HRP-conjugated donkey anti-mouse antibody (DAMPO; VN04-2 and IgG2a). Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence) (FIGS. 1, **2** and **3**). All targets had periplasmic fractions competing with the neutralizing antibodies. From these clones, based on their sequence, clones were recloned in an expression vector derived from pUC119 which contains the LacZ promoter, a resistance gene for ampicillin or carbenicillin, a multicloning site and the gen3 leader sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector codes for a C-terminal c-myc tag and a (His)6 tag. NANOBODIES® (V_{HH} sequences) were produced and purified via the His-tag on Talon beads. Purified NANOBODIES® (V_{HH} sequences) were shown to bind their respective antigen as shown in FIGS. 4 and 5.

Example 8

Determining Competition Efficiency by Titration of Purified NANOBODY® (V_{HH} Sequence)

In order to determine competition efficiency of hRSV F_{TM}- and H5N1 HA binding NANOBODIES® (V_{HH} sequences), the positive clones of the binding assay were tested in an ELISA competition assay setup.

In short, 2 μg/ml F_{TM}- or 2.5 μg/ml HA was immobilized on Maxisorp microtiter plates (Nunc) and free binding sites were blocked using 4% Marvel in PBS. Next, a dilution series of purified NANOBODIES® (V_{HH} sequences) were allowed to bind to the antigen for 30 minutes before 100 ng/ml (0.67 nM) Synagis® or VN04-2 was incubated. Irrelevant NANOBODIES® (V_{HH} sequences) against other viral coat proteins were used as negative controls (202 against H5N1 for hRSV competition, 191, and 192 against hRSV for H5N1 competitions). The results are shown in FIGS. 6 and 7. NANOBODIES® (V_{HH} sequences) were found for both hRSV and H5N1 competing with monoclonal antibodies.

Example 9

Cell Based and Animal Experiments

To investigate if selected NANOBODIES® (V_{HH} sequences) recognize different epitopes, epitope mapping could be performed by using monoclonal antibodies which recognize known epitopes. Examples of antibodies against hRSV that may be used are:

- Synagis® (Palivizumab, MedImmune, humanized monoclonal antibody, as described in Zhao & Sullender 2005, J. Virol. 79: 3962), directed to an epitope in the A antigenic site of the F protein, non-competing with 9C5.
- 9C5 (HyTest Ltd) (described in Krivitskaia et al. 1999, Vopr. Virusol 44: 279), neutralizing mouse monoclonal, hampers the virus penetration into the cell, recognizes epitope Fla of RSV F-protein, non-competing with Synagis®.
- 101F (WO 06/050280), humanized mouse monoclonal, directed to an epitope of the RSV F-protein comprising amino acids 423-436 as minimal peptide, non-competing with Synagis® and 9C5.

In vitro neutralization assays of selected NANOBODIES® (V_{HH} sequences) against virus are used to investigate the neutralizing capacity of the NANOBODIES® (V_{HH} sequences). One example is the rabies virus neutralization assay, Rapid Fluorescent Focus Inhibition Test (RFFIT) (Standard procedure from WHO Laboratory Techniques in Rabies, 1996), where a standard quantity of free rabies virus is pre-incubated with different dilutions of NANOBODIES® (V_{HH} sequences). Then the NANOBODY® (V_{HH} sequence)-virus mixture is added on a monolayer of susceptible Baby Hamster Kidney (BHK) cells. Twenty-four hours later, cells are fixed and stained with a green-fluorescent anti-rabies conjugate to quantify infected cells. Absence of fluorescent cells indicates prior neutralization of the virus inoculum. The neutralizing capacity of a NANOBODY® (V_{HH} sequence) preparation is

expressed in International Units (IU)/m1 in reference to the WHO standard (=anti-rabies IgG purified from sera of vaccinated humans).

To investigate the in vivo neutralizing capacity of rabies infection by the NANOBODIES® (V_{HH} sequences), intracerebral inoculation in mice is used, where both the virus and the NANOBODIES® (V_{HH} sequences) are administered directly in the brain.

Example 10

Bi- and Trivalent NANOBODIES® (V_{HH} Sequences)

Increased avidity and function have been observed for NANOBODIES® (V_{HH} sequences) that are bi- or trivalent with either homo- or heteromers of selected NANOBODIES® (V_{HH} sequences). This is an option to target viral trimeric spikes, either different epitopes or the same epitopes on the spike.

Protocols are available for construction of a trivalent NANOBODY® (V_{HH} sequence) connected by Gly-Ser linkers of any desired length and composition. It is based on the separate PCR reactions (1 for the N-terminal, 1 for the middle (if trivalent) and 1 for the C-terminal VHH subunit) using different sets of primers. Different linker lengths can also be introduced by the primers.

Example 11

Screening for NANOBODIES® (V_{HH} Sequences) Binding Different Epitopes of the Trimeric Spike Proteins

For hRSV different monoclonal antibodies are available recognizing different epitopes of the F_{TM}- protein. In order to screen for NANOBODIES® (V_{HH} sequences) recognizing three different epitopes the following antibodies or Fab fragments were used: mouse monoclonal 9C5 (3ReS21, Hytest), 101F Fab (WO 2006/050280) and Synagis® (Medimmune). They all bind to different epitopes on the F_{TM}- protein and were used for competition with selected NANOBODIES® (V_{HH} sequences). 9C5 is believed to bind to an epitope around amino acid 389, 101F at amino acids 422-438 and Synagis® at amino acids 255-280 (see FIG. 8).

For competition with 9C5, 2 μg/ml F_{TM-} protein was coated in a 96 well plate, blocked and then 20 μl periplasmic fractions was added for 30 minutes before the competitor, 9C5 (100 ng/ml) was added. They were competing for 1 hour before 1/5000 HRP conjugated rabbit anti-mouse antibody was added and incubated for 1 hour. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence). Several periplasmic fractions were found to compete with 9C5 indicating

recognition of another epitope than Synagis® and 101F (FIG. 9).

For competition with 101F Fab, hRSV F_{TM}- protein was coated in a concentration of 1 μg/ml. The plate was blocked with 1% casein and the purified NANOBODIES® (V_{HH} sequences) were added starting at 500 nM and then diluted 1/3. Three nM of 101F Fab was used for competition for 1 hour before addition of mouse anti-HA (1/2000) was added. After 1 hour, HRP conjugated rabbit anti-mouse antibody was added (0.65 μg/ml). Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence). Two NANOBODIES® (V_{HH} sequences) were found to compete with 101F Fab, NB6 (191-E4) and NB4 (192-H1) (FIG. 10).

Example 12

Surface Plasmon Resonance for Affinity Measurements

To measure the affinity of selected NANOBODIES® (V_{HH} sequences), Surface Plasmon resonance was used. For preincubation of the Sensorchip CM5, 10 μg/ml hRSV F_{TM}- protein was left on for 120 seconds. For immobilization by amine coupling, EDC/NHS was used for activation and ethanolamine HCl for deactivation (Biacore, amine coupling kit). 100 nM Synagis® was added and then 100 nM of the NANOBODIES® (V_{HH} sequences). Evaluation of the off-rates was performed by fitting a 1:1 interaction model (Langmuir binding model) by Biacore T100 software v1.1. The off-rates and affinity constants are shown in Table C-2. NB6 (191-E4) shows a high off-rate and the Kd was 700 pM. NB2 (191-D3) had a Kd of 2.05 nM. NB6 (191-E4) has been shown to bind to the 101F epitope and NB2 (191-D3) to the Synagis® epitope. Note that NB4 is also competing with Synagis® and may thus be recognizing yet a different epitope.

Example 13

NANOBODIES® (V_{HH} Sequences) Targeting the Sialic Acid Binding Site of Influenza Hemagglutinin

Hemagglutinin (HA) on Influenza viruses binds sialic acid on cells during infection. The sialic acid binding site of he HA forms a pocket which is conserved between Influenza strains. Most HAs of avian influenza viruses preferentially recognize sialic acid receptors containing the α(2,3) linkage to galactose on carbohydrate side chains (human viruses, the α(2,6) linkage). To increase the chance of isolating neutralizing NANOBODIES® (V_{HH} sequences), a functional selection approach can be used—identify NANOBODIES® (V_{HH} sequences) that compete with soluble 2,3 sialic acid (or 2,6 sialic acid for some mutational drift variants). This would select for NANOBODIES® (V_{HH} sequences) targeting the sialic

acid binding site of HA. These NANOBODIES® (V_{HH} sequences) are likely to be the most potent at neutralizing H5N1.

We have selected NANOBODIES® (V_{HH} sequences) binding to H5N1 HA. To identify, from these NANOBODIES® (V_{HH} sequences), the NANOBODIES® (V_{HH} sequences) binding to the sialic acid binding site on hemagglutinin, the following experiments were performed. Fetuin (from fetal calf serum, F2379, Sigma-Aldrich, St. Louis, Mo.) was coated (10 μg/ml) in a 96 well plate and incubated over night at 4° C. The plate was blocked in 2% BSA and then 0.7 μg/ml biotinylated HA (HA-bio) and 10 μl periplasmic fractions of the NANOBODIES® (V_{HH} sequences) (202-C2; SEQ ID NO: 136, 202-F3; SEQ ID NO: 150, 202-D5; SEQ ID NO: 140, 202-E5; SEQ ID NO: 145, 202-B7; SEQ ID NO: 131, 202-E7; SEQ ID NO: 147, 202-C8; SEQ ID NO: 138, 202-D8; SEQ ID NO: 142, 202-F8; SEQ ID NO: 152, 202-E11; SEQ ID NO: 143) or purified NANOBODY® (V_{HH} sequence) (203-B1; SEQ ID NO: 2431, 203-H1; SEQ ID NO: 2434, 203-E12; SEQ ID NO: 2435, 203-H9; SEQ ID NO: 2445, 203-B12; SEQ ID NO: 2439, 203-A9; SEQ ID NO: 2438, 203-D9; SEQ ID NO: 2441, 202-C8; SEQ ID NO: 138, 189-E2; SEQ ID NO: 2448) were added for competition. After incubation for 1 hour, HRP conjugated streptavidin was added and incubated for 1 hour. Binding specificity of HA-bio not recognized by periplasmic fractions was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence). Results of competition between periplasmic fractions and fetuin for binding to HA-bio is shown in FIG. 11. Results of HA binding by purified NANOBODIES® (V_{HH} sequences) and of competition between purified NANOBODIES® (V_{HH} sequences) and fetuin for binding to HA-bio is shown in FIGS. 27 A and B respectively. Several NANOBODY® (V_{HH} sequence) clones showed competition which may indicate that the competing NANOBODIES® (V_{HH} sequences) recognize the sialic acid binding site on the HA.

Example 14

In Vitro Neutralization of Virus Infection

To investigate in vitro neutralization of NANOBODIES® (V_{HH} sequences) in periplasmic fractions against Rabies virus, the rabies virus neutralization assay, Rapid Fluorescent Focus Inhibition Test (RFFIT) (Standard procedure from WHO Laboratory Techniques in Rabies, 1996) was used. A standard quantity of free rabies virus was pre-incubated with different dilutions of NANOBODIES® (V_{HH} sequences) in periplasmic fractions and then the periplasmic fraction-virus mixture was added on a monolayer of susceptible Baby Hamster Kidney (BHK) cells. Twenty-four hours later, cells were fixed and stained with a green-fluorescent anti-rabies conjugate to quantify infected cells. Absence of fluorescent cells indicated prior neutralization of the virus inoculum. The neutralizing capacity of the NANOBODY® (V_{HH} sequence) (peri) preparations was expressed in International Units

(IU)/m1 in reference to the WHO standard (=anti-rabies IgG purified from sera of vaccinated humans). The neutralization assay showed several periplasmic fractions with NANOBODIES® (V_{HH} sequences) neutralizing the rabies virus (Table C-1). All neutralizing periplasmic fractions were selected against the Rabies G protein (monoclonal antibody and total elution) and showed competition with the mouse monoclonal IgG2a antibody directed against rabies virus and with neutralizing capacity. Llama sera and polyclonal periplasmic fractions selected against the inactivated virus and the G protein were included as well as controls for both the polyclonal periplasmic fractions and the monoclonal periplasmic fractions. Only polyclonal and monoclonal periplasmic fractions selected against the G protein showed neutralization.

Example 15

In Vitro Neutralization of hRSV Infection

The hRSV micro neutralization assay was used to investigate in vitro neutralization capacity of selected purified hRSV NANOBODIES® (V_{HH} sequences). In here, Hep2 cells were seeded at a concentration of 1.5×10^4 cells/well into 96-well plates in DMEM medium containing 10% fetal calf serum (FCS) supplemented with Penicillin and Streptomycin (100 U/ml and 100 μg/ml, respectively) and incubated for 24 hours at 37° C. in a 5% CO_2 atmosphere. The virus stock used is referred to as hRSV strain long, Long LM-2 and Long M2 (used interchangeably) all referring to a virus stock derived from ATCC VR-26 of which the sequence of the F protein corresponds to P12568 or M22643. The virus stock has been passaged several times from the ATCC stock. The sequence of the F-protein was confirmed to be identical to P12568 (see example 23). A standard quantity of hRSV strain Long was pre-incubated with serial dilutions of purified NANOBODIES® (V_{HH} sequences) in a total volume of 50 μl for 30 minutes at 37° C. The medium of the Hep2 cells was replaced with the premix to allow infection for 2 hours, after which 0.1 ml of assay medium was added. The assay was performed in DMEM medium supplemented with 2.5% fetal calf serum and Penicillin and Streptomycin (100 U/m1 and 100 μg/ml, respectively). Cells were incubated for an additional 72 hours at 37° C. in a 5% CO2 atmosphere, after which cells were washed twice with 0.05% Tween-20 in PBS and once with PBS alone, after which cells were fixed with 80% cold acetone (Sigma-Aldrich, St. Louis, Mo.) in PBS (100 μl/well) for 20 minutes at 4° C. and left to dry completely. Next the presence of the F-protein on the cell surface was detected in an ELISA type assay. Thereto, fixed Hep2 cells were blocked with 2% Bovine Serum Albumin (BSA) solution in PBS for 1 hour at room temperature, than incubated for 1 hour with anti-F-protein polyclonal rabbit serum (Corral et al. 2007, BMC Biotechnol. 7: 17) or Synagis® (2 μg/ml). For detection goat Anti-rabbit-HRP conjugated antibodies or goat Anti-Human IgG, Fcγ fragment specific-HRP (Jackson ImmunoResearch, West Grove, Pa.) was used, after which the ELISA was developed according to standard procedures.

The hRSV in vitro neutralization potency of a panel of 15 NANOBODIES® (V_{HH} sequences) identified in previous examples were analyzed. The NANOBODIES® (V_{HH} sequences) consisted of 4 groups:

- Group 1 consisted of hRSV F protein specific NANOBODIES® (V_{HH} sequences) (192C4; SEQ ID NO: 163, 191D3; SEQ ID NO: 159, 192F2; SEQ ID NO: 167, 192C6; SEQ ID NO: 164, 192H2; SEQ ID NO: 169, 192A8; SEQ ID NO: 160, 192C10; SEQ ID NO: 162) recognizing antigenic site II of the F protein. Antigenic site II (also referred to as site A) was identified by mutations found in the F protein in viral escape mutants and although antigenic site II is often found to be referred to as the region aa 250-275, antibodies typically fail to recognize linear peptides representing this region (Arbiza et al. 1992, J. Gen. Virol. 73: 2225-2234). Antibodies specific to antigenic site II may be neutralizing or not (Garcia-Barreno et al. 1989, J. Virol. 63: 925-932). Palivizumab (Synagis®) is a typical example of a mAb binding to antigenic site II (Zhao and Sullender 2005, J. Virol. 79: 3962-3968). Competition with palivizumab was used to assign the antigenic site for the Nanobod-NANOBODIES® (V_{HH} sequences)ies (see example 7).
- Group 2 consisted of hRSV F-protein specific NANOBODIES® (V_{HH} sequences) (191E4; SEQ ID NO: 166, 192B1; SEQ ID NO: 161, 192C10; SEQ ID NO: 162) recognizing antigenic site IV-VI of the F protein (Lopez et al. 1998, J. Virol. 72: 6922). Antigenic site IV-VI was identified by mutations found in the F protein in viral escape mutants and this site can be found to be referred to as the region aa 423-436. For this antigenic site it has been shown that antibodies may recognize linear peptides (Arbiza et al. 1992, J. Gen. Vir. 73: 2225-2234). Antibodies specific to antigenic site IV-VI may be neutralizing or not (Garcia-Barreno et al. 1989, J. Virol. 63: 925-932). 101F is a typical example of a mAb binding to antigenic site IV-VI (Wu et al. 2007, J. Gen. Virol. 88: 2719-2723). Competition with a Fab of 101F was used to assign the antigenic site for the NANOBODIES® (V_{HH} sequences) (see example 11).
- Group 3 consisted of hRSV F-protein specific NANOBODIES® (V_{HH} sequences) (192H1; SEQ ID NO: 168, 192D3; SEQ ID NO: 165, 192B1; SEQ ID NO: 161) for which the antigenic site could not be attributed, either because NANOBODIES® (V_{HH} sequences) were not competing with 101F or palivizumab or they were showing competition to both 101F and palivizumab.
- As controls, 3 NANOBODIES® (V_{HH} sequences) specific for H5 hemagglutinin from influenza (202A5; SEQ ID NO: 128, 202G3; SEQ ID NO: 154, 202E5; SEQ ID NO: 145) were used.

The neutralization assay showed that NANOBODIES® (V_{HH} sequences) 191D3, 192C4 and 192F2 can neutralize RSV Long infection, with 191D3 being more potent than Synagis®

Fab and 101F Fab (FIG. 18). The other NANOBODIES® (V_{HH} sequences) recognizing antigenic site II could not inhibit virus infection at the highest concentration tested (3 μM).

Example 16

Immunizations

Two llamas (212 and 213) were immunized intramuscularly in the neck with 1 mg of RNA-inactivated RSV strain long A (Hytest, Turku Finland; #8RSV79), followed by 4 boosts of 0.5 mg RSV in a biweekly regimen. Two llamas (206 and 207) were immunized intramuscularly with 1 mg of RNA-inactivated RSV strain long A, boosted with 0.25 mg of RSV after 2 weeks, followed by 3 boosts with 50 μg of recombinant hRSV F_{TM}-NN (membrane anchorless form of the fusion protein, 70 kDa: Corral et al. 2007; BMC Biotechnol. 7: 17) in a biweekly regimen. For all immunizations the antigens were prepared as oil-PBS emulsions with Stimune as adjuvant.

For library construction, blood was collected from all animals 4 days and 10 days after the fourth immunization, while also a Lymph node biopsy was taken 4 days after the fourth immunization. For the NANOCLONE® procedure, 100 mL blood was collected 11 days after the final boost from llamas 206 and 207.

Example 17

Library Construction

Phage libraries from immune tissues of llamas 206, 207, 212 and 213 were constructed as described in Example 2. Phage was prepared according to standard methods and stored at 4° C. for further use, making phage libraries 206, 207, 212 and 213.

Example 18

NANOBODY® (V_{HH} Sequence) Selection with the F-Protein of hRSV

To identify NANOBODIES® (V_{HH} sequences) recognizing the fusion protein of RSV, libraries 156, 157, 206, 207, 212 and 213 were used for selection on F_{TM}-NN (membrane anchorless form of the Long fusion protein, 70 kDa; Corral T. et al. 2007, BMC Biotechnol. 7: 17) as described in Example 3. In addition, selections were done using inactivated hRSV strain Long (Hytest #8RSV79). The F_{TM}-NN protein (25 ng/well) or RSV (5 to 50 μg/well) was immobilized on Nunc Maxisorp ELISA plates, next to a control with 0 μg/ml antigen. Bound phages were eluted from the F_{TM}-NN using trypsin, Synagis® (Palivizumab, humanized

monoclonal antibody, described in Zhao and Sullender 2005, J. Virol. 79: 396), or 101F Fab (WO 06/050280, humanized monoclonal antibody) in the first round of selection. Outputs from the first round selections eluted with Synagis® or 101F Fab were used for second round selections, using either Numax Fab (Motavizumab or MEDI-524, a third-generation humanized monoclonal antibody product evolved from palivizumab; WO 06/050166), Synagis® or 101F Fab for elution. Remicade (Infliximab, anti-TNF) was used as a control for Synagis®, while Omnitarg Fab (anti-Her2; PCT/EP2008/066363) served as control for Numax Fab and 101F Fab. A 100 molar excess of Synagis®, Numax Fab or 101F Fab was used in order to identify NANOBODIES® (V_{HH} sequences) binding specifically to antigenic sites II or IV-VI epitopes on the RSV F-protein. To obtain NANOBODIES® (V_{HH} sequences) specific for the antigenic site IV-VI, second round selections were performed using two biotinylated peptides: at first, a peptide comprising residues 422-436 of the F-protein (Long) (Abgent, San Diego, Calif.) encompassing the 101F binding epitope (Wu et al. 2007, J. Gen. Virol. 88: 2719-2723), secondly, a peptide mimic of the epitope of Mab19 (HWSISKPQ-PEG4-K-biotin) (Chargelegue et al. 1998, J. Virol. 72: 2040-2056).

Outputs of both rounds of selections were analyzed for enrichment factor (phage present in eluate relative to controls). Based on these parameters the best selections were chosen for further analysis. Individual colonies were picked and grown in 96 deep well plates (1 mL volume) and induced by adding IPTG for NANOBODY® (V_{HH} sequence) expression. Periplasmic extracts (volume: ˜80 μl) were prepared according to standard methods.

For testing of selected clones in RSV neutralization assays, periplasmatic extracts from 10 ml cultures were partially purified by using IMAC PhyTips (Phynexus Inc, San Jose, Calif.). In here 800 μl of periplasmatic extracts was loaded onto Phytips 200+ columns prepacked with immobilized metal affinity chromatography resin, followed by elution of His-tagged NANOBODIES® (V_{HH} sequences) in 30 μl of 0.1M glycine-HCl/0.15M NaCl (pH3), after which eluates were neutralized with 5 μl of 0.5M Tris-HCl pH8.5.

Example 19

NANOBODY® (V_{HH} Sequence) Selection with F_{TM}-NN of RSV Using NANOCLONE® Technology

Peripheral blood mononuclear cells (PBMCs) were prepared from blood samples using Ficoll-Hypaque according to the manufacturer's instructions. Antigen specific B-cells expressing heavy chain antibodies on their surface were isolated from the PBMCs via FACS sorting (for a description of the NANOCLONE® technology reference is made to WO 06/079372). Thereto, F_{TM}-NN protein was labeled with Alexa Fluor 488 dye (Invitrogen, Carlsbad, Calif.; cat. nr. A20000) and subsequently desalted to remove residual non-conjugated Alexa Fluor 488 dye according to the manufacturer's instructions.

Pre-immune (background control) and immune PBMC of a llama were stained with fluorescent dye conjugated IgG1 (conventional heavy+light chain immunoglobulins), IgG2- and IgG3 (heavy chain immunoglobulin classes) specific mouse monoclonal antibodies, fluorescently labeled DH59B antibody (CD172a) (VMRD, Inc. Pullman, Wash.; Cat No. DH59B; Davis et al. 1987, Vet. Immunol. Immunopathol. 15: 337-376) and Alexa 488 labeled antigen. TOPRO3 was included as a live/dead cell discriminator dye. IgG1+ B-lymphocytes, monocytes, neutrophils and dead cells were gated out and therefore rejected from sorting. Antigen-specific (A488+) IgG2− or IgG3 positive B cells were single cell sorted individually into separate PCR plate wells containing RT-PCR buffer.

For llama 206, 1.9% antigen positive cells of the total amount of IgG2/IgG3 positive living cells was obtained (1.0% in pre-immune reference sample), for llama 207 4.2% positive cells were obtained (0.7% in pre-immune reference sample). Heavy chain variable region genes were amplified directly from these B-cells by single-cell RT-PCR and nested PCR. PCR products were subsequently cloned into a TOPO-adapted expression vector derived from pUC119 which contained the LacZ promoter, a resistance gene for ampicillin or carbenicillin, a multicloning site and the gen3 leader sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector coded for a C-terminal c-myc tag and a (His)6 tag. The resulting constructs were transformed in TOP10 *Escherichia coli* cells via high throughput electroporation. Single clones were grown in 96 deep well plates (1 ml volume) and induced by adding IPTG for NANOBODY® (V_{HH} sequence) expression. Periplasmic extracts (volume: ˜80 μl) were prepared via osmotic shock and analyzed for binding to F_{TM}- in a binding ELISA as described in example 6. In total, 8 positive F_{TM}-NN binders (4 from llama 206, 4 from llama 207) were obtained out of 52 cloned VHHs.

Example 20

Screening for NANOBODIES® (V_{HH} Sequences) that Bind to Antigenic Site II or IV-VI

Periplasmic extracts containing single NANOBODIES® (V_{HH} sequences) were analyzed for binding to the antigen site II or IV-VI, using an Alphascreen® assay (Perkin Elmer; Waltham, Mass.) (Garcia-Barreno et al. 1989, J. Virol. 63: 925-932). In this setup F_{TM}-NN is bound simultaneously by Fabs of Synagis® and 101F, allowing detection of NANOBODIES® (V_{HH} sequences) that interfere with binding of each of the respective antigenic sites II and IV-VI. In here, periplasmic extracts were added to F_{TM}-NN protein (0.3 nM) and incubated for 15 minutes. Subsequently biotinylated Fab Synagis® (0.3 nM) and

Fab 101F conjugated acceptor beads (10 μg/ml) were added and this mixture was incubated for 1 hour. Finally streptavidin-coated donor beads (10 μg/ml) were added and after 1 hour incubation the plate was read on the Envision microplate reader. Periplasmic

extracts were diluted 25-fold which corresponds roughly to a final concentration of 40 nM. The assay was validated by titration of the known competitors of Synagis®, mabs 18B2 (Argene, Varilhes, France; 18042 N1902) and 2F7 (Abcam, Cambridge, UK; ab43812). Also Synagis® Fab, Numax Fab, and 101F Fab were analyzed, with Numax Fab having the lowest IC50 value (8.6 E-11 M) followed by Synagis® Fab (5.97 E-10 M) and 101F Fab (1.12 E-9 M). For the screening of periplasmatic extracts (at 1/25 dilution) both Numax Fab (40 nM) and 101F Fab (40 nM) were used as positive controls, while irrelevant periplasmatic extracts served as negative controls. Clones that interfered with binding to F_{TM}-NN protein in the Alphascreen® more than 75% relative to the negative controls were identified as hit. In total 341 hits were identified out of 1856 clones, derived from all 6 llamas but the majority coming from llamas 206 and 207. In addition, out of 8 clones obtained from NANOCLONE® selections 3 clones showed competition.

The correct antigen site (II or IV-VI) of the competitors was deconvoluted by means of a competition ELISA with biotinylated Synagis® Fab (2 nM) or biotinylated 101F Fab (3 nM) for binding to F_{TM}-NN protein (1 μg/ml). The protocol is essentially the same as described in example 7, with the following modifications. Periplasmatic extracts were diluted 1/10 and mixed with the biotinylated Fab prior to binding to the immobilized F_{TM}-NN protein. Detection occurred via Extravidin-HRP conjugated secondary antibodies (Sigma-Aldrich, St. Louis, Mo.; Cat. No. E2886).

All hits were subjected to sequence analysis and classified into families according to their CDR3 sequences. In total 133 unique sequences were derived from llamas 206, 207, 212 and 213, classified into 34 different families (Table C-4). Only 6 families containing 15 unique sequences were classified as binding antigenic site II. All remaining clones were binding antigenic site IV-VI. Eight sequences were non-competing binders identified in binding ELISA to hRSV. Also five new families were identified from libraries 156 and 157, of which one identified as binding antigenic site II, and the remaining as binding antigenic site IV-VI. Also new family members of previously identified families from llamas 156 and 157 were identified.

Example 21

Screening for RSV Neutralizing NANOBODIES® (V_{HH} Sequences)

From all six hRSV libraries 163 unique sequences (160 identified from phage libraries, 3 derived from NANOCLONE®) were analyzed for RSV Long neutralizing capacity in a micro-neutralization assay as partially purified proteins. The screening was essentially performed as described in example 15, using a fixed volume of Phytips purified NANOBODIES® (V_{HH} sequences) (20 μl). The detection of F-protein on the Hep2 cell surface was done using Synagis® (2 μg/ml), followed by goat Anti-Human IgG, Fcγ fragment specific-HRP (Jackson

ImmunoResearch, West Grove, Pa.).

In addition to the previously identified RSV neutralizing NANOBODIES® (V_{HH} sequences) LG191D3 and LG192C4, which were included as positive controls in the screening, 5 new antigenic site II clones showed strong RSV Long neutralizing activity: 1E4 (also referred to as 207D1; SEQ ID NO: 211), a newly identified family member of 191D3 (SEQ ID NO: 159), 7B2 (SEQ ID NO: 364), NC23 (SEQ ID NO: 380), and two members of the same family 15H8 (SEQ ID NO: 371) and NC41 (SEQ ID NO: 372) (Tables A-1, C-4). None of the antigenic site IV-VI specific NANOBODIES® (V_{HH} sequences) showed more than very weak neutralizing activity for hRSV Long LM-2 strain.

Example 22

Construction, Production and Characterization of hRSV NANOBODIES® (V_{HH} Sequences)

Five new neutralizing NANOBODIES® (V_{HH} sequences) selected from the screening described above (1E4, 7B2, 15H8, NC23 and NC41) as well as 2 antigenic site IV-VI NANOBODIES® (V_{HH} sequences) (NC39; SEQ ID NO: 359, 15B3; SEQ ID NO: 286) were expressed, purified and further characterised. Thereto the encoding sequences were recloned in an expression vector derived from pUC119 which contained the LacZ promoter, a resistance gene for kanamycin, a multicloning site and the OmpA signal peptide sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector coded for a C-terminal c-myc tag and a (His)6 tag.

Expression occurred in *E. coli* TG-1 cells as c-myc, His6-tagged proteins in a culture volume of 1 L. Expression was induced by addition of 1 mM IPTG and allowed to continue for 3 hours at 37° C. After spinning the cell cultures, periplasmic extracts were prepared by freeze-thawing the pellets and resuspension in dPBS. These extracts were used as starting material for immobilized metal affinity chromatography (IMAC) using Histrap FF crude columns (GE healthcare, Uppsala, Sweden). NANOBODIES® (V_{HH} sequences) were eluted from the column with 250 mM imidazole and subsequently desalted towards dPBS.

All purified NANOBODIES® (V_{HH} sequences) were shown to bind to the F-protein in a binding ELISA to F_{TM}-NN protein and to hRSV. Results for hRSV binding are shown in Table C-5. In short, 1 μg/ml of F_{TM}-NN or 5 μg/ml hRSV (Hytest Turku, Finland) were immobilized directly on Maxisorp microtiter plates. Free binding sites were blocked with 1% casein. Serial dilutions of purified NANOBODIES® (V_{HH} sequences) were allowed to bind the antigen for 1 hour. NANOBODY® (V_{HH} sequence) binding was revealed using a rabbit-anti-VHH secondary antibody, and final detection with a HRP-conjugated goat-anti-rabbit antibody. Binding specificity was determined based on OD values compared to

irrelevant NANOBODY® (V_{HH} sequence) controls.

To determine the precise binding affinities of the purified NANOBODIES® (V_{HH} sequences), a kinetic analysis was performed using Surface Plasmon resonance analysis on the F_{TM}-NN protein, following the procedure described in example 12. Results are shown in Table C-5.

The ability of purified NANOBODIES® (V_{HH} sequences) to compete with Synagis® Mab or biotinylated Synagis® Fab for binding to F_{TM}-NN was determined in ELISA following the procedure described in examples 8 and 20. FIG. 19 shows a representative example of a competition ELISA wherein purified NANOBODIES® (V_{HH} sequences) compete with biotinylated Synagis® Fab for binding to F_{TM}-NN. As summarized in Table C-5, the six RSV neutralizing NANOBODIES® (V_{HH} sequences) all competed with Synagis®, albeit to different extents. NANOBODIES® (V_{HH} sequences) 15H8 and NC41 competed to a lesser extend, which may indicate an altered binding epitope within antigenic site II than the other NANOBODIES® (V_{HH} sequences).

NANOBODIES® (V_{HH} sequences) 15H8 and NC41 also had relatively low affinities (K_D values of 16 and 8.1 nM, respectively). NANOBODIES® (V_{HH} sequences) 7B2 and NC23 showed off-rates in the 10^{-4} (1/s) range, resulting in K_D values around 1 nM, confirming the strong binding to hRSV observed in ELISA. NANOBODIES® (V_{HH} sequences) 191D3 and 1E4 showed low nM affinities due to very high on-rates. The antigenic site IV-VI binders 15B3 and 191E4 show the highest affinities for F_{TM}-NN of the panel with sub-nanomolar affinities.

Example 23

In Vitro Micro Neutralization of Distinct hRSV Strains

The potency of purified NANOBODIES® (V_{HH} sequences) in neutralization of different type A and B RSV strains was tested by the in vitro micro neutralization assay (see example 15). Viral stocks of RSV Long (Accession No. P12568; ATCC VR-26; see example 15), RSV A-2 (ATCC VR-1540; lot nr. 3199840) and RSV B-1 (ATCC VR-1580; lot nr. 5271356) were prepared into Hep2 cells and subsequently titrated to determine the optimal infectious dose for use in the micro neutralization assay. Results of neutralization potencies of the different purified NANOBODIES® (V_{HH} sequences) are shown in Table C-5. While all six NANOBODIES® (V_{HH} sequences) that recognize the Synagis® epitope could efficiently neutralize type A strains Long and A-2, they failed to neutralize infection with the B-1 strain or did so at concentrations >1 μM. The 101F competitors 15B3 and 191E4 showed very weak neutralization potency on the B-1 strain only when administrated at μM concentrations.

The sequences of the respective F-proteins of the different RSV strains were verified by means of reverse-transcriptase PCR and subsequent sequence analysis. Briefly, total RNA was isolated from RSV-infected Hep2 cells using RNeasy mini kit (Qiagen, Venlo, Netherlands), after which complementary DNA was prepared using Superscript III reverse transcriptase kit (Invitrogen, Carlsbad, Calif.). The F-protein of RSV A strains was amplified and sequenced using the primers described in Kimura et al. 2004 (Antiviral Research 61: 165-171). For amplification of the RSV B-1 strain F-protein the following primers were used: FB1_outer_for: cttagcagaaaaccgtga (SEQ ID NO: 2419); FB1_outer_rev: tgggttgatttgggattg (SEQ ID NO: 2420); FB1_seq_1123-for: ggactgatagaggatggta (SEQ ID NO: 2421); FB1_seq_1526-rev: gctgacttcacttggtaa (SEQ ID NO: 2422). The sequence of RSV B-1 strain corresponded to Accession nr P13843, with an additional point mutation Ser540Leu. The sequence for the RSV Long M2 strain corresponded completely to the reported sequence (Accession nr M22643). The sequence for the strain RSV A-2 corresponded to Accession M11486. See also Table A-3.

Example 24

Construction, Production and Characterization of Multivalent hRSV NANOBODIES® (V_{HH} Sequences)

Multivalent NANOBODY® (V_{HH} sequence) constructs connected by Gly-Ser linkers of different lengths and composition were generated by means of separate PCR reactions (1 for the N-terminal, 1 for the middle (in case of trivalent) and 1 for the C-terminal NANOBODY® (V_{HH} sequence) subunit) using different sets of primers encompassing specific restriction sites. Similarly, multivalent NANOBODY® (V_{HH} sequence) constructs connected by Ala-Ala-Ala linker were generated. All constructs were cloned into an expression vector derived from pUC119 which contained the LacZ promoter, a resistance gene for kanamycin, a multicloning site and the OmpA signal peptide sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector coded for a C-terminal c-myc tag and a (His)6 tag. In case a 35 Gly-Ser-linker was present in the multivalent construct, an expression vector was used derived from pUC119 which contained the LacZ promoter, a resistance gene for kanamycin and the OmpA signal peptide sequence. Directly downstream of the signal peptide a multiple cloning site was present for NANOBODY® (V_{HH} sequence) insertion, followed by a 35Gly-Ser linker encoding DNA sequence and a second multiple cloning site for cloning of a second NANOBODY® (V_{HH} sequence) sequence. In frame with the resulting NANOBODY® (V_{HH} sequence)-35Gly-Ser-NANOBODY® (V_{HH} sequence) coding sequence, the vector coded for a C-terminal c-myc tag and a (His)6 tag. Table C-6 lists the multivalent constructs generated with RSV-specific NANOBODIES® (V_{HH} sequences). The sequences of the multivalent constructs are shown in Table A-2.

Multivalent RSV NANOBODY® (V_{HH} sequence) constructs were expressed, purified and further characterized. Production was done in *E. coli* TG1 cells, followed by purification from the periplasmic fraction via the His-tag by IMAC and desalting, essentially as described in example 22. For certain trivalent constructs (e.g. RSV401, RSV404, RSV406) production was done in *P. pastoris* followed by purification from the medium fraction. All trivalent NANOBODIES® (V_{HH} sequences) were subjected to gel filtration as a final step to remove possible bivalent and monovalent degradation products.

Binding of purified multivalent NANOBODIES® (V_{HH} sequences) to the hRSV F-protein was confirmed in ELISA on both F_{TM}- protein and on hRSV (see example 22). For the majority of NANOBODIES® (V_{HH} sequences) the formatting into bivalent and trivalent constructs resulted in a clear but limited (up to 10-fold increase) avidity effect, with the exception of multivalents of 7B2 and NC23 which showed similar EC50 values as their monovalent counterparts (FIG. 20).

Example 25

Potency of Bi- and Trivalent Constructs to Neutralize hRSV

The potency of the NANOBODY® (V_{HH} sequence) constructs was evaluated in the RSV neutralization assay on different RSV strains (see examples 15 and 23). Bivalent NANOBODIES® (V_{HH} sequences) binding antigenic site II showed marked increases in potencies of 100- to 1000-fold (i.e. much higher than the increase in affinity) in neutralization of Long relative to their monovalent counterparts, with IC50 values ranging from 50-380 pM, being better or similar to Numax Fab. On the RSV B-1 strains however, the potency increase was much less strong, and none of the dimeric constructs was more potent than Synagis®. Surprisingly, this could be overcome by the generation of trivalent constructs, as shown in FIG. 21. Trivalent constructs with three NANOBODIES® (V_{HH} sequences) binding antigenic site II were at least 1000-fold more potent neutralizers on RSV B-1 strains than their monovalent counterparts.

FIG. 22 illustrates that the linker length did not have a clear effect on the gain in potency of bivalent 191D3 constructs compared to monovalent 191D3.

Example 26

Potency of Bi- and Trivalent Biparatopic Constructs to Neutralize hRSV

Biparatopic constructs consisting of one NANOBODY® (V_{HH} sequence) binding antigenic site II and one NANOBODY® (V_{HH} sequence) binding antigenic site IV-VI were analysed for

neutralization. Biparatopic-bivalent constructs generally showed a flatted curve in the neutralization assay, hampering accurate determination of IC50 values (FIGS. 21, **23**). In spite of this, neutralization was improved significantly on both strains (see e.g. RSV205; FIG. 21). This remarkable gain in function was also noted for a second pair of antigenic site II and IV-VI binders, 191D3-191E4. For this pair different linker lengths and orientations were compared, showing that shortening of the linker length clearly enhances the IC50, but only for one orientation (FIG. 23).

Also biparatopic constructs with two different NANOBODIES® (V_{HH} sequences) binding to antigenic site II, 7B2 and 15H8, were analysed for neutralization (RSV204 and 206). Also in this case significant improvement in potency was noted especially for the B-1 strain were potency increased at least 1000-fold versus the monomeric NANOBODIES® (V_{HH} sequences).

Trivalent biparatopic constructs of 7B2 and 15B3 were even more potent neutralizers of both Long and B-1 strains and did not show the flattened curves as observed with bivalent biparatopic constructs (FIG. 21).

Example 27

Reactivity of Monovalent NANOBODIES® (V_{HH} Sequences) with Escape Mutants of the Long Strain

A number of escape mutants, described in Lopez et al. 1998 (J. Virol. 72: 6922-6928), and specific for antigenic site II (R47F/4, R47F/7, RAK13/4, R7C2/11, R7C2/1) or IV-VI (R7.936/1, R7.936/4, R7.936/6, R7.432/1) or the combination of both (RRA3), were selected for testing their reactivity with 10 monovalent NANOBODIES® (V_{HH} sequences), including NANOBODY® (V_{HH} sequence) 191 C7 (EVQLVESGGGLVQAGGSLRLSCAASGSSGVINAMAWHRQAPGKERELVAHISSGGS TYYGDFVKGRFTISRDNAKDTVYLQMNSLKPEDTAVYYCHVPWMDYNRRDYWGQ GTQVTVSS; SEQ ID NO: 2423) previously identified as not binding to antigenic sites II or IV-VI.

This assay was performed according to Lopez et al. 1998 (J. Virol. 72: 6922-6928). In brief, each NANOBODY® (V_{HH} sequence) was tested at 0.2 μg/ml in ELISA using antigen extracts of HEp-2 cells infected with the different escape mutants. Absorbance results were normalized for reactivity on the reference virus strain (Long wild type) strain as well as on the control NANOBODY® (V_{HH} sequence) 191C7. Results are shown in Table C-7.

A reactivity of >75% is indicated as a filled black square, dark hatched squares correspond to a reactivity between 75 and 50%, light hatched squares correspond to a reactivity of 25-50% and less than 25% reactivity is indicated by a blank square. In general

NANOBODIES® (V_{HH} sequences) already identified as antigenic site II binders in previous examples (192C4, 191D3, 191F2, NC23, 15H8, 7B2 and NC41) were found to be sensitive to typical mutations in antigenic site II, while the other NANOBODIES® (V_{HH} sequences) already identified as antigenic site IV-VI binders were indeed sensitive for mutations in these sites.

Example 28

Reactivity of Multivalent NANOBODIES® (V_{HH} Sequences) with Escape Mutants of the Long Strain

Subsequently a number of multivalent constructs was analyzed on a limited panel of escape viruses to assess binding. This assay was performed according to Lopez et al. 1998 (J. Virol. 72: 6922-6928). In brief, each NANOBODY® (V_{HH} sequence) was tested at 0.1 μg/ml for monovalent NANOBODIES® (V_{HH} sequences) and at 0.05 μg/ml for bi- and trivalent NANOBODIES® (V_{HH} sequences) in ELISA using antigen extracts of HEp-2 cells infected with the different escape mutants. Absorbance results were normalized for reactivity on the reference virus strain (Long wild type) strain as well as on the control NANOBODY® (V_{HH} sequence) (191E4; SEQ ID NO: 166, in this particular assay). Results are shown in Table C-8.

A reactivity of >75% is indicated as a filled black square, dark hatched squares correspond to a reactivity between 75 and 50%, light hatched squares correspond to a reactivity of 25-50% and less than 25% reactivity is indicated by a blank square. Remarkably, multivalent constructs showed improved binding compared to their monovalent counterpart, to the mutant virus R7C2/11. In addition the biparatopic construct RSV403 was not sensitive to any of the mutants.

Example 29

Intranasal Delivery of Bivalent NANOBODY® (V_{HH} Sequence) RSV101

To test the capacity of NANOBODY® (V_{HH} sequence) RSV101 (SEQ ID NO: 2382) to neutralize virus in vivo, a mouse model was used. In this model, female Balb/c mice (9-10 weeks old) were inoculated intranasally with 100 μg of purified RSV101 dissolved in 50 μl PBS. As an irrelevant NANOBODY® (V_{HH} sequence) control, the bivalent NANOBODY® (V_{HH} sequence) 12D2biv was used. In addition, one group of mice received 100 μg Palivizumab (Synagis®) and a fourth group received PBS only. Five hours later, 10^6 infectious units of the RSV A2 strain were administered intranasally. Four days and 1 day before virus

infection and 1 and 4 days after infection mice were treated with cyclophosphamide (first dosing at 3 mg/kg; subsequent dosing at 2 mg/kg all administered s.c.) to suppress the immune system and as such to increase virus replication.

Three and 5 days after viral challenge, mice were killed; lungs were removed, homogenized and cleared from tissue by centrifugation. Sub-confluent Hep-2 cells, incubated in serum-free medium, were infected with serial dilutions of cleared lung homogenates. Four hours after infection the medium was removed and replaced by fresh medium containing 1% FCS and 0.5% agarose. Two to three days after infection the agarose overlay was removed to allow staining of RSV-plaques by an anti-RSV antibody.

Infectious virus (pfu/lung) was recovered from all animals in the negative control groups (PBS and 12D2biv) in lung homogenates on day 3 (FIG. 24A) and 5 (FIG. 24B) after challenge. In FIG. 24C, the mean of infectious virus titers (pfu/lung) is represented. None of the animals in the RSV 101 and Synagis-treated group had detectable infectious virus on day 3 and 5 post challenge. Intranasal delivery of bivalent NANOBODY® (V_{HH} sequence) RSV101 protected against infection and replication of RSV strain A2 in mice.

Example 30

Functionality of NANOBODY® (V_{HH} Sequence) RSV101 after Intranasal Administration

In order to test whether NANOBODIES® (V_{HH} sequences) or palivizumab antibodies might still be present in lungs 3 and 5 days after inoculation, lung homogenates of PBS treated mice were pre-incubated for 1 h with the same volume of lung homogenates from the different experimental groups described in Example 29, prepared either three or five days post-infection.

As shown in FIG. 25A, incubation of lung homogenates from PBS treated mice with lung homogenates prepared three days after infection from either RSV101 or palivizumab but not 12D2biv treated mice neutralized the virus present in the lung homogenates from PBS treated mice. In contrast, none of the lung homogenates of mice treated with RSV101 or Synagis prepared five days after infection could severely neutralize the virus present in the lung homogenates of PBS treated mice (FIG. 25B).

Taken together, these data show that the functional bivalent NANOBODY® (V_{HH} sequence) RSV 101 remains present and functionally active in the lungs for at least 72 hours after administration.

To further demonstrate the presence of functional virus-neutralizing NANOBODIES® (V_{HH} sequences) in the lung homogenates, 500 plaque forming units (pfu) of RSV were incubated

with different amounts of lung homogenates. These mixtures were incubated for 90 minutes at room temperature. Next, mixtures were put on HepG2 cells grown in 96 well plates. After 2 hours cells were washed and an overlay of growth medium with 0.5% agarose was added. After three days RSV plaques were visualized (FIG. 54). From the data (FIG. 54) it is clear that lunghomogenates from all 5 mice that received RSV101 NANOBODY® (V_{HH} sequence) three days before mice were killed, neutralized the 500 pfu of RSV when 8 and 2 μl of homogenates were used. This was not observed using lung homogenates form contole NANOBODY® (V_{HH} sequence) (12B2biv) treated mice.

Example 31

Viral RNA is not Detected in the Lungs of Mice Pre-Treated Intranasally with RSV101

The results described in Example 29 demonstrated that no infectious virus was present in the lungs of mice treated with RSV 101. However, there was still the possibility that virus had infected cells and that viral genomic RNA was replicated with release of non-infectious viral particles or without release of viral particles. To investigate this possibility, the presence of viral RNA was determined by qPCR. RNA was isolated from 100 μl of each long homogenate (1000 μl) prepared 5 days post-infection. By the use of an M-gene specific primer RSV genomic RNA specific cDNA was synthesized and quantified by qPCR (in duplicate). The level of viral genomic RNA in each lung homogenate was calculated relative to a lung sample which showed the lowest qRT-PCR signal (normalized to value of 1). As shown in Table C-9, the presence of relative viral genomic RNA in lungs of mice treated with RSV101 and Synagis® was reduced strongly compared to PBS or 12D2biv treated mice.

Example 32

The HA-Pseudotyped Neutralization Assay

A HA pseudotyped neutralization assay was developed as described in Temperton et al. 2007 (Temperton N J, Hoschler K, Major D et al. A sensitive retroviral pseudotype assay for influenza H5N1-neutralizing antibodies. Influenza and Other Respiratory Viruses 2007 1: 105-112). The construction of HA pseudotyped viruses and assays was also done according to Temperton et al. 2007.

Plasmids and Cell Lines

Plasmid pI.18/VN1194 HA was constructed at NIBSC (Hertfordshire, UK). The full-length HA ORF from A/Vietnam/1194/04 was amplified by PCR and cloned into the expression vector pI.18. This backbone plasmid is a pUC-based plasmid incorporating promoter and

Intron A elements from human cytomegalovirus.

The MLV and HIV gag/pol constructs have been described previously (Besnier C, Takeuchi Y, Towers G. 2002, Restriction of lentivirus in monkeys. Proc. Natl. Acad. Sci. USA 9: 11920-11925) The luciferase (Luc) reporter construct MLV-Luc has been described in Op De Beeck A, Voisset C, Bartosch B et al. 2004 (Characterization of functional hepatitis C virus envelope glycoproteins. J. Virol. 78: 2994-3002). Vesicular stomatitis virus envelope protein (VSV-G) expression vector pMDG has been described previously (Naldini L, Blomer U, Gallay P et al. 1996, In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. Science 272: 263-267). All cell lines were cultured in Dulbecco's modified eagle medium (DMEM) with Glutamax and high glucose (Gibco, Paisley, Scotland, UK), supplemented with 10% fetal calf serum and penicillin/streptomycin, except for HEK 293T cells (15% fetal calf serum).

Viral Vector Production and Infection of Target Cells

Confluent plates of 293T cells were split 1:4 the day before transfection. Each plate of 293T cells was transfected with 1 μg gag/pol construct, 1.5 g Luc reporter construct, and 1.5 g HA- or VSV-G-expressing construct by using the Fugene-6 transfection reagent. At 24 h post-transfection, 1 U of exogenous neuraminidase (Sigma, St. Louis, Mo., USA) was added to induce the release of HA-pseudotyped particles from the surface of the producer cells. Supernatant was harvested 48 and 72 h post-transfection, filtered through 0.45-lm filters, and stored at −80° C. MLV vector titers were measured on human 293T, quail QT6, canine MDCK, porcine PK15 and ST-IOWA cells and are presented as infectious units (IU) per milliliter. Briefly, cells were infected with vector, and Luc titers were determined 72 h later by Luc assay. Titers were expressed as RLU for Luc.

MLV(HA) Pseudotype Neutralization Assay

Serum samples (5 n1) were heat inactivated at 56° C. for 30 min, twofold serially diluted in culture medium, and mixed with MLV(HA) virions (10 000 RLU for Luc) at a 1:1 v/v ratio. Purified NANOBODIES® (V_{HH} sequences) (10 or 20 n1) were diluted to 100 n1 and twofold serially diluted in culture medium, and mixed with MLV(HA) virions (10 000 RLU for Luc) at a 1:1 v/v ratio. After incubation at 37° C. for 1 h, 1×10^4 293T cells were added to each well of a 96-well flat-bottomed plate. Relative light units (RLU) for Luc were evaluated 48 h later by luminometry using the Promega Bright-Glo system (Promega, Madison, Wis., USA) according to the manufacturer's instructions. IC90/IC50-neutralizing antibody titers were determined as the highest serum dilution resulting in a 90/50% reduction of infection (as measured by marker gene transfer) compared with a pseudotype virus only control. For Luc, titers <100 are designated negative.

Example 33

Llamas Develop High Virus-Neutralizing Antibody Titers after Immunizations with Purified H5 HA

Sera taken from immunized llamas before (pre-immune) and 21 and 48 days after the first immunization was tested in the pseudotyped neutralization assay as described in Example 32 (FIG. 26). Pre-immune serum showed no neutralizing activity, while IC90s of 25600 to 51200 were present in llama 140 and 163, respectively.

Example 34

Identification of NANOBODIES® (V_{HH} Sequences) that Neutralize HA Pseudotyped Virus

Several purified NANOBODIES® (V_{HH} sequences) were tested in the pseudo typed virus neutralization assay described in Example 32. In FIG. 28, the neutralization of a single 10 fold dilution of different NANOBODIES® (V_{HH} sequences) (202-A5; SEQ ID NO: 128, 202-B10; SEQ ID NO: 130, 202-B7; SEQ ID NO: 131, 202-C1; SEQ ID NO:134, 202-C2; SEQ ID NO: 136, 202-C9; SEQ ID NO: 139, 202-D5; SEQ ID NO: 140, 202-E11; SEQ ID NO: 143, 202-E5; SEQ ID NO: 145, 202-E7; SEQ ID NO: 147, 202-F4; SEQ ID NO: 151, 202-F8; SEQ ID NO: 152, 202-G11; SEQ ID NO: 153, 202-G3; SEQ ID NO: 154, 202-G8; SEQ ID NO: 155, 202-A12; SEQ ID NO: 127, 202-E4; SEQ ID NO: 2447, 202-A10; SEQ ID NO: 126, 202-C8; SEQ ID NO: 138, 202-E6; SEQ ID NO: 146) is shown. Only NANOBODY® (V_{HH} sequence) 202-C8 strongly reduced luciferase activity, indicative for a virus neutralizing activity of this NANOBODY® (V_{HH} sequence). The identification of two more virus-neutralizing NANOBODIES® (V_{HH} sequences) 203-B12 (SEQ ID NO: 2439) and 203-H9 (SEQ ID NO: 2445) is depicted in FIG. 29.

Example 35

Combinations of NANOBODIES® (V_{HH} Sequences)

Combined treatment with different virus neutralizing antibodies might results in additive or even synergistic neutralizing effect (Zwick M B, Wang M, Poignard P, Stiegler G, Katinger H, et al. 2001, Neutralization synergy of human immunodeficiency virus type 1 primary isolates by cocktails of broadly neutralizing antibodies. J Virol, 75: 12198-12208; Laal S, Burda S, Gorny M K, Karwowska S, Buchbinder A et al. 1994, Synergistic neutralization of human immunodeficiency virus type 1 by combinations of human monoclonal antibodies. J. Virol. 68: 4001-4008; Li A, Baba T W, Sodroski J, Jolla-Pazner S, Gomy M K, et al. 1998,

Synergistic neutralization of simian-human immunodeficiency virus SERV by triple and quadruple combinations of human monoclonal antibodies and high-titer anti-human immunodeficiency. J. Virol. 72: 3235-40). However, this was not observed when combinations of 202-C8 with 203-B12, 202-C8 with 203-H9 or 203-B12 with 203-H9 were tested in the pseudotyped neutralization assay (FIG. 30).

Example 36

Bi- and Trivalent NANOBODIES® (V_{HH} Sequences)

Protocols are available for construction of a bivalent or trivalent NANOBODY® (V_{HH} sequence) connected by Gly-Ser linker(s) of any desired length and composition. It is based on the separate PCR reactions (1 for the N-terminal, 1 for the middle (if trivalent) and 1 for the C-terminal VHH subunit) using different sets of primers. Different linker lengths can also be introduced by the primers.

Bivalent and trivalent NANOBODIES® (V_{HH} sequences) with different linker lengths from 202-C8 and 203-B12 and 203-H9 were constructed (SEQ ID NO's: 2423 to 2430; Table A-4). When tested in the pseudotyped neutralization assays all bivalent and trivalent NANOBODIES® (V_{HH} sequences) showed superior neutralization potencies compared to the monovalent building blocs. (FIG. 31).

To test the potency of different NANOBODY® (V_{HH} sequence) formats against different H5 strain viruses, lentiviral pseudotyped viruses were used. For transfection, 5×10^6 HEK-293T cells were plated 24 h prior to addition of a complex comprising plasmid DNA and Fugene 6™ that facilitated DNA transport into the cells (as described by the manufacturer; Roche, UK). The human immunodeficiency virus type 1 (HIV-1) gag-pol construct pCMV-A8.91 and firefly luciferase reporter construct (pCSLW, where the luciferase gene has been cloned into pCSGW in place of GFP) were transfected concurrently with the required H5 HA envelope construct (pI.18-H5HA from different H5 clades) at a μg ratio of 1:1.5:1 respectively. 24 hours post-transfection, 1 U exogenous bacterial NA was added to each plate to effect particle release into the supernatant. At 48 and 72 hrs post-transfection, virus was harvested by filtration through a 0.45 uM filter and stored at −80 C until needed. Neutralization assays were performed very similar to the previously described MLV(HA) assays (Example 32).

When bivalent and trivalent NANOBODIES® (V_{HH} sequences) with different linker lengths from 202-C8 and 203-H9 were tested against these different H5 variants using the lentiviral pseudotyped neutralization assays all bivalent and trivalent NANOBODIES® (V_{HH} sequences) showed superior neutralization potencies compared to the monovalent building blocs (FIGS. 57 and 58). While certain viruses where hardly neutralized by the

monovalent, such variants were efficiently neutralized by bivalent and/or trivalent NANOBODIES® (V_{HH} sequences).

Example 37

In Vivo Neutralization of Influenza Virus by NANOBODY® (V_{HH} Sequence) 202-C8

To test the capacity of NANOBODY® (V_{HH} sequence) 202-C8 to neutralize virus in vivo, a mouse model was used. In this model, female Balb/c mice (6-7 weeks old) were inoculated intranasally with 100 μg of purified 202-C8 dissolved in 50 μl PBS. As an irrelevant NANOBODY® (V_{HH} sequence) control, the RSV NANOBODY® (V_{HH} sequence) 191-D3 (SEQ ID NO: 159) was used. In addition, one group of mice received PBS only. Four hours later, 1 LD50 of the mouse adapted NIBRG-14 virus (Temperton et al. 2007) was administered intranasally. The NIBRG-14 virus contains the HA (with the polybasic cleavage site removed) and the NA of the A/Vietnam/1194/2004 (H5N1) virus. The internal viral genes are of the A/Puerto Rico/8/1934(H1N1).

Four and six days after viral challenge, mice were killed, lungs were removed and homogenized. Viral titers (TCID50) were determined by infection of MDCK cells with serial dilutions of lung homogenates. The presence of virus in cell supernatant was determined by hemagglutination assays (Table C-10). Titers were calculated according the method of Reed, L. J. and Muench, H. 1938 (A simple method of estimating fifty percent endpoints. The American Journal of Hygiene 27: 493-497). A value of "0" was entered if no virus was detected. The geometric mean and standard deviation are reported for each group at each time point.

Mice treated with 202-C8 never showed any sign of disease during the whole experiment. The PBS and 191-D3-treated mice showed clinical signs, including ruffled fur, inactivity, hunched posture, and depression.

Virus was recovered from all animals in the negative control groups (PBS and 191-D3) in lung homogenates on day 4 and 6 after challenge. None of the animals in the 202-C8-treated group had detectable virus titers on day 4 and 6 post challenge (Table C-10).

Example 38

Functionality of NANOBODY® (V_{HH} Sequence) 202-C8 in the Lungs after Inoculation

To test how long NANOBODY® (V_{HH} sequence) 202-C8 remains active in the lungs after

intranasal inoculation, female Balb/c mice (6-7 weeks old) were inoculated intranasally with 100 g of purified 202-C8 dissolved in 50 l PBS. As an irrelevant NANOBODY® (V_{HH} sequence) control the RSV NANOBODY® (V_{HH} sequence) 191-D3 was used. In addition, one group of mice received PBS only. All mice received 1 LD50 of the mouse adapted NIBRG-14 intranasally, but virus was given 4, 24 or 48 hours after inoculation of the NANOBODIES® (V_{HH} sequences). Four days after viral challenge, mice were killed, lungs were removed and homogenized. Viral titers (TCID50) were determined by infection of MDCK cells with serial dilutions of lung homogenates. The presence of virus in cell supernatant was determined by hemagglutination assays. Titers were calculated according the method of Muench and Reed. A value of "0" was entered if no virus was detected. The geometric mean and standard deviation are reported for each group at each time point (Table C-11).

Mice pretreated with 202-C8 never showed any signs of disease during the whole experiment. The PBS and 19-D3-treated mice showed clinical signs, including ruffled fur, inactivity, hunched posture, and depression and a reduction in body weight (FIG. 32, right panel).

Virus was recovered from all animals pretreated with the control NANOBODY® (V_{HH} sequence) 191-D3 or PBS. Virus could not be detected in the lungs of mice that were treated with 202-C8, 4 and 24 hours before virus inoculation. No virus could be detected in lungs of three mice of seven treated with 202-C8 48 hours before virus inoculation (FIG. 32, left panel and Table C-11). Viral titers in the remaining 4 mice were on average reduced 50 fold compared to the viral titers found in the lungs of mice treated with 191-D3 48 hours before vial inoculation.

Taken together, these data show that the monovalent NANOBODY® (V_{HH} sequence) 202-C8 remains actively present in the lungs for at least 48 hours after intranasal administration.

Example 39

Surface Plasmon Resonance for Affinity Measurements

To measure the affinity of selected NANOBODIES® (V_{HH} sequences), Surface Plasmon resonance was used. Two thousand Reference units (RU), H5 was coupled on a Sensorchip CM5 in 10 mM sodium acetate pH 5.5 and immobilized by aminecoupling (Biacore, aminecoupling kit). Dilutions of the NANOBODIES® (V_{HH} sequences) were added at concentrations 250-62.5 nM and run over a reference flow channel with no HA and then over the HA coupled flow channel at a flow rate of 5 μl/min. Evaluation of the KA and KD was performed by fitting a 1:1 interaction model (Langmuir binding model), removing the background from the reference flow channel. The kinetic curves of the NANOBODIES® (V_{HH} sequences) (62.5 nM) are shown in FIG. 33. The 202-C8 has a KD of 10 nM, the 203-

B12 of 30 nM and the 203-H9 of 15.5 nM.

Example 40

Determination of Binding Efficacy of Purified Multivalent NANOBODIES® (V_{HH} Sequences) to H5

In order to determine binding specificity to H5, the different multivalent NANOBODIES® (V_{HH} sequences) were tested in an ELISA binding assay in different concentrations. In short, 2 μg/ml of H5 were immobilized directly on Maxisorp microtiter plates (Nunc). Free binding sites were blocked using 4% Marvel in PBS. Next, Dilutions (1/10) of the NANOBODIES® (V_{HH} sequences) starting with 10 pM in 100 μl 2% Marvel PBST were allowed to bind to the immobilized antigen. After incubation and a wash step, NANOBODY® (V_{HH} sequence) binding was revealed using a rabbit-anti-VHH secondary antibody (a VHH). After a wash step the NANOBODIES® (V_{HH} sequences) were detected with a HRP-conjugated goat-anti-rabbit antibody (GARPO). Binding specificity was determined based on OD values compared to controls (192-C4; SEQ ID NO: 163) against HRSV and 213-H7-15GS-213-H7 (SEQ ID NO: 2427) against Rabies). The multivalent NANOBODIES® (V_{HH} sequences) show higher binding capacity than the monovalent (FIG. 34).

Example 41

Multivalent NANOBODIES® (V_{HH} Sequences) Blocking the Interaction of H5 with Sialic Acid on Fetuin

To investigate if the multivalent NANOBODIES® (V_{HH} sequences) were able to block the interaction of H5 with sialic acid on fetuin, the same experimental set up was used as described in Example 13. Fetuin (from fetal calf serum, F2379, Sigma-Aldrich) was coated (10 μg/ml) in a maxisorb 96 well plate and incubated over night at 4° C. The plate was blocked in 2% BSA and then 0.7 μg/ml biotinylated HA (HA-bio) and different dilutions of purified multivalent NANOBODIES® (V_{HH} sequences) were added for competition, diluted 1/10, starting with 500 nM. After incubation for 1 hour, HRP conjugated streptavidin was added and incubated for 1 hour. Binding specificity of HA-bio not recognized by purified multivalent NANOBODIES® (V_{HH} sequences) was determined based on OD values compared to controls having received control NANOBODIES® (V_{HH} sequences) (192-C4 against HRSV and 213H7-15GS-213H7 against Rabies). Results of competition between the purified multivalent NANOBODIES® (V_{HH} sequences) and fetuin for binding to HA-bio is shown in FIG. 35. The multivalent NANOBODY® (V_{HH} sequence) clones showed increased competition compared to the monovalent which may indicate that the competing

NANOBODIES® (V_{HH} sequences) recognize the sialic acid binding site on the HA and that multivalent NANOBODIES® (V_{HH} sequences) have an increased capacity to block this site.

Example 42

Pharmacokinetics of 191D3, ALX-0081 and RANKL008A in the Male Wistar Rat after Single Intratracheal or Intravenous Administration

42.1

Test Items

Test items are described in Table C-12.

42.2

Methods

Animal Model

101 male Wistar rats (approximately 300 gram and 11 weeks old) were used for this study, a strain bred by Charles River Laboratories, Germany. The animals were held for at least 6 days for adaptation. Following the initial health check, the animals were weighed and allocated by means of a computerised randomisation program to the test groups; only healthy animals were used.

The sterile test substances were thawed in a water bath at 25° C. while swirling gently for 10 minutes. For intratracheal dosing, no further dilutions were required. For intravenous administration, the required amount of test substance was diluted in sterile DPBS ((Dulbecco's modified) Phosphate Buffered Saline) down to the desired concentrations. The test item formulations were freshly prepared within 4 hours prior to dosing.

Dose and Route of Administration

The different test groups and the dose levels are given in Table C-13. The i.v. bolus dose was given into a tail vein. The amount of test item for i.v. administration was adjusted to each animal's current body weight. The i.t. dose was administered intratracheally with a syringe with a blunt stainless steel dosing needle, after deep anaesthetization with isoflurane. The amount of test item for i.t. administration was set to 100 μL/animal, irrespective of body weight. Based on the actual body weights of the animals, an approximate dose in mg/kg could be calculated from the averaged body weights for comparison with the i.v. route: 4

mg/kg for RSV NB2, 5 mg/kg for ALX-0081 and 5 mg/kg for RANKL008a.

The average body weight of intratraceally dosed animals was on average 0.315 kg (RSV NB2 group), 0.317 kg (ALX-0081 group), 0.323 kg (RANKL008a group). As these animals received a fixed dosing of 100 μL/animal, the corresponding mean dose per b.w. were calculated at 3.6 mg/kg (RSV NB2 group), 3.1 mg/kg (ALX-0081 group), 3.2 mg/kg (RANKL008a group).

Blood and BALE Sampling and Processing.

After i.v. dosing, blood was sampled (approximately 300 μL) at 0.05, 0.25, 0.5, 1, 2, 4, 6, and 24 hours from the tail vein of RSV NB2- and ALX-0081-dosed animals and at 0.05, 0.25, 0.5, 1, 2, 4, 8, 24, and 48 hours from RANKL008a-dosed animals. All blood samples were placed on melting ice. Within approximately 30 minutes after sampling, the blood samples were centrifuged at 5° C. for 10 minutes (1500 g). Citrated plasma was stored in polypropylene tubes at approximately ≦−75° C. until dispatch on dry ice to the Sponsor.

After intratracheal dosing, blood, lungs, and BALF were collected (at necropsy following deep anaesthesia with isoflurane) at 0.05, 0.333, 1, 2, 4, 6, and 24 hours from RSV NB2-dosed rats and ALX-0081-dosed rats and at 0.05, 0.333, 1, 2, 4, 8 and 24 hours from animals dosed with RANKL008a. By means of an aorta punction 4 mL of blood was withdrawn. Within 42 minutes after sampling, the blood samples were centrifuged at 5° C. for 10 minutes (1500 g). Citrated plasma was stored in polypropylene tubes at approximately ≦−75° C. until dispatch on dry ice to the Sponsor. Following the removal of blood, lungs were harvested. First, the lungs including trachea were rinsed with iced DPBS and weighed. Then, BALF was collected. Five mL lavage fluid (DPBS) was carefully put into the lungs. After approximately 10 seconds, as much fluid as possible was returned to the syringe. BALF was transferred to an empty tube and directly stored on melting ice. This procedure was repeated. The second collection of BALF was added to the first collection. The volume of BALF that was collected was documented and reported. Subsequently, BALF was stored at approximately ≦−75° C. until dispatch on dry ice to the Sponsor.

Determination of RSV NB2 in Rat Plasma or BALE

96-well microtiter plates (Maxisorp, Nunc, Wiesbaden, Germany) were coated overnight at 4° C. with 100 μl hRSV (12.5 μg/mL, Hytest. Turku, Finland). Thereafter wells were aspirated, blocked (RT, 1 h, PBS-0.1% casein) and washed. The standards, QC, and predilutions of the test samples were prepared in a non-coated (polypropylene) plate in 100% rat plasma or BALF and incubated for 30 min at RT while shaking at 600 rpm. A 1/10 dilution of the samples in PBS-0.1% casein (final concentration of rat plasma or BALF is 10%) was transferred to the coated plate and incubated for 1 hr at RT while shaking at 600 rpm. After three washing steps with PBS-0.05% Tween20, the plates were incubated with

polyclonal rabbit anti-NANOBODY® (V_{HH} sequence) monoclonal K1 (1/2000 in PBS-0.1% casein, in-house) for 1 hr at RT while shaking at 600 rpm. After 3 washing steps with PBS-0.05% Tween20, 100 μl horseradish peroxidase (HRP) labeled polyclonal goat anti-rabbit (1/2000 in PBS-0.1% casein, DakoCytomation, Glostrup, Denmark) was incubated for 1 hr at RT while shaking at 600 rpm. Visualization was performed covered from light for 20 min with 100 μl 3,3′,5,5′-tetramethylbenzidine (esTMB, SDT, diluted 1/3). After 20 min, the colouring reaction was stopped with 100 μl 1N HCl. The absorbance was determined at 450 nm, and corrected for background absorbance at 620 nm. Concentration in each sample was determined based on a sigmoidal standard curve. The lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) of the different assays are listed in Table C-14.

Determination of ALX-0081 in Rat Plasma or BALE

96-well microtiter plates (Maxisorp, Nunc) were coated overnight at 4° C. with 100 μl vWF in PBS (2.5 μg/mL, Haemate P1200/500—ZLB Behring). Thereafter wells were aspirated, blocked (RT, 1 h, PBS-0.1% casein) and washed. The standards, QC, and predilutions of the test samples were prepared in a non-coated (polypropylene) plate in 100% rat plasma or BALF and incubated for 30 min at RT while shaking at 600 rpm. A 1/5 dilution of the samples in PBS-0.1% casein (final concentration of rat plasma or BALF is 20%) was transferred to the coated plate and incubated for 1 hr at RT while shaking at 600 rpm. After three washing steps with PBS-0.05% Tween20, the plates were incubated with the anti-ALX0081 NB vWF12B2-G59-12B2-BIO (1 μg/ml in PBS-0.1% casein, in-house) for 30 min at RT while shaking at 600 rpm. After 3 washing steps with PBS-0.05% Tween20, 100 μl streptavidin-HRP (1/2000 in PBS-0.1% casein, DakoCytomation) was incubated for 30 min at RT while shaking at 600 rpm. Visualization was performed covered from light for 15 min with 100 μl 3,3′,5,5′-tetramethylbenzidine (esTMB, SDT, diluted 1/3). After 15 min, the coloring reaction was stopped with 100 μl 1N HCl. The absorbance was determined at 450 nm, and corrected for background absorbance at 620 nm. Concentration in each sample was determined based on a sigmoidal standard curve. The LLOQ and ULOQ of the different assays are listed in Table C-15.

Determination of RANKL008a in rat plasma or BALE

96-well microtiter plates (Maxisorp, Nunc) were coated overnight at 4° C. with 100 μl neutravidin in PBS (2 μg/mL, Pierce, Rockford, Ill.). Wells were aspirated and blocked. After 3 washing steps with PBS-0.05% Tween20, biotinylated RANKL (0.5 μg/mL in PBS-0.1% casein) was captured by incubating 100 μl for 1 hr at RT while shaking at 600 rpm. After this incubation step, wells were washed. The standards, QC, and predilutions of the test samples were prepared in a non-coated (polypropylene) plate in 100% rat plasma or BALF and incubated for 30 min at RT while shaking at 600 rpm. A 1/10 dilution of the samples in

PBS-0.1% casein (final concentration of rat plasma or BALF is 10%) was transferred to the coated plate and incubated for 1 hr at RT while shaking at 600 rpm. After three washing steps with PBS-0.05% Tween20, the plates were incubated with polyclonal rabbit anti-NANOBODY® (V_{HH} sequence)monoclonal R23 (1/2000 in PBS-0.1% casein, in-house) for 1 hr at RT while shaking at 600 rpm. After 3 washing steps with PBS-0.05% Tween20, 100 μl horseradish peroxidase (HRP) labelled polyclonal goat anti-rabbit (1/5000 in PBS-0.1% casein, DakoCytomation, Glostrup, Denmark) was incubated for 1 hr at RT while shaking at 600 rpm. Visualization was performed covered from light for 10 min with 100 μL 3,3′,5,5′ -tetramethylbenzidine (esTMB, SDT, diluted 1/3). After 10 min, the coloring reaction was stopped with 100 μL 1N HCl. The absorbance was determined at 450 nm, and corrected for background absorbance at 620 nm. Concentration in each sample was determined based on a sigmoidal standard curve. The LLOQ and ULOQ of the different assays are listed in Table C-16.

Non-Compartmental Pharmacokinetic Data Analysis

Individual plasma and mean BALF concentration-time profiles of all rats were subjected to a non-compartmental pharmacokinetic analysis (NCA) using WinNonlin Professional Software Version 5.1 (Pharsight Corporation, Mountain View Calif., USA). The pre-programmed Models 200 and 201 were used to analyse the intratracheal and intravenous data, respectively. The linear-up/log down trapezoidal rule was used to calculate the area under the concentration-time data.

1.3

Results

Plasma Concentrations of RSV NB2, ALX-0081 and RANKL008a

The observed plasma concentration-time data of the individual animals after a single i.v. administration and of the mean (n=4 animals/time-point; destructive sampling) plasma concentration-time data after a single i.t. administration of RSV NB2, ALX-0081, and RANKL008a are shown in FIGS. 36 (i.v; data for all compounds), **37** (RSV NB2 i.v. and i.t. data), **38** (ALX-0081 i.v. and i.t. data), and **39** (RANKL008a i.v. and i.t. data). The individual (i.v.) and both individual and mean plasma concentrations (i.t.) are listed in Tables C-17, C-18 and C-19, respectively.

Plasma Pharmacokinetic Analysis of RSV NB2, ALX-0081 and RANKL008a

An overview of the basic pharmacokinetic parameters obtained by non-compartmental PK analysis of RSV NB2 (4 mg/kg i.v. & 3.6 mg/kg i.t.), ALX-0081 (5 mg/kg i.v. & 3.1 mg/kg i.t.) and RANKL008a (5 mg/kg i.v. & 3.2 mg/kg i.t.) is given in Tables C-20, C-21 and C-22.

The PK parameters discussed herein were obtained using non-compartmental analysis (NCA). For rat 1 and 2 (RSV NB2 i.v.), rat 6 (ALX-0081 i.v.) and rat 9 (RANKL008a i.v.) difficulties in blood sampling occurred, and due to the limited data, these animals were excluded from subsequent pharmacokinetic calculations. The terminal parameters for some of the animals were calculated based on only two data-points in the terminal phase.

After i.v. administration of RSV NB2 4 mg/kg and ALX-0081 5 mg/kg comparable plasma PK profiles were observed (FIG. 36). This was also reflected in similar pharmacokinetic parameters for the monovalent RSV NB2 and bivalent ALX-0081. The mean clearance was estimated at 363 mL/hr/kg and 337 mL/hr/kg for RSV NB2- and ALX-0081-dosed rats. The corresponding mean Vss values were 250 mL/kg (RSV NB2) and 252 mL/kg (ALX-0081). The plasma concentrations of these NANOBODIES® (V_{HH} sequences) were only detectable up to six hours (detection limit of 4 ng/mL for RSV NB2 and 3.75 ng/mL for ALX-0081) and the terminal half-lives were calculated at 0.926 hours for RSV NB2 and 2.06 hours for ALX-0081. For the trivalent RANKL008a administered intravenously (5 mg/kg), substantially lower mean clearance (9.00 mL/hr/kg) and Vdss values were calculated. The terminal half-lives were appreciably longer (12.6 hours). This is explained by the fact that RANKL008a is a half-life extended NANOBODY® (V_{HH} sequence) (through binding of the ALB8 component) which is cross reactive with rat albumin, but with lower affinity relative to human serum albumin.

After i.t. administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008a (3.2 mg/kg), comparable terminal half-lives in the plasma were observed for the three NANOBODIES® (V_{HH} sequences) (RSV NB2: 9.48 hr, ALX-0081: 10.5 hr and RANKL008a: 13.0 hr). For RSV NB2 and ALX-0081 the half-lives are longer after i.t. administration than after i.v. administration. It is conceivable that for these rapidly cleared compounds, the absorption is the rate limiting step resulting in flip-flop kinetics (i e kinetics are absorption rate controlled and the terminal phase is driven by the slow absorption from the site of administration (the lung) to the systemic circulation.

The exposure after i.t. administration was lower for all NANOBODIES® (V_{HH} sequences) as compared to that after i.v. administration. This resulting bioavailabilities were 22.1%, 13.9%, and 6.9% for RSV NB2 (16.6 kD), ALX-0081 (27.9 kD), and RANKL008a (40.9 kD), respectively.

For lung topical applications (RSV NB2), a high pulmonary exposure is desired. It could be expected that a faster and more complete absorption (resulting in a higher bioavailability) would not benefit pulmonary exposure. Therefore, RSV NANOBODIES® (V_{HH} sequences) with a higher molecular weight (f.e. a trivalent RSV NANOBODY® (V_{HH} sequence)) could possibly lead to enhanced local (pulmonary) exposures.

The current data indicate that systemic exposure to NANOBODIES® (V_{HH} sequences) can

be achieved after intratracheal administration, suggesting that the pulmonary route may be viable as non-invasive method of delivery of NANOBODIES® (V_{HH} sequences). Notably, the use of specific delivery formulations and/or devices could significantly improve bioavailability after pulmonary application. It is suggested that the bioavailability may be improved around 5 times (i.t. vs aerosol—see e.g. table 2 in Patton J., Fishburn S., Weers J. 2004, The Lung as a Portal of Entry for Systemic Drug Delivery. Proc. Am. Thorac. Soc. 1: 338-344).

BALE Concentrations of RSV NB2, ALX-0081 and RANKL008a

The mean observed BALF concentration-time profiles after a single intratracheal administration of RSV NB2, ALX-0081 and RANKL008a to male rats is shown in FIG. 40. Individual and mean BALF concentrations are listed in Table C-23 and C-24, respectively.

The terminal half-lives of the three NANOBODIES® (V_{HH} sequences) in BALF were based on the two last data-points only. Of note is also that there was quite some inter-individual variability as indicated by the large standard deviations (see Table C-24). After i.t. administration, comparable terminal half-lives were observed in plasma (RSV NB2 9.48 hr, ALX-0081 10.5 hr and RANKL008a 13.0 hr) and in BALF (RSV NB2 16.0 hr, ALX-0081 9.21 hr and RANKL008a 11.6 hr), supporting the notion that the plasma kinetics are likely absorption rate controlled.

Following intratracheal administration, the RSV NB2, ALX-0081, RANKL008a NANOBODY® (V_{HH} sequence) exposure in BALF was observed for at least 24 hours (i.e. the last sampling time for BALF).

Amounts of RSV NB2, ALX-0081 and RANKL008a in BALE

After intratracheal dosing broncho-alveolar lavage fluid (BALF) was collected at necropsy as described in detail earlier.

Theoretically, the amount of NANOBODY® (V_{HH} sequence) in the lung at a given time-point can be obtained by multiplying the measured concentration of each BALF sample by the volume of DPBS added (10 mL), provided that the NANOBODY® (V_{HH} sequence) is efficiently washed out. These individual calculated amounts and their corresponding mean (+SD) values are listed in Table C-25 and C-26, respectively.

Note however that large variations occurred in the recovery of the BALF. For some animals it was possible to recover 9.5 mL fluid after injecting 10 mL DPBS, while for other animals only 3 mL was recovered. Furthermore, since the lavage is performed twice and combined, in a single vial, it is impossible to determine how much volume was recovered from the first or second lavage separately. Moreover, it is also unknown whether there are differences in the concentration of the first and second lavage.

The result is that overestimations of the true amount of NANOBODY® (V_{HH} sequence) may occur when multiplying the measured BALF concentrations are simply multiplied with the theoretical volume of 10 mL DPBS.

Alternatively, if the amount of NANOBODY® (V_{HH} sequence) is estimated by multiplying the measured concentration of each BALF sample by the actual recovered volume of BALF, this may result in underestimations of the actual amount of NANOBODY® (V_{HH} sequence) in case significant amounts of NANOBODY® (V_{HH} sequence) are present in unrecovered BALF.

Therefore, the true amount of NANOBODY® (V_{HH} sequence) in BALF should theoretically be comprised between the amount calculated via the theoretical BALF volume or the actual BALF volume. It is important to note that the larger the recovered volume, the more accurate the calculations are expected to be. Since the average recovered volume is on average ca. 7 mL (Table C-27), both calculation methods should not provide very different results. The individual calculated amounts and mean (+SD) values based on actual recovered volumes are listed in Table C-28 and C-29, respectively.

By dividing the calculated amount of NANOBODY® (V_{HH} sequence) by the actual amount dosed (RSV NB2: 1.14 mg, ALX-0081: 0.985 mg, RANKL008a: 1.03 mg), the recovered fraction of the dose was calculated. Expressed as a percentage, the dose normalized individual calculated amounts and their corresponding mean (+SD) values based on the theoretical BALF volume (10 mL) and actual recovered volumes are listed in Tables C-30 to C-33.

By dividing the calculated amount of NANOBODY® (V_{HH} sequence) by the actual amount dosed, the recovered fraction of the dose could be compared across time: The highest mean amount to dose percentages via actual and theoretical volume are 35.7% and 49.5% for RSV NB2 (After 20 minutes), 74.0% and 98.3% for ALX-0081 (After 4 minutes) and 47.1% and 67.4% for RANKL008A (After 1 hour), respectively. Thus for ALX-0081 almost the total fraction of the dose could be recovered in the BALF, while for RSV NB2 and RANKL008a, the fraction was lower: approximately 50% of the dose. The highest individual amount to dose percentages via actual and theoretical volume are 76.6% and 117.3% for RSV NB2, 145% and 182% for ALX-0081 and 84.1% and 120% for RANKL008a at time-point 1 hour post-dose. As expected, the variability was appreciable.

After 24 hours, the fraction of the dose recovered in BALF was lower for all NANOBODIES® (V_{HH} sequences) than at earlier time-points. The mean fraction recovered ranged from 12.4% to 16.5% via the theoretical volume and ranged from 8.46% to 12.5% via the actual volumes for the three tested NANOBODIES® (V_{HH} sequences).

42.3

Conclusions

After i.v. administration to rats, similar PK characteristics were observed for RSV NB2 and ALX-0081. For RANKL008a, substantially lower clearance values and longer terminal half-lives were observed. This may be explained by binding of the anti-HSA NANOBODY® (V_{HH} sequence) of RANKL008a to rat albumin.

The current data indicate that systemic exposure to NANOBODIES® (V_{HH} sequences) can be achieved after intra-tracheal administration, suggesting that the pulmonary route may be viable as non-invasive method for the delivery of NANOBODIES® (V_{HH} sequences). The limited data also suggested that the systemic bioavailability seems to decrease with increasing molecular weight.

After i.t. administration comparable terminal half-lives were observed for the three NANOBODIES® (V_{HH} sequences). For RSV NB2 and ALX-0081 the half-lives are longer after i.t. administration than after i.v. administration, suggesting that that absorption is the rate limiting step because the drug is slowly absorbed from its site of dosing (i.e. the lung) to the circulation. Comparable terminal half-lives are observed both in plasma and in BALF. This observation further enhances the possibility that the kinetics could be absorption rate controlled.

Following intra-tracheal administration, the RSV NB2, ALX-0081, RANKL008a NANOBODY® (V_{HH} sequence) exposure in BALF was observed for at least 24 hours (i.e. the last sampling time for BALF).

Following intra-tracheal administration, systemic exposure to the RSV NB2, ALX-0081 NANOBODY® (V_{HH} sequence) in plasma was observed for at least 24 hours (i.e. the last sampling time of plasma after intra-tracheal administration. Following i.v. administration both of these NANOBODIES® (V_{HH} sequences) without anti-HSA were no longer detectable at 24 hours.

FIG. 41 and FIG. 42 further illustrate the experimental results.

Example 43

Further Studies with an Anti-RSV NANOBODY® (V_{HH} Sequence) Construct

Example 43.1

Prophylactic Study with RSV407 in Cotton Rat

In this study cotton rats are treated either i.m. or intranasally with RSV neutralizing NANOBODY® (V_{HH} sequence) constructs (RSV 407; SEQ ID NO: 2415) or control (PBS). Viral RSV challenge is administered intranasally 1 hour later. At day 4, animals are sacrificed and RSV titers determined by Q-PCR in nasal and lung washes as well as in nasal and lung tissue.

Example 43.2

Therapeutic Study with RSV407 in Cotton Rat

RSV therapeutic studies have been described in the past; e.g. by Crowe and colleagues (1994, Proc. Nat. Ac. Sci.; 91: 1386-1390) and Prince and colleagues (1987, Journal of Virology 61:1851-1854).

In this study cotton rats are intranasally infected with RSV. Twenty-four hours after infection a first group of animals are treated with RSV neutralizing NANOBODY® (V_{HH} sequence) constructs (RSV 407) or control (PBS). Treatment is administered to pulmonary tissue by intranasal or aerosol administration. Treatment is repeated at 48 and 72 hours. At day 4 animals are sacrificed and RSV titers determined by Q-PCR in nasal and lung washed as well as in nasal and lung tissue.

In the second group, treatment is only initiated 3 days after infection and repeated at day 4 and 5. Finally, at day 6 animals are sacrificed and RSV titers determined by Q-PCR in nasal and lung washed as well as in nasal and lung tissue.

Example 43.3

Lung to Systemic

In this study the lung tissue of rats is exposed to an RSV neutralizing NANOBODY® (V_{HH} sequence) (RSV407) by intratracheal or aerosol administration. Serum and BAL samples are taken at regular time points up to 3 days after administration. The NANOBODY® (V_{HH} sequence) concentration is measured by means of ELISA and samples are subjected to RSV microneutralization as described in Example 15. By combining the information from the ELISA and the neutralization assay the RSV IC50 of each sample can be determined to assess systemic bioavailabilty of functional RSV NANOBODY® (V_{HH} sequence).

Example 44

Screening Procedures, for Hep2 Cells Infected with RSV B-1

In addition to the identification of NANOBODIES® (V_{HH} sequences) that are potent neutralizers of RSV Long strain in a microneutralization assay, NANOBODIES® (V_{HH} sequences) can also be screened for their ability to neutralize RSV B-1. Clones obtained from selections against the F-protein and RSV, specifically from trypsin elutions, competitive elution with 101F Fab or with linear peptides (see Example 18), were subjected to an alternative screening procedure that included binding to the F-protein of RSV B-1.

As a first step, approximately 1000 periplasmatic extracts were analyzed for binding to F_{TM-} NN protein (1 μg/ml) in ELISA (see Example 20). On average, 44% of all clones were identified as binders (>2-fold over background), with 27% identified as strong binders (>3-fold). Only 10% of all binders originated from llamas 212 and 213.

Binders were subjected to a competition ELISA with Synagis® (67 pM) for binding to RSV Long (10 μg/ml; Hytest #8RSV79) to identify clones of epitope Class II. Detection of Synagis® was done using goat anti-human-HRP conjugated IgG (Jackson ImmunoResearch Laboratories, Inc., Cat. No. 109-035-098). This assay resulted in 9 hits (Table C-34).

In a similar manner, periplasmatic extracts were analyzed in a competition ELISA with 101F Fab to identify clones of epitope Class IV-VI (see Example 20). Detection was done using anti-HA monoclonal antibody (Zymed, 32-6700, 1389267), followed by anti-mouse-HRP conjugated antibody (Dako, Cat. No. P0260). Of the 90 competitors identified, the best 101F Fab competitors were further tested at dilutions ranging from 1/100-1/1000 to allow differentiation between clones (Table C-34).

As third step, the Class II and IV-VI epitope clones were analyzed for binding to Hep2 cells infected with RSV B-1 strains. In this assay, Hep2 cells were seeded into 96-wells plates and infected with an RSV B-1 strain, essentially following the procedure described for the neutralization assay (see Example 15). After three days the cells were fixed with ice-cold acetone and plates were used in an ELISA assay using periplasmic extracts at different dilutions. NANOBODY® (V_{HH} sequence) binding to Hep2-B1 infected cells was detected using anti-VHH rabbit polyclonal antibody, followed by goat Anti-rabbit-HRP conjugated antibodies, after which the ELISA was developed according to standard procedures. In general, the Class II epitope clones proved weaker binders to Hep2-B1 cells than clones of the epitope Class IV-VI (Table C-34).

Sequence analysis reduced the total number of competing NANOBODIES® (V_{HH} sequences). Clones 8A1 (SEQ ID NO: 249), 8B10 (SEQ ID NO: 342) and 1B2 (SEQ ID NO: 166) were found as multiple copies which were all ranked amongst the strongest binders to Hep2 B-1-infected cells. Clone 1B2 was identical to the sequence of the previous identified 191E4. The unique sequence 19E2 (SEQ ID NO: 301) belongs to the large family 4. From the group of Synagis® competitors, clones 19C4 (also referred to as 15H8; SEQ ID NO: 371)

and 1G8 (SEQ ID NO: 2578) were the best RSV B-1 binders. Based on the binding to both RSV long and B-1, on sequence, and on 101F competition, a selection was made from 101F competitors for further analysis as purified proteins (Table C-34).

Example 45

Immunization of Llamas with Rabies Virus

Two llamas were immunised with rabies virus antigen and lymphocytes were collected as a source of virus-specific single-chain antibody mRNA. Immunised llamas had identification numbers 183 and 196, source: N.V. Neerhofdieren Bocholt, location: animal facilities of the Belgian Scientific Institute of Public Health (IPH, authorisation nr. LA1230177). All experimental procedures were approved by the Ethical Committee of the IPH and the Veterinary and Agrochemical Research Centre (VAR) (advice nr. 070515-04).

Inactivated Rabies Vaccine Merieux HDCV, marketed by Sanofi Pasteur MSD for use in humans, was the antigen. This vaccine contains the Wistar strain of the Pitman Moore virus grown on human diploid WI38 lung cells (PM/WI38 1503 3M). It contains human albumin, but no adjuvant. The vaccine was injected in the neck and the suspension divided over two spots (0.5 ml/spot) at day 0, 7, 28, 35, 57. Blood lymphocytes were collected on EDTA on day 42, 49 and 62 (Table C-35).

Both llamas developed protective titers of neutralizing antibodies in the range of 15-35 IU/ml. Lymphocytes were successfully collected from the blood. Lymph nodes were not distinguishably enlarged, which made them difficult to find. For this reason, lymph nodes were not used as a source of lymphocytes.

Example 46

In Vitro Neutralisation Potency of Monovalent NANOBODY® (V_{HH} Sequence) Clones with the RFFIT Assay

The neutralizing potency of NANOBODY® (V_{HH} sequence) clones was determined and the most potent clones were selected to make bivalent and biparatopic combinations for further in vivo experiments. The clones were pre-selected by their capacity to bind to a substrate of purified glycoprotein G (Platelia II ELISA plates). Some of the selected clones competed with monoclonal antibody 8-2, which recognizes an epitope on the antigenic site IIa of the rabies surface glycoprotein G (Montaño-Hirose J A, Lafage M, Weber P, Badrane H, Tordo N, Lafon M. 1993, Protective activity of a murine monoclonal antibody against European bat lyssavirus 1 (EBL1) infection in mice. Vaccine 11: 1259-66).

The neutralizing potency of NANOBODY® (V_{HH} sequence) or antibody preparations was determined with the Rapid Fluorescent Focus Inhibition Test (RFFIT). This test is a virus-neutralisation assay which uses Baby Hamster Kidney (BHK)-21 cells as susceptible targets. Infection of cells is visualized by staining with a fluorescein isothiocyanate (FITC)-coupled anti-nucleocapsid conjugate (Bio-Rad Laboratories, France). The virus strain used is the highly virulent and neurotropic Challenge Virus Standard (CVS)-11 (genotype 1 genus Lyssavirus, Family Rhabdoviridae). CVS-11 was obtained from the American Type Culture Collection (ATCC reference VR959). The in vitro neutralizing potency is expressed in International Units (IU)/m1 in reference to "The Second International standard for Anti-rabies Immunoglobulin" purchased from the United Kingdom National Institute for Biological Standards and Control. A serum titer of 0.5 IU/ml is considered protective in vivo. RFFIT was performed according to the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Office International des Epizooties, 2008) and IS017052 norms (BELAC Accreditation 081-TEST). The results are shown in Table C-36.

The majority of NANOBODY® (V_{HH} sequence) clones (15/16), which were isolated from the immunised llamas and selected based on their binding capacities to glycoprotein G, were neutralizing (0.50 IU/ml) in the RFFIT. In general, their potency was significantly lower compared to the reference monoclonal antibody (Mab) RV1C5 (0.17 nM IC_{50}). The clones with the strongest potency were 212-C12 (8 nM IC_{50}), 213-E6 (14 nM IC_{50}) and 212-F6 (18 nM IC_{50}). Control NANOBODIES® (V_{HH} sequences), which were raised against another virus (human respiratory syncytial virus) or Toll-like receptor 3, were not neutralizing.

Example 47

Potency of Combinations of Monovalent Antibodies

The potency of a combination of two different monovalent NANOBODIES® (V_{HH} sequences) (no linkage) and the synergistic effect on the neutralizing potency compared to the monovalent clones was investigated.

The neutralizing potency of combinations and single clones was determined by RFFIT. Competition binding experiments showed that clones 213-E6, 214-E8 and 213-H7 bind to the same major epitope on the glycoprotein G, whereas 212-C12 binds to a different major epitope. The results are shown in Table C-37.

All tested combinations of monovalent clones yielded no additive effect on the neutralizing potency. Synergistic effects were not observed even with clones which bind to different major epitopes.

Example 48

Cross-Neutralization of Selected Clones Against Divergent Genotype 1 and 5 Lyssa Virus

Clones that were selected against the genotype 1 CVS-11 strain were examined for their ability to cross-neutralize other genotype 1 lyssaviruses (laboratory strains and street isolates; obtained from Prof. S. Van Gucht, Scientific Institute of Public Health, Rabies Laboratory, Brussels, Belgium).

Cross-neutralisation against a genotype 5 lyssavirus (European bat lyssavirus-1, EBLV-1; obtained from Prof. S. Van Gucht, Scientific Institute of Public Health, Rabies Laboratory, Brussels, Belgium) was also examined. Most human cases of rabies (>99%) are caused by genotype 1 lyssaviruses. EBLV-1 circulates in certain species of bats (mainly *Eptesicus serotinus*) in Europe.

Evelyn-Rotnycki-Abelseth (ERA) is an attenuated genotype 1 strain which is used as an oral vaccine for immunisation of wild life (ATCC reference VR322). Chien Beersel (CB)-1 is a virulent genotype 1 virus isolated from the brain of a rabid dog which was imported from Morocco to Belgium (Le Roux I. and Van Gucht S. 2008. Two cases of imported canine rabies in the Brussels area within six months time. WHO Rabies Bulletin 32(1), Quarter 1). The EBLV-1 strain 8919FRA belongs to genotype 5 and was isolated from an *Eptesicus serotinus* bat in France (Bourhy et al. 1992. Antigenic and molecular characterization of bat rabies virus in Europe. J Clin Microbiol. 30(9):2419-26). The strain was provided by Dr. L. Dacheux form the Pasteur Institute of Paris (MTA DB/EB-08/420). The viral stocks were grown in BHK-21 cells, except for CB-1 which was grown in neuroblastoma N2a cells. The lysates of infected cell cultures were centrifuged at 20000×g for 20 minutes at 4° C. and supernatants were stored at −80° C.

In addition, 7 genotype 1 strains were provided by Dr. L. Dacheux from the Pasteur Institute of Paris in the form of infected mouse brains. Six strains were wild isolates, among which an isolate from a dog from Cambodia (9912CBG, accession nr.

EU086169/EU086132), a fox from France (9147FRA, accession nr. EU293115), a raccoon dog from Poland 9722POL), a human patient from Thailand (8740THA), a dog from the Ivory Coast (07059IC, accession nr. EU853615/FJ545659) and a dog from Niger (9009NIG, accession nr. EU853646). One brain was infected with the laboratory CVS IP13 strain.

The neutralizing potency against ERA, CB-1 and EBVL-1 was determined in an RFFIT adapted with the virus of interest. Neutralisation was defined as a minimal neutralizing potency of 0.50 Equivalent Units (EU)/ml.

For the infected brains, an alternative neutralisation assay was developed. Briefly, ten-fold dilutions of the infected brain suspensions were pre-incubated with a 1/50 dilution of the

stock solution of NANOBODY® (V_{HH} sequence) for 90 minutes at 37° C. and 5% CO_2. Then, susceptible neuroblastoma N2a cells were added to the mix. Two days later, infection of the cells was measured by staining with a FITC-coupled anti-nucleocapsid conjugate (Bio-Rad Laboratories, France). Neutralisation was defined as a minimum hundred-fold reduction of the infectious titer in comparison to an irrelevant NANOBODY® (V_{HH} sequence) control (172-B3 anti-TLR3).

Results are shown in Table C-38 (ERA), Table C-39 (CB-1), Table C-40 (EBLV-1) and Table C-41 (infected brain). Table C-42 gives an overview of the neutralisation profile of all tested clones.

In general, most clones which neutralized the prototype CVS-11 strain also neutralized most other genotype 1 viruses. An exception is clone 212-C12, which proved to be a relative potent neutralizer of CVS-11, but did not neutralize 3 out of 9 other genotype 1 strains. 214-F8 neutralized all 10 genotype 1 strains. 213-E6 neutralized 9 out of 10 genotype 1 strains and 213-H7 neutralized 8 out of 10 genotype 1 strains. Attention should be drawn to the fact that for 213-E6 and 213-H7 a relative low amount of NANOBODY® (V_{HH} sequence) was used in the assay (respectively 0.1 and 1.7×10^{-3} IU). Neutralisation might have been complete if higher amounts had been used. Seven of the sixteen anti-rabies clones, including clones 213-H7 and 214-E8, were also able to neutralize the divergent EBLV-1 strain. This indicates that the epitope recognized by these clones is highly conserved among lyssaviruses.

Example 49

Potency of Bivalent and Biparatopic NANOBODY® (V_{HH} Sequence) Combinations Measured with the RFFIT Assay

The potential synergistic effect on the neutralizing potency of the linkage of two similar (bivalent) or different (biparatopic) NANOBODIES® (V_{HH} sequences) compared with the monovalent clones was investigated.

The neutralizing potency of bivalent and biparatopic clones was determined using RFFIT as described above. Different fusion proteins were developed with 3 Gly-Ser linkers: 5GS, 15GS or 25GS. Sequences of multivalent NANOBODY® (V_{HH} sequence) constructs against rabies are given in Table A-6. NB6-18GS-NB6 (RSV115; SEQ ID NO: 2394) is a control bivalent NANOBODY® (V_{HH} sequence) which was raised against another virus (human respiratory syncytial virus). Data on neutralization of EBLV-1 strain is shown in Table C-40. Data on neutralization of wild type genotype 1 strains and a laboratory CVS strain in suspensions of infected mouse brain is shown in Table C-41. Table C-42 gives an overview of the neutralisation profile of all tested clones. The results of neutralization of CVS-11 are

shown in Table C-43.

The majority of the tested bivalent and biparatopic NANOBODIES® (V_{HH} sequences) had a significantly higher potency than the corresponding monovalent clones. For example, the biparatopic combination 214E8-15GS-213H7 was 600-fold more potent that the monovalent NANOBODIES® (V_{HH} sequences). In general, the bivalent combinations seemed less potent than the biparatopic combinations. The most potent bivalent combinations had a neutralizing potency between 15 and 36 IU/nM (213H7-15GS-213H7, 213E6-5GS-213E6, 214F8-15GS-214F8). For the most potent biparatopic combinations, this ranges between 80 and 230 IU/nM (213E6-15GS-213H7, 213H7-15GS-214F8, 214E8-15GS-213H7). This is comparable to the neutralizing potency of the anti-rabies monoclonal antibody RV1C5 (Santa Cruz) (194 IU/nM). Most of the potent combinations had a 15GS linker.

Example 50

In Vivo Neutralisation of Virulent CVS-11 with Monovalent/Bivalent NANOBODIES® (V_{HH} Sequences) Using the Brain as the Susceptible Target System: Intracerebral Inoculation in Mice

50.1

In Vivo Neutralization by Monovalent NANOBODIES® (V_{HH} Sequences)

Whether NANOBODIES® (V_{HH} sequences) (monovalent, bivalent or biparatopic), which proved to be potent neutralizers in vitro, can also neutralize the virus in vivo and prevent lethal infection of the brain was investigated. Outbred Swiss mice (5-6 weeks old) were inoculated intracerebrally with rabies virus CVS-11 pre-incubated with 1 IU of NANOBODY® (V_{HH} sequence), 1 IU of monoclonal antibody (mab 8-2) or PBS (negative control) (6 to 9 mice/group). Prior to inoculation, the mix of virus and NANOBODY® (V_{HH} sequence) or antibody was incubated at 37° C., 5% CO_2 for 30 min. A volume of 20 μl (10 μl virus+10 μl NANOBODY® (V_{HH} sequence)) was inoculated into the brain by transcranial introduction of a 26G needle. Neutralizing units (IU) were determined using the in vitro RFFIT assay. A viral dose of $10^{1.5}$ $TCID_{50}$/mouse was used based on preliminary experiments with different doses of virus preincubated with 1 IU of mab 8-2. This preliminary work indicated that a dose of 1 IU of mab 8-2 was able to protect all mice from lethal infection (0% mortality) upon intracerebral inoculation with $10^{1.5}$ $TCID_{50}$, which was not the case at higher virus doses (10^2 $TCID_{50}$ CVS+1 IU mab 8−2=43% mortality). Mice were examined for (rabies) disease signs each work day and a clinical score was given per

day per mice. Clinical scores ranged from 0 (no disease signs) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis). At score 6, mice were sacrificed by cervical dislocation. The experiment was ended at 28 days post inoculation (DPI).

The results for monovalent antibodies are shown in FIG. 43 and Table C-44. The peak clinical score and the mean time of death of the NANOBODY® (V_{HH} sequence) groups were not significantly different from the control groups, in contrast to the monoclonal antibody group ($P<0.01$, one-way ANOVA with Dunnett's post-Test).

The monoclonal antibody (mab 8-2) provided full protection against an intracerebral challenge with $10^{1.5}$ $TCID_{50}$ CVS-11. Pre-incubation with an irrelevant NANOBODY® (V_{HH} sequence) (191-G2) did not protect the mice from lethal infection (100% mortality). Mice which were inoculated with the virus alone developed 71% mortality. The fact that mortality was higher with the irrelevant NANOBODY® (V_{HH} sequence) was probably a coincidence and not due to a potentially harmful effect of the NANOBODY® (V_{HH} sequence). In preliminary experiments, mice which received NANOBODY® (V_{HH} sequence) alone did not develop signs of disease. Also, the clinical course of the mice which received virus+irrelevant NANOBODY® (V_{HH} sequence) resembled the typical rabies pattern. The anti-rabies NANOBODY® (V_{HH} sequence) 213-E6 provided a partial protection against the rabies virus with a mortality of 57%. The Kaplan Meier survival curve of 213-E6 resembles a typical “staircase” profile similar to that of the survival curve with monoclonal antibody at higher virus concentrations. Remarkably, anti-rabies NANOBODY® (V_{HH} sequence) 212-C12 did not protect (100% mortality) in vivo, although this was one of the most potent clones in vitro with BHK cells as the susceptible targets.

This experiment demonstrates that partial protection can be achieved with monovalent NANOBODY® (V_{HH} sequence) in the intracerebral challenge model. The in vitro and in vivo potencies are poorly correlated. Although the NANOBODIES® (V_{HH} sequences) and antibody were used at the same in vitro dose of 1 IU, their in vivo potency was clearly different (mab 8-2>213-E6>212-C12).

50.2

In Vivo Neutralization by Bivalent NANOBODIES® (V_{HH} Sequences)

Bihead NANOBODIES® (V_{HH} sequences) were tested using the same intracerebral challenge model. The results for bivalent and biparatopic antibodies are shown in FIG. 44 and Table C-45. The peak clinical score ($P<0.01$) and the mean time of death ($P<0.05$) of the bihead (bivalent and biparatopic) NANOBODY® (V_{HH} sequence) groups were significantly different from those of the 191-G2 control group (one-way ANOVA with Dunnett's post-

Test).

As in the previous experiment, the monoclonal antibody 8.2 provided full protection against an intracerebral challenge with $10^{1.5}$ $TCID_{50}$ CVS-11, whereas high mortality (87.5%) was observed after pre-incubation with an irrelevant NANOBODY® (V_{HH} sequence) (191-G2). The bivalent combinations 214E8-15GS-214E8 and 213H7-15GS-213H7 and all biparatopic combinations yielded complete protection against the intracerebral rabies virus challenge (0% mortality). The bivalent combination 212C12-15GS-212C12 yielded now clear partial protection (22.2% mortality). Based on the mortality data with both monovalent and bivalent 212-C12, it is likely that the epitope which is recognized by this clone is less suited for neutralisation in brain than in vitro.

Results of a further experiment with bivalent and biapratopic NANOBODIES® (V_{HH} sequences) are shown in FIG. 48 and in Table C-48. 214-E8-15GS-212-C12, 213E6-25GS-212-C12, 213-E6-15GS-13H7 induced 100% of protection. 213-E6-5GS-212-C12 presented a weak mortality (14.3%) very later during this experiment (FAT was very lighty positif). 213-E6-5GS-213-E6 and 214-E8-15GS 213-E6 induce a total protection while 213-E6-15GS-214-E8 induced only a partial one.

The combination of NANOBODIES® (V_{HH} sequences) in a bivalent or biparatopic conformation induces a synergistic increase of both the in vitro and in vivo potencies. A same in vitro dose of 1 IU is much more effective in the bivalent/biparatopic conformation than in the monovalent conformation.

This experiment presents data from day 0-21. We expect that there will be no further changes in clinical signs or mortality in day 21-28.

50.3

Detection of Virus in Mouse Brains

The brains of the mice inoculated with $10^{1.5}$ $TCID_{50}$ CVS-11 mixed with an anti-rabies NANOBODY® (V_{HH} sequence) (1 IU 213-E6) were stained for the presence of viral antigens. Acetone-fixed brain smears were subjected to immunofluorescence staining with an FITC-conjugated anti-nucleoprotein antibody (FAT).

FIG. 51A demonstrates the abundant presence of viral antigens in the brain of a mouse at 7 DPI with $10^{1.5}$ $TCID_{50}$ CVS-11 mixed with an irrelevant NANOBODY® (V_{HH} sequence) (192-G2). The mouse had a clinical score of 6 at the time of euthanasia. FIG. 51B shows the absence of viral antigens in the brain of a mouse at 7 DPI with $10^{1.5}$ $TCID_{50}$ CVS-11 mixed with an anti-rabies NANOBODY® (V_{HH} sequence) (1 IU 213-E6). The mouse presented no clinical disease signs at the time of euthanasia.

50.4

Intracerebral Inoculation of Mice with Dose of 10^2 $TCID_{50}$

Most bivalent and biparatopic NANOBODIES® (V_{HH} sequences) provide good protection against a viral dose of $10^{1.5}$ $TCID_{50}$. In this experiment, we examined whether the bivalent 213E6-15GS-213H7 also offers protection against a dose of 10^2 $TCID_{50}$ CVS-11. Mab RV1C5 (anti-G IgG_{2a}, Santa Cruz sc-57995) was used as a control antibody.

Results are shown in Table C-49 and FIG. 52. Even at a higher viral dose of 10^2 $TCID_{50}$, the bivalent combination 213E6-15GS-213H7 provided full protection, whereas in preliminary experiments (data not shown) 100% mortality was observed with the monovalent NANOBODIES® (V_{HH} sequences) at the same viral dose. In a future experiment, we will test 213E6-15GS-213H7 with an even higher viral dose of 10^3 $TCID_{50}$.

Example 51

In Vivo Protection of Mice by Intranasal Application of NANOBODY® (V_{HH} Sequence)

Monovalent NANOBODIES® (V_{HH} sequences) against rabies were tested in intranasal mice model. The NANOBODIES® (V_{HH} sequences) were injected intranasally after preincubation with two different virus doses.

Outbred Swiss mice (5-6 weeks old) were inoculated intranasally with rabies virus CVS-11 pre-incubated with 1 IU of NANOBODY® (V_{HH} sequence) or monoclonal antibody (mab 8-2). Prior to inoculation, the mix of virus and NANOBODY® (V_{HH} sequence) or antibody was incubated at 37° C., 5% CO_2 for 30 min. Mice were first anesthetized with isoflurane and fixed with the head held up. A volume of 25 μl (12.5 μl virus+12.5 μl NANOBODY® (V_{HH} sequence)) was inoculated on top of the nostrils with a micropipette. Immediately after application, the inoculum is inhaled in the nose through the rapid and superficial breathing of the anesthetized animal. A viral dose of 10^3 (IN20090310) or 10^2 $TCID_{50}$ (IN20090210, IN20090414) was used. Mice were examined for (rabies) disease signs each work day and a clinical score was given per day per mice. Clinical scores ranged from 0 (no disease signs) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis). At score 6, mice were sacrificed by cervical dislocation. The experiment ends at 35 DPI.

The results are shown in FIGS. 47A and B and Table C-47. At the lower virus dose, 213-E6 and 212-C12 present 100% of protection while at the higher dose they present a partial protection.

Both the monovalent 213-E6 and bivalent 214E8-15GS-213H7 provided full protection against disease in the intranasal inoculation model when introduced together with the virus at a viral dose of 10^2 $TCID_{50}$. At a higher dose of 10^3 $TCID_{50}$ protection was partial.

Remarkably, the monovalent clone 212-C12 provided relative good protection in this model, whereas in the intracerebral inoculation model we observed no protection with this clone. To confirm this observation, we performed an additional experiment in which we inoculated part of the mice intranasally and part intracerebrally with CVS-11+212-C12 (FIG. 53 and Table C-50). Again, intranasally inoculated mice were fully protected, whereas intracerebral inoculation yielded 100% mortality.

The mortality and survival curve of the group inoculated with the mix of virus and irrelevant NANOBODY® (V_{HH} sequence) 191-D3 is comparable to that of mice inoculated with virus only in previous experiments.

Surprisingly, we observed no protection with the mab 8-2, despite the fact that this mab proved to be a very potent neutralizer in the in vitro models and in the intracerebral inoculation model. In this experiment, the mortality was even higher (89%) and the median survival time was shorter (9 days) than in group with the irrelevant NANOBODY® (V_{HH} sequence) (respectively 66% and 13 days). This experiment will be repeated with another mab (RV1C5).

Example 52

In Vivo Protection of Mice by Intranasal Application of NANOBODY® (V_{HH} Sequence) Followed One Day Later by Intranasal Challenge with the Virulent Neurotropic CVS-11 Strain

Intranasal challenge with a virulent neurotropic rabies virus quickly leads to invasion of the brain, most probably upon entry and infection of the sensory neurons of the olfactory epithelium.

To examine whether prior intranasal administration of anti-rabies NANOBODIES® (V_{HH} sequences) can protect mice from an intranasal challenge with rabies virus one day later, outbred Swiss mice (5-6 weeks old) were treated with an intranasal dose of NANOBODY® (V_{HH} sequence) (1 IU) or mab (1 IU). One day later, the mice received an intranasal challenge of 10^2 $TCID_{50}$CVS-11 per mouse. For intranasal inoculation, a volume of 25 μl/mouse was applied in both nostrils under isoflurane anesthesia. Mice were examined for (rabies) disease signs each work day and a clinical score was given per day per mouse. Clinical scores ranged from 0 (no disease signs) to 7 (conjunctivitis, weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis). At score 6,

mice were sacrificed by cervical dislocation. The experiment ended at 35 DPI with virus. The results are shown in FIG. 45 and Table C-46. The peak clinical score and the mean time of death of the anti-rabies NANOBODY® (V_{HH} sequence) groups (212-C12, 213-E6) was not significantly different from the 191-G2 control group, in contrast to the monoclonal antibody group ($P<0.01$, one-way ANOVA with Dunnett's post-Test).

Similar to the intracerebral inoculation model, we observed full protection with mab 8-2 (0% mortality), no protection with NANOBODY® (V_{HH} sequence) 212-C12 (87.5% mortality) and minor protection with NANOBODY® (V_{HH} sequence) 213-E6 (75% mortality).

Example 53

Generation of NANOBODY® (V_{HH} Sequence) Constructs

For the expression of the NANOBODY® (V_{HH} sequence) constructs the GS Gene Expression System™ by Lonza (Basel, Switzerland) is used, which comprises the serum-free and suspension-adapted CHOK1SV cell line and the expression plasmid pEE12.4. The starting point of the construction of the NANOBODY® (V_{HH} sequence) constructs is the reverse translation of the amino acid sequence into the corresponding nucleotide sequence, optimized for expression in a CHO cell line. This optimization for expression can for instance be done by GeneArt (Regensburg, Germany) or by other companies specialized in gene synthesis. On the N-terminal end of the NANOBODY® (V_{HH} sequence) construct a generic secretion signal is added, which allows for the endogenous protein to be exported into the growth medium and which is cleaved off upon secretion out of the cell. Such a generic signal sequence can, for instance, be the murine heavy chain leader sequence, the murine light chain leader sequence, any other antibody heavy or light chain leader sequence, the IL-2 secretion signal, etc., as are known in the art. Optionally, 5′ to the end of the secretion signal an optimized Kozak sequence is added, which initiates effective translation from the mRNA transcript. The consensus sequence recommended by Lonza consists of a 9-mer (5′-GCCGCCACC-3′; SEQ ID NO: 2638), and directly precedes the ATG start codon. The NANOBODY® (V_{HH} sequence) construct is terminated by a double stop codon to increase translation efficiency of the construct.

The NANOBODY® (V_{HH} sequence) construct including all aforementioned features is typically cloned into the HindIII/EcoRI cloning sites; which requires absence of these sites within the NANOBODY® (V_{HH} sequence) construct. Cloning into the HindIII/EcoRI sites on the pEE12.4 plasmid results in the removal of most of the multiple cloning site. The recombinant plasmid is transformed into an appropriate *E. coli* strain (e.g., TOP10), and positive clones are selected for by ampicillin or carbenicillin in the growth medium. The plasmid is amplified and isolated using a plasmid isolation kit.

To transfect the cells, the recombinant plasmid DNA is linearized for instance by digestion with a restriction endonuclease (e.g., PvuI) that cuts the DNA only once; this facilitates the recombination of the plasmid DNA into the cells genome. Freshly thawed CHOK1 SV cells are kept in culture (e.g., in CD CHO medium, Invitrogen) and are expanded. An aliquot of about 2×10^7 cells is electroporated with 40 g of linearized plasmid, using e.g., the BioRad electroporation device (Bio-Rad Gene Pulser. Hercules, Calif.). The transfected cells are resuspended in CD CHO medium and after 1 day put under selective pressure, e.g., in glutamine-deficient medium. To increase selective pressure the medium is supplemented with 66.6 μM methionine sulfoximine after 1 culturing day. The cells are kept under selective pressure, and allowed to expand, either as single cell clones (after limiting dilution), or as a batch culture. Expression levels of the recombinant protein are then determined by e.g. a binding ELISA.

The IgG1-hinge region between the NANOBODY® (V_{HH} sequence) and the immunoglobulin IgG1 constant domain CH2-CH3 can optionally be extended by a 9GS linker (GGGGSGGGS; SEQ ID NO: 2639) or exchanged by another hinge region, e.g., as derived from IgG3 (ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCP RCP; SEQ ID NO: 2640). In a format where one NANOBODY® (V_{HH} sequence) is preceding and another NANOBODY® (V_{HH} sequence) following the IgG-Fc domain, the second C-terminal NANOBODY® (V_{HH} sequence) can be fused to the Fc domain either directly (no linker), or e.g., by a 9GS linker.

Non-limiting embodiments of the NANOBODY® (V_{HH} sequence) Fc fusion construct include:

(1) NC41::15GS::NC41::G1-hinge::IgG1-Fc

(2) NC41::15GS::NC41::9GS-G1-hinge::IgG1-Fc

(3) NC41::15GS::NC41::G3-hinge::IgG1-Fc

(4) NC41::G1-hinge::IgG1-Fc::NC41

(5) NC41::9GS-G1-hinge::IgG1-Fc::NC41

(6) NC41::G3-hinge::IgG1-Fc::NC41

(7) NC41::G1-hinge::IgG1-Fc::9GS::NC41

(8) NC41::9GS-G1-hinge::IgG1-Fc::9GS::NC41

(9) NC41::G3-hinge::IgG1-Fc::9GS::NC41

(10) NC41::G1-hinge::IgG1-Fc::15B3

(11) NC41::9GS-G1-hinge::IgG1-Fc::15B3

(12) NC41::G3-hinge::IgG1-Fc::15B3

(13) NC41::G1-hinge::IgG1-Fc::9GS::15B3

(14) NC41::9GS-G1-hinge::IgG1-Fc::9GS::15B3

(15) NC41::G3-hinge::IgG1-Fc::9GS::15B3

(16) NC41::NC41::IgG1-Fc

(17) NC41::IgG1-Fc::NC41

(18) 191D3::15GS::191E4::G1-hinge::IgG1-Fc

(19) 191D3::15GS::191E4::9GS-G1-hinge::IgG1-Fc

(20) 191D3::15GS::191E4::G3-hinge::IgG1-Fc

(21) 191D3::G1-hinge::IgG1-Fc::NC41

(22) 191D3::9GS-G1-hinge::IgG1-Fc::191E4

(23) 191D3::G3-hinge::IgG1-Fc::191E4

(24) 191D3::G1-hinge::IgG1-Fc::9GS::191E4

(25) 191D3::9GS-G1-hinge::IgG1-Fc::9GS::191E4

(26) 191D3::G3-hinge::IgG1-Fc::9GS::191E4

(27) 191D3::191E4::IgG1-Fc

(28) 191D3::IgG1-Fc::191E4

Non-limiting examples of NANOBODY® (V_{HH} sequence) constructs of the invention are also provided in FIG. 46. The sequences of the above constructs (1)-(28) are provided in Table A-5 below. A nucleic acid sequence corresponding to (16) and (17) with random codon usage is also shown in Table A-5 below.

Example 54

Cross-Reactivity of NANOBODY® (V_{HH} Sequence) 202-C8

Cross-Reactivity of Mono-, Bi- and/or Trivalent NANOBODY® V_{HH} Sequence) 202-C8

Potential heterosubtypic cross-reactivity of monovalent 202-C8 (SEQ ID NO: 138), bivalent 202-C8 (SEQ ID NO's: 2423 to 2424) and trivalent 202-C8 (SEQ ID NO's: 2425 to 2426) is assessed in an in vitro neutralization assay using PR8 (H1N1), X47 (H3N2) and NIBRG-14 (H5N1) viruses. Neutralization is tested in a hemagglutination inhibition assay using chicken red blood cells and in a virus microneutralization assay using MDCK cells as targets.

In Vivo Neutralization of Mono-, Bi- and/or Trivalent NANOBODY® (V_{HH} Sequence) 202-C8

An in vivo experiment with the 202-C8 variants (mono-, bi- and/or trivalent) that display good cross-reactive potential is performed. Mice are treated with the mono-, bi- and/or trivalent 202-C8 NANOBODIES® (V_{HH} sequences) and subsequently challenged with 1 LD_{50} of mouse-adapted PR8, X47 or NIBRG-14 virus.

Groups of 3 mice are used. At t=0 mice receive 100 microgram of 202-C8 (mono-, bi- or trivalent), 100 microgram of 191-D3 (control NANOBODY® (V_{HH} sequence)) or 50 μl of PBS intranasally. Four hours later mice are challenged with 1 LD_{50} of mouse adapted NIBRG-14, PR8 or X47 virus. As an indicator of morbidity, body weight of mice is determined on a daily basis. On day 4 after challenge all mice are sacrificed and lung homogenates prepared in 1 ml PBS. The amount of infectious virus in the lung homogenates is determined by titration on MDCK cells and by a genome specific qRT-PCR. The experiment is repeated at least one time.

Example 55

Evaluation of Proteolytic Resistance of Bivalent RSV NANOBODY® (V_{HH} Sequence) in Mouse Lungs

The proteolytic resistance of the bivalent RSV101 (191D3-15GS-191D3; SEQ ID NO: 2382) in mouse lungs was evaluated by analysis of mouse lung homogenates and compared with control NANOBODY® (V_{HH} sequence) 12B2biv.

NANOBODY® (V_{HH} sequence) was administered to mice 5 hours prior to infections with RSV. Lungs were removed and homogenized 3 or 5 days after infection with RSV. In short, lungs from 5 mice were homogenized and 40 μl SDS-sample buffer (6× Laemli/20% β-mercapto) was added to 200 μl homogenate. As a positive control, 100 ng of RSV101 (0.1 mg/ml) in PBS was used to obtain a 10 μg/ml solution (5 μl NB2biv+45 μl PBS+25 μl SB (Invitrogen NP0008; Lot 401488)+DTT (10 mg/ml)).

24 μl (=20 μl lung homogenate) of samples and 15 μl of positive control were loaded on a 12% gel (NuPAGE Bis-Tris Invitrogen NP0341BOX; Lot 8031371) and run for 45 min at 200V. As marker Precision Plus Dual Color Protein Standard (Biorad; 161-0374) was used.

After the run, the gel was transferred to a nitrocellulose membrane (Invitrogen i-blot dry blotting system; program2: 6 min at 23V) and blocked with Odyssey blocking buffer (Li-cor 927-40000; Lot 2782) for 1 h at RT. All incubation and wash steps were done on a rolling plate (100 rpm). The membrane was incubated with polyclonal rabbit antiserum K1 (as primary antibody diluted 1/1000 in Odyssey blocking buffer) for 1 h at RT. Washing was carried out 3×5 min with PBS/0.1% Tween20. Detection was done with goat anti-rabbit IgG (H+L)-DyLight800 (Pierce 35571; Lot IH112638; diluted 1/10000 in Odyssey blocking buffer) for 1 h at RT. Subsequent washing was carried out 3×5 min with PBS/0.1% Tween20. The membrane was scanned with the Odyssey Infrared Imager system (in the 800 channel) (Sensitivity on Odyssey: Linear manual 4; Licor Biosciences).

Results of the Western blot are shown in FIG. 49. The positive control was well detected by the K1 antiserum. RSV101 was also detected in the lung homogenates, however with lower intensity.

Determination of the concentration was done with the Odyssey v3.0 software (FIG. 55 and Table C-51).

Example 56

Neutralization of Escape Mutants of the Long Strain by Formatted NANOBODIES® (V_{HH} Sequences)

In examples 27 and 28, the binding of monovalent NANOBODIES® (V_{HH} sequences) to typical antigenic site II and/or IV-VI RSV escape mutants has been described. Binding of NANOBODIES® (V_{HH} sequences) specifically recognizing these antigenic sites was almost lost or significantly reduced. Formatting of these NANOBODIES® (V_{HH} sequences) into bi- or trivalent constructs partially restored binding activity but not for all three escape mutant viruses. Binding to the escape mutant R7C2/1 (mutation K272E in antigenic site II) remained below the level of 25% for any bi- or trivalent construct consisting solely of antigenic site II binding NANOBODIES® (V_{HH} sequences). The NANOBODIES® (V_{HH} sequences) 15B3 and 191E4, which are binding to antigenic site IV-VI, were the only NANOBODIES® (V_{HH} sequences) (as such or in biparatopic constructs) able to bind this mutant at a level of 75% or more.

More detailed analysis of the data indicated that binding towards R7C2/1 slightly increased when the valency of the NANOBODY® (V_{HH} sequence) was increased. The binding of 7B2 constructs was 0, 4.4 and 13% respectively for the monovalent, bivalent (RSV 106) and trivalent (RSV400) formats. Such a low level of residual binding is expected to result in very high loss of potency to neutralize RSV.

The neutralizing potency of NANOBODIES® (V_{HH} sequences) was assessed on the same selected set of escape mutants as described in example 28. For this purpose the monovalent NANOBODIES® (V_{HH} sequences) 7B2, 15H8 and NC41 were compared to their respective trivalent counterparts, RSV400, RSV 404 and RSV 407. Of note, in example 28 only RSV400 was assessed for binding these escape mutants. In addition also the biparatopic trivalent molecule RSV403 (7B2-15B3-7B2) was analyzed for its neutralizing capacity.

The hRSV micro neutralization assay was essentially performed as described in example 15. In brief, Hep2 cells were seeded at a concentration of 1.5×10^4 cells/well into 96-well plates in DMEM medium containing 10% fetal calf serum (FCS) supplemented with Penicillin and Streptomycin (100 U/ml and 100 μg/ml, respectively) and incubated for 24 hours at 37° C. in a 5% CO_2 atmosphere. Viral stocks of different viruses were prepared into Hep2 cells and subsequently titrated to determine the optimal infectious dose for use in the micro neutralization assay. A standard quantity of the specific hRSV strain was pre-incubated with serial dilutions of purified NANOBODIES® (V_{HH} sequences) in a total volume of 50 μl for 30 minutes at 37° C. The medium of the Hep2 cells was replaced with the premix to allow infection for 2 hours, after which 0.1 ml of assay medium was added. The assay was performed in DMEM medium supplemented with 2.5% fetal calf serum and Penicillin and Streptomycin (100 U/m1 and 100 μg/ml, respectively). Cells were incubated for an additional 72 hours at 37° C. in a 5% CO2 atmosphere, after which cells were washed twice with 0.05% Tween-20 in PBS and once with PBS alone, after which the cells were fixed with 80% cold acetone (Sigma-Aldrich, St. Louis, Mo.) in PBS (100 μl/well) for 20 minutes at 4° C. and left to dry completely. Next the presence of the F-protein on the cell surface was detected in an ELISA type assay. Thereto, fixed Hep2 cells were blocked with 5% Porcine Serum Albumin solution in PBS for 1 hour at room temperature, than incubated for 1 hour with anti-F-protein polyclonal rabbit serum (Corral et al. 2007, BMC Biotechnol. 7: 17) or Synagis® (2 μg/ml). For detection goat Anti-rabbit-HRP conjugated antibodies or goat Anti-Human IgG, Fcγ fragment specific-HRP (Jackson ImmunoResearch, West Grove, Pa.) was used, after which the ELISA was developed according to standard procedures.

As shown in FIGS. 50 A-C, the monovalent NANOBODIES® (V_{HH} sequences) had almost no neutralizing potential towards the antigenic site II escape mutant viruses R7C2/11 and R7C2/1. The potency to neutralize the R7.936/4 antigenic site IV-VI variant was comparable to the potency to neutralize the wild type Long strain. These data are in line with the binding data of example 27 and the epitope mapping as described for these NANOBODIES® (V_{HH} sequences) in example 20.

The trivalent molecules however, were potently neutralizing all 3 escape mutants (FIGS. 50 D-G). Maximal inhibition was observed at concentrations as low as about 20 nM while this level of inhibition was not observed for the monovalent Nbs at concentrations up to 2 μM. The potent neutralization of R7C2/1, almost equivalent to the neutralization of R7C2/11, is

most surprising since example 28 showed a very significant loss of binding activity for the trivalent molecule RSV400 which was expected to result in a very high loss of neutralization potency.

The bivalent IgG Palivizumab (Synagis®), also recognizing antigenic site II was not able to block replication of R7C2/1 or R7C2/11 significantly at concentrations of about 0.2 μM. At this concentration an IC50 was not reached while R7.936/4 and wild type Long virus were neutralized with an IC50 of a few nM (data not shown).

Example 57

Screening for NANOBODIES® (V_{HH} Sequences) that Compete with C179 for Binding Hemagglutinin H5 of Influenza

C179 is a mouse monoclonal antibody which neutralizes H1, H2 and H5 subtypes influenza viruses. It does not prevent attachment of viruses to sialic acid, but instead binds to a rather conserved region on the stem of HA. Monoclonal antibody C179 neutralizes virus by stabilizing the metastable HA and prevents as such the low pH-induced conformational change and fusion of viral and cellular membranes. To isolate NANOBODIES® (V_{HH} sequences) with a similar binding and neutralizing characteristic, competition assays were set up between NANOBODIES® (V_{HH} sequences) that bind H5 hemagglutinin and the monoclonal, neutralizing antibodies C179 (Okuno et al. 1993, J. Virol. 67: 2552-2558). In short, the H5 antigen was immobilized on Maxisorp microtiter plates (Nunc) and free binding sites were blocked using 4% Marvel in PBS. Next, 125 ng/ml of C179 was preincubated with 10 and 20 μl of periplasmic extract containing NANOBODY® (V_{HH} sequence) of the different clones. The competing antibody was allowed to bind to the immobilized antigen with or without NANOBODY® (V_{HH} sequence). After incubation and a wash step, antibody binding was revealed using a HRP-conjugated donkey anti-mouse antibody. Binding specificity was determined based on OD values compared to controls having received no NANOBODY® (V_{HH} sequence).

This way, 4 NANOBODIES® (V_{HH} sequences) were identified which competes with C179 (LG203G8; SEQ ID NO: 2683, LG203E7; SEQ ID NO: 2682, LG203H10; SEQ ID NO: 2446 and LG203G3; SEQ ID NO: 2442) (FIG. 56).

Example 58

Optimization of Linker Length of NC41 Trivalents

To determine the impact of the linker length of trivalents of NC41, different constructs with linkers ranging from 3Ala, 9GS, 15GS, to 20GS linkers (RSV408, RSV409, RSV407 and

RSV410 resp.) were generated. All four NC41 trivalents were able to completely neutralize both RSV B-1 and Long strains (FIG. 5). No effect of linker length was observed in neutralization of RSV Long, as all constructs were equally potent. By contrast, the constructs with 9GS and 3Ala linkers had increased IC50 values on the B-1 strain, indicating that a minimal linker length of 15GS is required for maximal potency. This may be explained by the observation that bivalent NC41 constructs already are very potent neutralizers on Long, while on the B-1 strain the potency difference between bivalent and trivalent NC41 is much larger (see example 25). In RSV408 and RSV409 the accessibility of the middle NANOBODY® (V_{HH} sequence) may be less optimal.

Example 59

Humanization of NANOBODY® (V_{HH} Sequence) NC41

The sequence of NANOBODY® (V_{HH} sequence) NC41 was aligned to the human germline VH3-23. to allow selection of residues suitable for further humanization of the NANOBODY® (V_{HH} sequence) sequence. In addition, in silico analysis was done to identify residues that are potentially prone to post-translational modifications, such as Asp isomerisation, and to identify mutations that might improve the chemical stability. The CDR regions and the so-called Hallmark residues, which are known to be essential for the stability and potency of NANOBODIES® (V_{HH} sequences) were excluded for modification.

For NC41 in total 11 positions were selected for mutation to the corresponding human residue: Four mutations were simultaneous introduced (Val5Leu, Ala14Pro, Glu44Gly, Gln108Leu), as these residues were not expected to dramatically affect the NANOBODY® (V_{HH} sequence) function (based on data from other NANOBODIES® (V_{HH} sequences)). In this basic variant, seven residues of which it was unknown whether mutation to the human counterpart was allowed (Ser19Arg, Ile2Oleu, Ala74Ser, Gly78Leu, Ala83Arg, Asp85Glu, Arg105Gln) were mutated using a library approach, allowing either the wildtype or the corresponding human amino acid at each position. The resulting library, with a theoretical diversity of 128, was generated by gene assembly using overlapping oligonucleotide sequences containing degenerated codon use, and subsequently cloned into an expression vector derived from pUC119 which contained the LacZ promoter, a resistance gene for kanamycin, a multicloning site and the OmpA leader sequence. In frame with the NANOBODY® (V_{HH} sequence) coding sequence, the vector coded for a C-terminal c-myc tag and a (His)6 tag. NANOBODIES® (V_{HH} sequences) were produced in the periplasm of *E. Coli* (see Example 22). Library diversity was confirmed by sequence analysis.

Periplasmic extracts from 368 individual NC41 variants and wildtype NC41 were generated and subjected to a functional screening cascade to identify the best humanized NC41 variant, in terms of both potency and stability.

In a first step, RSV binding of humanized NC41 variants to RSV Long was determined in ELISA (Hytest, Turku Finland; #8RSV79) (see Example 22).

Moreover, the positive binders were analyzed for binding to Hep2 cells infected with RSV B-1 strain. In here, Hep2 cells were seeded into 96-wells plates and infected with RSV B-1 strain, essentially following the procedure described for the neutralization assay (see Examples 15 and 21). Three days later cells were fixed with ice-cold acetone and plates were used in an ELISA assay using periplasmic extracts at different dilutions. NANOBODY® (V_{HH} sequence) binding to Hep2-B1 infected cells was detected using anti-VHH rabbit polyclonal antibody, followed by goat Anti-rabbit-HRP conjugated antibodies, after which the ELISA was developed according to standard procedures.

Additionally, in order to verify if the introduced mutations affected the temperature stability, periplasmatic extracts of all binders were heated to 74° C. for 2 hours, which is 5° C. above the melting temperature of wildtype NC41. The binding to RSV long before and after heating was analyzed in ELISA, and the ratio of binding signal after vs before heating was taken as measure for temperature stability.

Finally, the kinetic off-rates of the variants were determined in Biacore assay on the F_{tm}-NN protein, as described in Examples 12 and 22.

All binders were sequenced and ranked according to their capacity to bind the F-protein of RSV. When analyzing the sequences of the strongest binders, a clear preference for Gln105 (human residue) was observed in all cases. Whereas the Ile20Leu mutation appeared underrepresented, for all other positions there was no clear preference for either the wild type or the human sequence, with variants containing up to 10 mutations compared to wildtype NC41. Notably, in one variant an additional pointmutation (Gly54Asp) within the CDR2 region was observed. This variant, NC41 variant 6, showed the lowest off-rate of all variants and wildtype NC41, resulting in affinity increase.

Based on the sequence and functional data, 18 variants (Table A-8) were selected for further characterization as purified proteins (FIG. 65). All variants were produced and purified, and potencies for neutralization of RSV Long and B-1 were determined in the micro neutralizations assay. While most variants showed very similar activity to wildtype NC41, several variants showed increased potency on both Long (2-fold) and B-1 (6-fold), with the strongest neutralizers being NC41 variants 6, 8, 9 17, and 18. Notably, variant 18 was maximally humanized at all 11 positions, with the additional introduction of Asp54 in the CDR2 region. Variant 10 and 11 were more potent in neutralizing B-1 strain than NC41, but not on Long strain.

For a select panel of NC41 variants the kinetic binding parameters were determined in Biacore on F_{tm}-NN protein (Table C-52) as described in Example 12 and 22. No significant

differences in the calculated data were observed for NC41 and the humanized NC41 variants 6, 8 and 17. It should be noted that the on-rates of all NC41 variants were at the detection limit of the instrument, but the off-rates could be ranked as v06<v17<NC41<v08. The impact of the Gly to Asp mutation in CDR2 (position 54) could be clearly demonstrated when comparing v17 and v18 as this is the only difference in these maximally humanized variants. Neutralization was tested for both the Long strain and the B-1 strain in two independent assays in comparison to the NC41 wild type as shown in table B-5. In both assays NC41v18 was more potent than NC41 on both viruses and in both assays NC41v18 was more potent than NC41v17 on the Long strain. The improved neutralization of NC41v18 was also observed for the B-1 strain in the second assay.

All NC41 variants were subjected to heat-induced unfolding to assess the effect of the introduced mutations on the stability of the protein. Thereto the melting temperature (Tm) was determined by stepwise increase in temperature in presence of Sypro Orange, a dye that binds to Trp residues that become exposed upon unfolding of the protein. All variants showed to have increased Tm relative to wildtype NC41 (69° C.), up to 9° C. for variant 18.

Three NC41 variants were formatted as trivalent constructs using 15GS linkers, NC41 variant 3 (RSV414), variant 6 (RSV426), and variant 18 (RSV427). Sequences are shown in Table A-9. All trivalents were produced and purified as described in Example 22. FIG. 67 shows the neutralization on both RSV Long and B-1 strains of two of the trivalent humanized NC41 variants with their corresponding monovalent NANOBODIES® (V_{HH} sequences). Trivalents of variant 3 and 6 were 81-91 times more potent neutralizers of Long than Synagis®, and similar to wildtype NC41 trivalent. On the B-1 strain RSV414 and RSV426 were ˜16 fold more potent neutralizers than Synagis, but here both were also slightly enhanced compared to the trivalent of wild type NC41 RSV407. The increased potency of monovalent variants 3 and 6 for B-1 thus appears to result in slightly improved trivalents.

Example 60

Immunisation Llamas with Foot-and-Mouth Disease Virus and Avian Influenza Virus

Two llamas were immunized with mixtures of Foot-and-mouth disease virus (FMDV) and avian influenza virus (AIV) strains (Table C-53) within the high containment unit of the Central Veterinary Institute of Wageningen University and Research Centre in Lelystad, the Netherlands. The AIV strains were all low pathogenic avian influenza strains that were propagated on embryonated eggs and were not inactivated. The FMDV strains were propagated on BHK-21 cells, inactivated by treatment with 10 mM binary ethyleneimine, and concentrated by two consecutive PEG6000 precipitations. Both AIV (for protocol see

Arora et. al. 1985, Analytical Biochemistry 144: 189-192) and FMDV antigens were finally purified using sucrose density gradients.

A total of three immunizations were given. The second immunization was given 28 days after the first immunization. The third immunization was given 21 days after the second immunization. All immunizations were given intramuscularly using Specol (Stimune) as an adjuvant (Bokhout et al. 1981, Vet. Immunol. Immunopath. 2: 491-500). Six days after the second and third immunization (34 and 55 days post primary immunization [DPI], respectively) 150 ml heparinized blood samples were taken for isolation of peripheral blood lymphocytes (PBLs) using Ficoll Paque Plus (GE Healthcare). Furthermore, serum was collected from both llamas at 0, 34 and 55 DPI.

The antibody response against H5 and H7 type haemagglutinin was determined using a haemagglutination inhibition test (HI) that was performed according to EU council directive 2005/94/EU. In this assay 25 μl HA antigen containing 8 haemagglutinating units was preincubated with 25 μl of a two-fold dilution series of sera for 1 hour at room temperature in a V-bottom shaped 96-well microtiter plate. After addition of 25 μl 1% chicken erythrocyte suspension and incubation at 4° C. for 45 min the HI titer was determined visually. Llama 3049, that was immunized with both H5 and H7 strains, developed HI titers against both H5 and H7 type antigen during the immunization procedure (Table C-54). Llama 3050, that was immunized with H5 but not with H7 type strains only developed a HI response against H5 antigen (Table C-54).

Example 61

Construction of Phage Display Libraries

Total RNA was isolated from about 10^8 PBLs obtained in example 60 using the RNeasy maxi kit (Qiagen). cDNA synthesis was performed using primer NotI-d(T)18 (Table C-55) and Superscript III reverse transcriptase (Invitrogen). The NANOBODY® (V_{HH} sequence) encoding fragments were amplified by PCR using primer VH2B in combination with either primer lam07, lam08 or BOLI-192 (Table C-55) and Amplitaq Gold DNA polymerase (Applied Biosystems). The PCR fragments were cut with PstI and NotI and ligated to similarly cut phage display vector pRL144 (Harmsen et al. 2005, Vaccine 23: 4926-4934).

By electroporation of *Escherichia coli* TG1 cells twelve libraries were obtained (Table C-56).

Example 62

Phage Display Selections

Phage libraries obtained in Example 61 were rescued by infection with VCS-M13 helperphage and phage particles were purification by two PEG precipitations (McCafferty and Johnson 1996, Construction and screening of antibody display libraries. In: Kay, BK, Winter, J, and McCafferty, J [eds], Phage display of peptides and proteins. Academic Press, San Diego, pp. 79-111). For phage display selections libraries pAL442, 443, 444, 448, 449 and 450 were pooled. Phage pannings were performed in 96-well polystyrene microtiter plates (Greiner) by direct coating of AI antigen. AI antigen had been obtained from propagation of AI strains on Madin Darby canine kidney (MDCK) cells grown in suspension on serum free medium (SFM4BHK21 medium, a prototype medium developed for BHK21 cells obtained from Hyclone) and that was 20-fold concentrated using a 100-kDa molecular weight cutoff centrifugation-concentration device. Alternatively, phage pannings were performed using recombinant his-tagged HAO trimer from H5N1 strain A/Anhui/1/2005 (Abcam, Cambridge, UK; Cat. No. ab53938) or recombinant his-tagged HA1 from H7N7 strain A/Chicken/Netherlands/01/03 (Abcam, Cambridge, UK; Cat. No. ab61286), both produced by HEK293 cells. For this purpose these recombinant antigens were captured in polystyrene microtiter plates coated with 2 μg/ml affinity purified polyclonal rabbit anti-his6 peptide antibody (Rockland, Cat. No. 600-401-382). Alternatively, phage display selections were performed using Drosophila S2 cell produced strep-tagged recombinant haemagglutinin derived from an H7N2 influenza strain (HAstr H7N2). Antigen concentrations used during panning were either 0.1 or 0.01 μg/ml. Phage libraries were added at 10^{10} TU per well. Bound phage were eluted by incubation in 1 mg/ml trypsin in PBS buffer for 30 min.

Example 63

Binding to Influenza Antigens in ELISA

Individual clones binding to influenza antigens in ELISA were screened using soluble NANOBODIES® (V_{HH} sequences) prepared according to a previously described protocol (McCafferty, J, and Johnson, K S, 1996, Construction and screening of antibody display libraries. In: Kay, BK, Winter, J, and McCafferty, J [eds], Phage display of peptides and proteins. Academic Press, San Diego, pp. 79-111). The influenza antigens were obtained from virus propagated on MDCK cells using serum free medium and further purified by sucrose density gradients. The authentic AIV antigens used in ELISA originated from the strains indicated in Table C-57.

Briefly, 96-well ELISA plates were coated with 1 μg/ml AIV antigen in 50 mM carbonate/bicarbonate buffer pH 9.6. These plates were then incubated with tenfold diluted *E. coli* culture supernatants in ELISA-buffer (1% skimmed milk; 0.05% Tween-20; 0.5M NaCl; 2.7 mM KCl; 2.8 mM KH_2PO_4; 8.1 mM Na_2HPO_4; pH 7.4). Bound NANOBODIES®

(V_{HH} sequences) were subsequently detected using a peroxidase-conjugated monoclonal antibody against the c-myc tag (Roche Applied Science, Mannheim, Germany) and stained with 3,3′,5,5′-tetramethylbenzidine.

After screening individual clones for binding to authentic AIV antigens 39 clones binding to AIV antigens from H5 strains and 50 clones binding to AIV antigen from H7 strains were sequenced. Sequence analysis was performed using the ABI3130 capillary sequencer (Applied Biosystems) and primer MPE26 (Table C-55). The 39 H5 binding clones encoded 25 different NANOBODIES® (V_{HH} sequences) that form six CDR3 groups (Table A-1 and Table C-58). The 50 H7 binding clones encoded 40 different NANOBODIES® (V_{HH} sequences) that form seven CDR3 groups (Table A-1 and Table C-59). With the exception of clone IV28, all H5 and H7 binding clones encoded NANOBODIES® (V_{HH} sequences) containing the hallmark amino acid residues typical of single-domain antibodies (Harmsen et al. 2000, Mol. Immunol. 37: 579-590).

Most H7 binding NANOBODIES® (V_{HH} sequences) of CDR3 group A contain a potential N-glycosylation site at position 84. Most H5 binding clones bind specifically to AIV antigens of three different H5 strains. However, clones of CDR3 group B also bind to antigen of an H1 strain (Table C-58). Furthermore, two clones (IV154 and IV155) that fall into two CDR3 groups bind to AIV antigen of H1, H7 and H5 strains (Table C-58). These clones probably bind to nucleoprotein, which is highly immunogenic and highly conserved between influenza strains of different serotypes. Consistent with this conclusion, these clones were selected in both panning rounds on authentic AIV antigens whereas most other clones were selected using recombinant haemagglutinin in the second round of phage display selection. Almost all 40 H7 binding NANOBODIES® (V_{HH} sequences) bind to AIV antigen of two H7 strains, but not to AIV antigen of H1 or H5 strains (Table C-59). Only clone IV18 appeared to bind to H5 antigen. However, the two clones that encoded NANOBODIES® (V_{HH} sequences) that are identical to IV18 did not show such cross reaction to H5 strains, suggesting that this cross reaction is an artifact.

Example 64

Yeast Expression of Selected NANOBODIES® (V_{HH} Sequences)

We selected eight H5 binding NANOBODIES® (V_{HH} sequences) and eight H7 binding NANOBODIES® (V_{HH} sequences) for small scale yeast (*Saccharomyces cerevisiae*) expression using plasmid pRL188 (Harmsen et al. 2007, Vet. Microbiol. 120: 193-206). This plasmid results in NANOBODY® (V_{HH} sequence) production with a C-terminal extension with amino acid sequence (SEQ ID NO: 3063; EPKTPKPQPQPQPQPQPNPTTESKCPHHHHHH). We preferably selected clones representing all CDR3 groups for such yeast expression. Insertion of the NANOBODY® (V_{HH} sequence)

coding sequence into pRL188 required the presence of a BstEII restriction endonuclease cleavage site in the FR4 coding region. This site was present in most NANOBODY® (V_{HH} sequence) clones, but not in all (Tables C-58 and C-59). As a result we could not yeast-produce IV151 and IV153, which are unique representatives of two CDR3 groups, in a *facile* manner. A person skilled in the art could produce such clones suitable for yeast expression by introduction of this BstEII site by site-directed mutagenesis. Furthermore, the subcloning of IV28 into pRL188 was not successful. NANOBODIES® (V_{HH} sequences) were expressed in *S. cerevisiae* under control of the GALT promoter and directed into the growth medium by fusion to the invertase signal peptide as described previously (Harmsen et al. 2007, Vet. Microbiol. 120: 193-206 and references therein). The NANOBODIES® (V_{HH} sequences) were purified from culture supernatant using immobilized-metal affinity chromatography. Purified NANOBODIES® (V_{HH} sequences) were concentrated and the buffer exchanged to phosphate-buffered saline by use of 5-kDa molecular weight cut-off centrifugal concentration devices (Biomax-5 membrane, Millipore, Bedford, Mass.). The protein concentration was determined using the Bio-Rad (Hercules, Calif.) protein assay.

Example 65

Characteristics of Yeast-Produced NANOBODIES® (V_{HH} Sequences)

65.1

Binding in ELISA

We next analysed the binding of the selected NANOBODIES® (V_{HH} sequences) to influenza antigens of strains of different serotypes. This ELISA was essentially performed as described in the previous section (Example 63) for screening of *E. coli* produced NANOBODIES® (V_{HH} sequences) but using a higher concentration of influenza antigen (see Table C-57) for coating (5 μg/ml) and using a peroxidase-conjugated anti-his6 monoclonal antibody (Roche Applied Science) for NANOBODY® (V_{HH} sequence) detection. The NANOBODIES® (V_{HH} sequences) that were selected for binding to H5 strains all react with all three H5 strains used (FIG. 66A). The five NANOBODIES® (V_{HH} sequences) of CDR3 group A did not cross react with strains of other H serotypes (FIGS. 66A and B). The single NANOBODY® (V_{HH} sequence) of CDR3 group B (IV146) cross reacted only with H1 and H2 strains (FIGS. 66A and B). The NANOBODIES® (V_{HH} sequences) IV154 and IV155, representing two CDR3 groups, cross reacted with all strains except H15N6 (FIGS. 66A and B). The NANOBODIES® (V_{HH} sequences) selected for binding to H7 strains all could bind to both H7 strains (FIG. 66D). Two NANOBODIES® (V_{HH} sequences) (IV1 and IV25) did not cross react to other strains whereas the other five nanobodies NANOBODIES® (V_{HH} sequences) (IV5, IV21, IV26, IV29 and IV37) showed weak cross reaction with an H2N3 and

an H6N5 strain (FIGS. 66C and D). These results of the yeast-produced NANOBODIES® (V_{HH} sequences) are consistent with the results of the *E. coli* produced NANOBODIES® (V_{HH} sequences) (Tables C-58 and C-59).

We next analysed the binding of NANOBODIES® (V_{HH} sequences) to selected authentic and recombinant antigens in ELISA by incubation of twofold dilution series of NANOBODIES® (V_{HH} sequences) with a starting concentration of 10 μg/ml. NANOBODIES® (V_{HH} sequences) bound to recombinant antigens were detected using a polyclonal rabbit anti-NANOBODY® (V_{HH} sequence) serum (R907) and peroxidase-conjugated swine anti-rabbit serum (Dako, P217) since the recombinant antigen also contains a his6 tag. After nonlinear regression analysis the NANOBODY® (V_{HH} sequence) concentration required to obtain an extinction at 450 nm of 0.2 (authentic antigens) or 1.0 (recombinant antigens) was interpolated. All NANOBODIES® (V_{HH} sequences) selected for binding to H5 strains could bind to H5N9 antigen with titers differing at most 5-fold (Table C-60). Six clones also could bind to two recombinant H5 antigens (Table C-60), demonstrating that they recognized haemagglutinin. Two further clones (IV154 and IV155) did not bind to both recombinant haemagglutinins at all. This further suggests that these clones bind to nucleoprotein, as suggested above based on their binding to authentic influenza antigens of many different H and N types. The NANOBODIES® (V_{HH} sequences) selected for binding to H7 strains all could bind to authentic antigen of two H7 type influenza strains and recombinant HA1 fragment (Table C-61), showing that they bind to haemagglutinin.

65.2

Virus Neutralization

We next determined the in vitro virus neutralizing capacity of the selected NANOBODIES® (V_{HH} sequences). For this purpose 100 tissue culture infective doses required to infect 50% of the wells ($TCID_{50}$) were preincubated with twofold dilution series of yeast-produced NANOBODIES® (V_{HH} sequences) for 1 hour at room temperature. These were subsequently added to MDCK cell monolayers in a serum free medium containing 3 μg/ml trypsin to enable virus replication. After two days of growth at 37° C. and 5% CO_2 influenza virus antigen in the wells was detected using an immunoperoxidase monolayer assay employing a nucleoprotein specific monoclonal antibody (HB65, also known as H16-L10-4; Yewdell et al. 1981, J. Immunol. 126: 1814-1819). Neutralization titers were calculated according to Reed and Muench (1938, Am. J. Hyg. 27: 493). Only clone IV146 could neutralize both H5 type viruses at the lowest concentration analysed (0.75 μg/ml), whereas all other NANOBODIES® (V_{HH} sequences) did not neutralize the two virus strains used at the highest concentration analysed of 50 μg/ml (Tables C-60 and C-61).

65.3

Inhibition of Hemagglutination

We similarly determined the ability of the yeast-produced NANOBODIES® (V_{HH} sequences) to inhibit haemagglutination using the protocol described (Example 60) above for analysis of llama sera. We could not detect any inhibition of haemagglutination at the highest NANOBODY® (V_{HH} sequence) concentration analysed (Tables C-60 and C-61).

Thus, clone IV146 neutralizes influenza virus without inhibiting haemagglutination. This is an unexpected finding since most previously isolated conventional monoclonal antibodies that neutralize influenza virus also inhibit haemagglutination. Clone IV146 also cross reacts in ELISA with H1 and H2 strains. This is again unexpected, since most conventional monoclonal antibodies binding haemagglutinin bind specifically to one haemagglutinin type. However, recently, H5 type haemagglutinin binding human monoclonal antibodies that cross react to H1 and H2 type strains, and neutralize virus without inhibiting haemagglutination were found by several groups (Throsby et al. 2008, Plos ONE 3; Sui et al. Nature Struct. Biol. 16: 265-273; Kashyap et al. 2008, Proc. Nat. Acad. Sci. 22: 5986-5991). These human mAbs bind to a relatively conserved epitope mainly present on the HA2 domain that is involved in initiating the fusion of the viral and host cell membranes, which is essential for infection. This epitope can be present in two conformations: a prefusion state which does not enable membrane fusion and another conformation that is competent for membrane fusion. The prefusion state is recognized by such broadly cross reactive neutralizing antibodies (Sui et al. Nature Struct. Biol. 16: 265-273; Ekiert et al., 2009, Science 324: 246-251), suggesting that the mechanism of virus neutralization by such antibodies relies on inhibition of a conformational change of HA into a conformation competent for fusion. The similarity in virus neutralization and strain specificity of IV146 with these human monoclonal antibodies suggests that IV146 also recognizes this conserved epitope on the HA2 domain that is involved in initiating membrane fusion.

Tables

TABLE A-2 Amino acid sequence of multivalent constructs that bind hRSV (including Myc-His tag SEQ ID Construct NO Sequence RSV101 2382 EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGM GWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTA VYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV102 2383 VQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTV YADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWG

QGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEAS
GRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQM
NSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISEEDLNG
AAHHHHHH RSV103 2384
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT
VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQA
GGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISR
DNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAE
QKLISEEDLNGAAHHHHHH RSV104 2385
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT
VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQA
PGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAA
ELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV105 2386
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTY
YADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWG
QGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAP
GKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADL
TSTNPGSYIYIWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV106 2387
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTY
YADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWG
QGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMG
WFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVY
YCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV107
2388 EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSAI
GAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGR
GTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPG
KEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTP
LNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV108 2389
EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSAI
GAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGR
GTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGW
FRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYY
CGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV109 2390
EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRTF
YADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDTASWNSGSFIYDWAYDHWG
QGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAP
GKEREFVAAISWSRGRTFYADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDT
ASWNSGSFIYDWAYDHWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHH RSV110 2391

EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRTF
YADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDTASWNSGSFIYDWAYDHWG
QGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMG
WFRQAPGKEREFVAAISWSRGRTFYADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVY
YCAVDTASWNSGSFIYDWAYDHWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV113
2392 EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
TYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYYA
LGWFRQAPGKEREGVSCISSSDHSTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDT
AVYYCAADPALGCYSGSYYPRYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV114
2393 EVQLVESGGGWVQAGGSLRLSCAASGRAFSSYAMGWIRQAPGKEREFVAGIDQSGEST
AYGASASGRFIISRDNAKNTVHLLMNSLQSDDTAVYYCVADGVLATTLNWDYWGQGTQ
VTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGWVQAGGSLRLSCAASGRAFSSYA
MGWIRQAPGKEREFVAGIDQSGESTAYGASASGRFIISRDNAKNTVHLLMNSLQSDDT
AVYYCVADGVLATTLNWDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV115 2394
EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIA
YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
WGQGTQVTVSSGGGGSGGGGSGGGGGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTF
SADTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLK
PEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAH HHHHH
RSV116 2395
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYV
LGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV201
2396 EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYD
YWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWF
RQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYY
CAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV202 2397
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYD
YWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSA
DTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPE
DTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHH HHH
RSV203 2398
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYD
YWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLS

CAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTV
DLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSAAAEQKLISE
EDLNGAAHHHHHH RSV204 2399
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNY
VLGWFRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDD
TAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV205
2400 EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYY
ALGWFRQAPGKEREGVSCISSSDHSTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPGD
TAVYYCAADPALGCYSGSYYPRYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV206
2401 EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSA
IGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYA
MGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDT
AVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV207
2402 EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSA
IGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYA
MGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDT
AVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV301
2403 EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIA
YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
WGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFR
QAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYT
CAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV302
2404 EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIA
YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRY
GMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPE
DTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISEEDLNGAAHHH HHH
RSV303 2405
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WGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSC
EASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTV
YLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSAAAEQKLISE
EDLNGAAHHHHHH RSV305 2406

EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
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GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYA
MGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDT
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2407 EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
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GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYV
LGWFRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV400
2408 EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSY
AMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPED
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SGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSV
KGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQ
VTVSSAAAEQKLISEEDLNGAAHHHHHH RSV401 2409
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSY
AMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPED
TAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVE
SGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHSTTYTDSV
KGRFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYWGQGTQV
TVSSAAAEQKLISEEDLNGAAHHHHHH RSV402 2410
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GRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQV
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EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSA
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SSAAAEQKLISEEDLNGAAHHHHHH RSV405 2413
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YGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKP
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DSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQ
GTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV406 2414
EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRT
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SGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRTFYADSV
KGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDTASWNSGSFIYDWAYDHWGQGTQ
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SSAAAEQKLISEEDLNGAAHHHHHH RSV408 2989
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TAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSAAAEQKLISEEDLNGAAHHHHHH RSV409
2990 EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
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SSAAAEQKLISEEDLNGAAHHHHHH RSV502 2995
EVQLVESGGGLVQAGGSLRLSCEASGRTFSSYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNPGAYYYTWAYD
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TVSSAAAEQKLISEEDLNGAAHHHHHH RSV514 3585
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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LSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKN
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SEEDLNGAAHHHHHH RSV515 3586
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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WGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRVSCAASGFTFNDYIMGWFR
QAPGKERMFIAAISGTGTIKYYGDLVRGRFTISRDNAKNTVYLRIDSLNPEDTAVYYC
AARQDYGLGYRESHEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGDSLRL
SCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNT
VYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSAAAEQKLIS

EEDLNGAAHHHHHH

TABLE A-3 F-protein sequences F-protein SEQ ID NO Sequence RSV LONG M-2 2416
MELPILKANAITTILAAVTFCFASSQNITEEFYQSTCSAVSKG
YLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDKY
KNAVTELQLLMQSTPAANNRARRELPRFMNYTLNNTKKTNVTL
SKKRKRRFLGFLLGVGSAIASGTAVSKVLHLEGEVNKIKSALL
STNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSCRIS
NIETVIEFQQKNNRLLEITREFSVNAGVTTPVSTYMLTNSELL
SLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVV
QLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCD
NAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIF
NPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRG
IIKTFSNGCDYVSNKGVDTVSVGNTLYYVNKQEGKSLYVKGEP
IINFYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELLHHV
NAGKSTTNIMITTIIIVIIVILLSLIAVGLLLYCKARSTPVTL SKDQLSGINNIAFSN RSV A-2 2417
MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKG
YLSALRTGWYTSVITIELSNIKKNKCNGTDAKVKLIKQELDKY
KNAVTELQLLMQSTQATNNRARRELPRFMNYTLNNAKKTNVTL
SKKRKRRFLGFLLGVGSAIASGVAVSKVLHLEGEVNKIKSALL
STNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSCSIS
NIETVIEFQQKNNRLLEITREFSVNAGVTTPVSTYMLTNSELL
SLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVV
QLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCD
NAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIF
NPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRG
IIKTFSNGCDYVSNKGVDTVSVGNTLYYVNKQEGKSLYVKGEP
IINFYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV
NAGKSTTNIMITTIIIVIIVILLSLIAVGLLLYCKARSTPVTL SKDQLSGINNIAFSN RSV B-1 2418
MELLIHRSSAIFLTLAVNALYLTSSQNITEEFYQSTCSAVSRG
YFSALRTGWYTSVITIELSNIKETKCNGTDTKVKLIKQELDKY
KNAVTELQLLMQNTPAANNRARREAPQYMNYTINTTKNLNVSI
SKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGEVNKIKNALL
STNKAVVSLSNGVSVLTSKVLDLKNYINNRLLPIVNQQSCRIS
NIETVIEFQQMNSRLLEITREFSVNAGVTTPLSTYMLTNSELL
SLINDMPITNDQKKLMSSNVQIVRQQSYSIMSIIKEEVLAYVV
QLPIYGVIDTPCWKLHTSPLCTTNIKEGSNICLTRTDRGWYCD
NAGSVSFFPQADTCKVQSNRVFCDTMNSLTLPSEVSLCNTDIF
NSKYDCKIMTSKTDISSSVITSLGAIVSCYGKTKCTASNKNRG
IIKTFSNGCDYVSNKGVDTVSVGNTLYYVNKLEGKNLYVKGEP

IINYYDPLVFPSDEFDASISQVNEKINQSLAFIRRSDELLHNV
NTGKSTTNIMITTIIIVIIVVLLLLIAIGLLLYCKAKNTPVTL SKDQLSGINNIAFSK

TABLE A-4 Amino acid sequence of multivalent constructs that bind hemagglutinin H5 of influenza Construct SEQ ID NO Sequence 202-C8-9GS- 2423
EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 202-C8
ISPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSL
TLTDSPDLRSQGTQVTVSSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSC
TGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGSNTDYADSVKGRFTISR
DNAKNTLYLQMNSLKPEDTALYYCRRSLTLTDSPDLRSQGTQVTVSS 202-C8-15GS- 2424
EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 202-C8
ISPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSL
TLTDSPDLRSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGG
SLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGSNTDYADSVKG
RFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSLTLTDSPDLRSQGTQVT VSS 202-C8-10GS-
2425 EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 202-C8-10GS-
ISPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSL 202-C8
TLTDSPDLRSQGTQVTVSSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLS
CTGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGSNTDYADSVKGRFTIS
RDNAKNTLYLQMNSLKPEDTALYYCRRSLTLTDSPDLRSQGTQVTVSSGG
GGSGGGGSEVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPG
KDLEYVSGISPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTA
LYYCRRSLTLTDSPDLRSQGTQVTVSS 202-C8-20GS- 2426
EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 202-C8-20GS-
ISPSGSNTDYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSL 202-C8
TLTDSPDLRSQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL
VQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGSNTDYA
DSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCRRSLTLTDSPDLRSQ
GTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSC
TGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGSNTDYADSVKGRFTISR
DNAKNTLYLQMNSLKPEDTALYYCRRSLTLTDSPDLRSQGTQVTVSS 203-B12- 2428
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMGWVRRAPGEGLEWVSS 15GS-203-B12
ISSGGALPTYADSVKGRFTISRDNVKNTLYLQMNSLKPEDTAVYSCEKYA
GSMWTSERDAWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQP
GGSLRLSCAASGFTFSSYAMGWVRRAPGEGLEWVSSISSGGALPTYADSV
KGRFTISRDNVKNTLYLQMNSLKPEDTAVYSCEKYAGSMWTSERDAWGQG TQVTVSS 203-
H9-5GS- 2429 EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 203-
H9 ISPSGGNTDYADSVKGRFTISRDNAKNTLYLQMNSLQPEDTALYYCRRSL
TLTDSPDLRSQGTQVTVSSGGGGSEVQLVESGGGLVQPGGSLRLSCTGSG
FTFSSYWMDWVRQTPGKDLEYVSGISPSGGNTDYADSVKGRFTISRDNAK

NTLYLQMNSLQPEDTALYYCRRSLTLTDSPDLRSQGTQVTVSS 203-H9-25GS- 2430
EVQLVESGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSG 203-H9
ISPSGGNTDYADSVKGRFTISRDNAKNTLYLQMNSLQPEDTALYYCRRSL
TLTDSPDLRSQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVE
SGGGLVQPGGSLRLSCTGSGFTFSSYWMDWVRQTPGKDLEYVSGISPSGG
NTDYADSVKGRFTISRDNAKNTLYLQMNSLQPEDTALYYCRRSLTLTDSP DLRSQGTQVTVSS

TABLE A-5 Sequences of multivalent Fc constructs SEQ Construct ID NO Sequence
NC41::15GS::NC41::G1- 2641
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKERE hinge::IgG1-Fc
FVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTA
VYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGGSGG
GGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGK
EREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPD
DTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK NC41::15GS::NC41::9GS- 2642
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VYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGGSGG
GGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGK
EREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPD
DTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGS
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
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VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK NC41::15GS::NC41::G3-
2643 EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKERE hinge::IgG1-Fc
FVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTA
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GGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGK
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FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT Fc
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSGGGGSGGGGS

GGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAP
GKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLK
PEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSGGGGSG
GGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
191D3::15GS::191E4:: 2980
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE G3-hinge::IgG1-Fc
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSGGGGSGGGGS
GGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAP
GKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLK
PEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSELKTPL
GDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSC
DTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK 191D3::G1-hinge:: 2981
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE IgG1-Fc::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKEVQLVESG
GGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWS
GGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSS
RIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::9GS-G1-hinge 2982
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE ::IgG1-Fc::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSGGGGSGGGSE
PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

KEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKER
EFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDT
ALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::G3-hinge:: 2983
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE IgG1-Fc::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSELKTPLGDTT
HTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPP
PCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKEVQLVES
GGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPW
SGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGS
SRIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::G1-hinge:: 2984
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE IgG1-Fc::9GS::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
SEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKER
EFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDT
ALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::9GS-G1-hinge 2985
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE ::IgG1-
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT Fc::9GS::191E4
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSGGGGSGGGSE
PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGW
FRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQ
MNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::G3-hinge:: 2986
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE IgG1-Fc::9GS::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSELKTPLGDTT

HTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPP
PCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGG
GSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKE
REFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPED
TALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS 191D3::191E4::IgG1- 2987
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE Fc
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSGGGGSGGGGS
GGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAP
GKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLK
PEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSSEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK 191D3::IgG1- 2988
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKERE Fc::191E4
FVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDT
AVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSSEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKEVQLVESG
GGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWS
GGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSS
RIYIYSDSLSERSYDYWGQGTQVTVSS

TABLE A-6 Amino acid sequence of multivalent Nanobody constructs that bind rabies virus
SEQ ID Construct NO: Sequence 213H7-15GS- 2427
EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYRMGWFRQAPGKEREFISTIS 213H7
WNGRSTYYADSVKGRFIFSEDNAKNTVYLQMNSLKPEDTAVYYCAAALIGGY
YSDVDAWSYWGPGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGS
LRLSCAASGRTLSSYRMGWFRQAPGKEREFISTISWNGRSTYYADSVKGRFI
FSEDNAKNTVYLQMNSLKPEDTAVYYCAAALIGGYYSDVDAWSYWGPGTQVT VSS 214E8-15GS-
2663 EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 214-E8

WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGSVQAGG
SLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIRWSGGDAYYDDSVKGRF
AITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYGSYTYGGSYDLWGQGTQ VTVSS
212C12-15GS- 2664
EVQLVESGGGLVQPGGSLRLSCAASGFTFGSSDMSWVRQAPGKGPEWVSGIN 212C12
SGGGRTLYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCATDLYGSS
WYTDYWSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLS
CAASGFTFGSSDMSWVRQAPGKGPEWVSGINSGGGRTLYADSVKGRFTISRD
NAKNTLYLQMNSLKSEDTAVYYCATDLYGSSWYTDYWSQGTQVTVSS 213E6-5GS- 2665
EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD 213E6
WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSEVQLVESGGGLVQAGASLRLSCAASGSTL
SRYGVGWFRQAPGKERELVASVDWSGSRTYYADSVKGRFTISRDNAKNTGYL
QMNSLKPDDTAVYYCAADSSVVPGIEKYDDWGLGTQVTVSS 213E6-25GS- 2666
EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD 213E6
WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGG
GLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVDWSGSRTYYA
DSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVPGIEKYDDWG LGTQVTVSS
214F8-15GS- 2667 EVQLVESGGDLVQAGGSLRLSCVASGSTYSINAMGWYRQAPGKLRELVAAFR
214F8 TGGSTDYADSVKGRFTISRDTAKNTVYLQMNSLKPEDTAVYYCNAEVIYYPY
DYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGDLVQAGGSLRLSCVA
SGSTYSINAMGWYRQAPGKLRELVAAFRTGGSTDYADSVKGRFTISRDTAKN
TVYLQMNSLKPEDTAVYYCNAEVIYYPYDYWGQGTQVTVSS 213E6-5GS- 2668
EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD 212C12
WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTF
GSSDMSWVRQAPGKGPEWVSGINSGGGRTLYADSVKGRFTISRDNAKNTLYL
QMNSLKSEDTAVYYCATDLYGSSWYTDYWSQGTQVTVSS 213E6-25GS- 2669
EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD 212C12
WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGG
GLVQPGGSLRLSCAASGFTFGSSDMSWVRQAPGKGPEWVSGINSGGGRTLYA
DSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCATDLYGSSWYTDYWSQG TQVTVSS
213E6-25GS- 2670 EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD
214E8 WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGG
GSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIRWSGGDAYYD
DSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYGSYTYGGSYD LWGQGTQVTVSS

213E6-15GS- 2671 EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD
213H7 WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLR
LSCAASGRTLSSYRMGWFRQAPGKEREFISTISWNGRSTYYADSVKGRFIFS
EDNAKNTVYLQMNSLKPEDTAVYYCAAALIGGYYSDVDAWSYWGPGTQVTVS S 214E8-5GS-
2672 EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 212C12
WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG
FTFGSSDMSWVRQAPGKGPEWVSGINSGGGRTLYADSVKGRFTISRDNAKNT
LYLQMNSLKSEDTAVYYCATDLYGSSWYTDYWSQGTQVTVSS 214E8-15GS- 2673
EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 212C12
WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGG
SLRLSCAASGFTFGSSDMSWVRQAPGKGPEWVSGINSGGGRTLYADSVKGRF
TISRDNAKNTLYLQMNSLKSEDTAVYYCATDLYGSSWYTDYWSQGTQVTVSS 214E8-25GS- 2674
EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 212C12
WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVE
SGGGLVQPGGSLRLSCAASGFTFGSSDMSWVRQAPGKGPEWVSGINSGGGRT
LYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCATDLYGSSWYTDYW SQGTQVTVSS
214E8-15GS- 2675 EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR
213H7 WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGG
SLRLSCAASGRTLSSYRMGWFRQAPGKEREFISTISWNGRSTYYADSVKGRF
IFSEDNAKNTVYLQMNSLKPEDTAVYYCAAALIGGYYSDVDAWSYWGPGTQV TVSS
213H7-15GS- 2676 EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYRMGWFRQAPGKEREFISTIS
214F8 WNGRSTYYADSVKGRFIFSEDNAKNTVYLQMNSLKPEDTAVYYCAAALIGGY
YSDVDAWSYWGPGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGDLVQAGGS
LRLSCVASGSTYSINAMGWYRQAPGKLRELVAAFRTGGSTDYADSVKGRFTI
SRDTAKNTVYLQMNSLKPEDTAVYYCNAEVIYYPYDYWGQGTQVTVSS 213E6-15GS- 2677
EVQLVESGGGLVQAGASLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVD 214E8
WSGSRTYYADSVKGRFTISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVP
GIEKYDDWGLGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGSVQAGGSLR
LSCAASGGTFNPYVMAWFRQAPGNEREFVARIRWSGGDAYYDDSVKGRFAIT
RDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYGSYTYGGSYDLWGQGTQVTV SS 214E8-15GS-
2678 EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 213E6
WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGA
SLRLSCAASGSTLSRYGVGWFRQAPGKERELVASVDWSGSRTYYADSVKGRF
TISRDNAKNTGYLQMNSLKPDDTAVYYCAADSSVVPGIEKYDDWGLGTQVTV SS 214F8-15GS-

2679 EVQLVESGGDLVQAGGSLRLSCVASGSTYSINAMGWYRQAPGKLRELVAAFR 213H7
TGGSTDYADSVKGRFTISRDTAKNTVYLQMNSLKPEDTAVYYCNAEVIYYPY
DYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAA
SGRTLSSYRMGWFRQAPGKEREFISTISWNGRSTYYADSVKGRFIFSEDNAK
NTVYLQMNSLKPEDTAVYYCAAALIGGYYSDVDAWSYWGPGTQVTVSS 214E8-5GS- 2680
EVQLVESGGGSVQAGGSLRLSCAASGGTFNPYVMAWFRQAPGNEREFVARIR 214E8
WSGGDAYYDDSVKGRFAITRDAAKNTVHLQMNSLKPEDTAVYYCAAATYGYG
SYTYGGSYDLWGQGTQVTVSSGGGGSEVQLVESGGGSVQAGGSLRLSCAASG
GTFNPYVMAWFRQAPGNEREFVARIRWSGGDAYYDDSVKGRFAITRDAAKNT
VHLQMNSLKPEDTAVYYCAAATYGYGSYTYGGSYDLWGQGTQVTVSS 212C12-5GS- 2681
EVQLVESGGGLVQPGGSLRLSCAASGFTFGSSDMSWVRQAPGKGPEWVSGIN 212C12
SGGGRTLYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCATDLYGSS
WYTDYWSQGTQVTVSSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFGS
SDMSWVRQAPGKGPEWVSGINSGGGRTLYADSVKGRFTISRDNAKNTLYLQM
NSLKSEDTAVYYCATDLYGSSWYTDYWSQGTQVTVSS

TABLE A-7 Linker sequences SEQ ID Linker NO: Sequences 5GS 2970 GGGGS 7GS 2971
SGGSGGS 9GS 2639 GGGGSGGGS 10GS 2972 GGGGSGGGGS 15GS 2662
GGGGSGGGGSGGGGS 18GS 2973 GGGGSGGGGSGGGGGGGS 20GS 2974
GGGGSGGGGSGGGGSGGGGS 25GS 2975 GGGGSGGGGSGGGGSGGGGSGGGGS 30GS 2976
GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS 35GS 2977
GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS G1 hinge 2660 EPKSCDKTHTCPPCP
9GS-G1 2661 GGGGSGGGSEPKSCDKTHTCPPCP hinge G3 hinge 2640
ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPE PKSCDTPPPCPRCPEPKSCDTPPPCPRCP

TABLE A-8 Sequences of humanized NC41 variants Nanobody SEQ ID NO: Sequence NC41 5
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGRGTQVTVSS NC41v01 2999
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTLYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v02 3000
EVQLLESGGGLVQPGGSLRISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v03 3001
EVQLLESGGGLVQPGGSLRISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v04 3002
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA

AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v05 3003
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v06 3004
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRDDITIGPPNVEGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v07 3005
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTLYLQMNSLAPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v08 3006
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v09 3007
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v10 3008
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v11 3009
EVQLLESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v12 3010
EVQLLESGGGLVQPGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v13 3011
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v14 3012
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v15 3013
EVQLLESGGGLVQAGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNAKNTLYLQMNSLAPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v17 3014
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCGA
GTPLNPGAYIYDWSYDYWGQGTLVTVSS NC41v18 3015
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVA
AINWRDDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCGA

GTPLNPGAYIYDWSYDYWGQGTLVTVSS

TABLE A-9 Amino acid sequence of multivalent humanized constructs that bind hRSV SEQ ID Nanobody NO: Sequence RSV414 2996
EVQLLESGGGLVQPGGSLRISCAASGGSLSNYVLGWFRQAPGKGREFVAAINWR
GDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYI
YDWSYDYWGQGTLVTVSSGGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRIS
CAASGGSLSNYVLGWFRQAPGKGREFVAAINWRGDITIGPPNVEGRFTISRDNS
KNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYIYDWSYDYWGQGTLVTVSSGGG
GSGGGGSGGGGSEVQLLESGGGLVQPGGSLRISCAASGGSLSNYVLGWFRQAPG
KGREFVAAINWRGDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYC
GAGTPLNPGAYIYDWSYDYWGQGTLVTVSS RSV426 2997
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVAAINWR
DDITIGPPNVEGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYI
YDWSYDYWGQGTLVTVSSGGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLS
CAASGGSLSNYVLGWFRQAPGKGREFVAAINWRDDITIGPPNVEGRFTISRDNA
KNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYIYDWSYDYWGQGTLVTVSSGGG
GSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPG
KGREFVAAINWRDDITIGPPNVEGRFTISRDNAKNTLYLQMNSLRPEDTAVYYC
GAGTPLNPGAYIYDWSYDYWGQGTLVTVSS RSV427 2998
EVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPGKGREFVAAINWR
DDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYI
YDWSYDYWGQGTLVTVSSGGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLS
CAASGGSLSNYVLGWFRQAPGKGREFVAAINWRDDITIGPPNVEGRFTISRDNS
KNTLYLQMNSLRPEDTAVYYCGAGTPLNPGAYIYDWSYDYWGQGTLVTVSSGGG
GSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGGSLSNYVLGWFRQAPG
KGREFVAAINWRDDITIGPPNVEGRFTISRDNSKNTLYLQMNSLRPEDTAVYYC
GAGTPLNPGAYIYDWSYDYWGQGTLVTVSS

TABLE A-10 Amino acid sequence of multivalent constructs that bind hRSV SEQ ID Construct NO Sequence RSV101 3016
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT
VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGM
GWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTA
VYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSS RSV102 3017
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTV
YADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWG
QGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEAS

GRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQM
NSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSS RSV103 3018
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT
VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQA
GGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISR
DNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYWGQGTQVTVSS RSV104
3019 EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRT
VYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYDYW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQA
PGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAA
ELTNRNSGAYYYAWAYDYWGQGTQVTVSS RSV105 3020
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTY
YADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWG
QGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAP
GKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADL
TSTNPGSYIYIWAYDYWGQGTQVTVSS RSV106 3021
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTY
YADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWG
QGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMG
WFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVY
YCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSS RSV107 3022
EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSAI
GAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGR
GTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPG
KEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTP
LNPGAYIYDWSYDYWGRGTQVTVSS RSV108 3023
EVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGWFRQAPGKEREFVAAISFRGDSAI
GAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGR
GTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYVLGW
FRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYY
CGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV109 3024
EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRTF
YADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDTASWNSGSFIYDWAYDHWG
QGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAP
GKEREFVAAISWSRGRTFYADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDT
ASWNSGSFIYDWAYDHWGQGTQVTVSS RSV110 3025
EVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMGWFRQAPGKEREFVAAISWSRGRTF
YADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVYYCAVDTASWNSGSFIYDWAYDHWG
QGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGRTFSSIAMG

WFRQAPGKEREFVAAISWSRGRTFYADSVKGRFIISRDDAANTAYLQMNSLKPEDTAVY
YCAVDTASWNSGSFIYDWAYDHWGQGTQVTVSS RSV113 3026
EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
TYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYYA
LGWFRQAPGKEREGVSCISSSDHSTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDT
AVYYCAADPALGCYSGSYYPRYDYWGQGTQVTVSS RSV114 3027
EVQLVESGGGWVQAGGSLRLSCAASGRAFSSYAMGWIRQAPGKEREFVAGIDQSGEST
AYGASASGRFIISRDNAKNTVHLLMNSLQSDDTAVYYCVADGVLATTLNWDYWGQGTQ
VTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGWVQAGGSLRLSCAASGRAFSSYA
MGWIRQAPGKEREFVAGIDQSGESTAYGASASGRFIISRDNAKNTVHLLMNSLQSDDT
AVYYCVADGVLATTLNWDYWGQGTQVTVSS RSV115 3028
EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIA
YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSGGGGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTF
SADTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLK
PEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS RSV116 3029
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYV
LGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV201 3030
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNSGAYYYAWAYD
YWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWF
RQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYY
CAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS RSV202 3031
EVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPR
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DTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTVDLQMNSLKPE
DTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS RSV203 3032
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YWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLS
CAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIAYYSDSVKGRFTMSRDNAKNTV
DLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDYWGQGTQVTVSS RSV204 3033
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TAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV205 3034
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WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYY
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TAVYYCAADPALGCYSGSYYPRYDYWGQGTQVTVSS RSV206 3035
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IGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYA
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MGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDT
AVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSS RSV301 3037
EVQLVESGGGLVQAGGSLRLSCAASGPTFSADTMGWFRQAPGKEREFVATIPWSGGIA
YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
WGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFR
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CAAELTNRNSGAYYYAWAYDYWGQGTQVTVSS RSV302 3038
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YYSDSVKGRFTMSRDNAKNTVDLQMNSLKPEDTALYYCAGSSRIYIYSDSLSERSYDY
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WGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSC
EASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTV
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GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSYA
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AVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSS RSV306 3041
EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
TYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRSFSNYV

LGWFRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV400 3042
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
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WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSY
AMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPED
TAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVE
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RSV401 3043
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WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGDSLRLSCAASGRTFSSY
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AVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVES
GGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVK
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RSV404 3046
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LGWFRQAPGKEREFVAAISFRGDSAIGAPSVEGRFTISRDNAKNTGYLQMNSLVPDDT
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YWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTYSR
YGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKP
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VESGGGLVQAGGSLRLSCEASGRTYSRYGMGWFRQAPGKEREFVAAVSRLSGPRTVYA
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LGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDT
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GGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDITIGPPNVEG
RFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTV SS
RSV408 3050
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSAAAEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKER
EFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLN
PGAYIYDWSYDYWGRGTQVTVSSAAAEVQLVESGGGLVQAGGSLSISCAASGGSLSNY
VLGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDD
TAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV409 3051
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQ
APGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCG
AGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSLSI
SCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNT
GYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSS RSV410 3052

EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLSISCAASGGS
LSNYVLGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSL
APDDTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGD
ITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYD
YWGRGTQVTVSS RSV411 3053
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYV
LGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESG
GGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHSTTYTDSVKG
RFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYWGQGTQVTV SS
RSV412 3054
EVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFRQAPGKEREGVSCISSSDHST
TYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDTAVYYCAADPALGCYSGSYYPRYDYW
GQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLSISCAASGGSLSNYV
LGWFRQAPGKEREFVAAINWRGDITIGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDT
AVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESG
GGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDITIGPPNVEG
RFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTV SS
RSV413 3055
EVQLVESGGGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDIT
IGPPNVEGRFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYW
GRGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYYA
LGWFRQAPGKEREGVSCISSSDHSTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPGDT
AVYYCAADPALGCYSGSYYPRYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESG
GGLVQAGGSLSISCAASGGSLSNYVLGWFRQAPGKEREFVAAINWRGDITIGPPNVEG
RFTISRDNAKNTGYLQMNSLAPDDTAVYYCGAGTPLNPGAYIYDWSYDYWGRGTQVTV SS
RSV502 3056
EVQLVESGGGLVQAGGSLRLSCEASGRTFSSYGMGWFRQAPGKEREFVAAVSRLSGPR
TVYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNPGAYYYTWAYD
YWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCEASGRTFSS
YGMGWFRQAPGKEREFVAAVSRLSGPRTVYADSVKGRFTISRDNAENTVYLQMNSLKP
EDTAVYTCAAELTNRNPGAYYYTWAYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQL
VESGGGLVQAGGSLRLSCEASGRTFSSYGMGWFRQAPGKEREFVAAVSRLSGPRTVYA
DSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYTCAAELTNRNPGAYYYTWAYDYWGQ
GTQVTVSS RSV513 3588

EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYY
ALGWFRQAPGKEREGVSCISSSDHTTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPED
TAVYYCAADPALGCYSGSYYPRYDFWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVES
GGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVK
GRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQV TVSS
RSV514 3589
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGLTLDYYALGWFR
QAPGKEREGVSCISSSDHTTTYTDSVKGRFTISWDNAKNTLYLQMNSLKPEDTAVYYC
AADPALGCYSGSYYPRYDFWGQGTQVTVSSGGGGSGGGGSEVQLVESGGGLVQAGDSLR
LSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKN
TVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSS RSV515 3590
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRVSCAASGFTFNDY
IMGWFRQAPGKERMFIAAISGTGTIKYYGDLVRGRFTISRDNAKNTVYLRIDSLNPED
TAVYYCAARQDYGLGYRESHEYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESG
GGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVKG
RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVT VSS
RSV516 3591
EVQLVESGGGLVQAGDSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGST
YYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDY
WGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRVSCAASGFTFNDYIMGWFR
QAPGKERMFIAAISGTGTIKYYGDLVRGRFTISRDNAKNTVYLRIDSLNPEDTAVYYC
AARQDYGLGYRESHEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGDSLRL
SCAASGRTFSSYAMGWFRQAPGKEREFVAAISWSDGSTYYADSVKGRFTISRDNAKNT
VYLQMNSLKPEDTAVYYCAADLTSTNPGSYIYIWAYDYWGQGTQVTVSS

TABLE C-1 Overview of the RFFIT tests on periplasmic fractions of the NANOBODIES ® (V_{HH} sequences) of the invention as described in Example 14. Rabies neutralizing antibody titer Sample (50% dilution) Remark Polyclonal anti-hRSV Lama C <0.5 IU/ml (<1/9) no neutralisation periplasmic fractions Polyclonal anti-rabies Lama 1 210 <0.5 IU/ml (<1/9) no neutralisation vaccine virus periplasmic fractions Polyclonal anti-rabies Lama 2 211 3.18 IU/ml (1/88) strong neutralisation glycoprotein G periplasmic fractions Monoclonal anti-hRSV 192-D3 <0.5 IU/ml (<1/9) no neutralisation periplasmic fractions 192-B6 <0.5 IU/ml (<1/9) no neutralisation 192-C4 <0.5 IU/ml (<1/9) no neutralisation Monoclonal anti-H5N1 202-C1 <0.5 IU/ml (<1/9) no neutralisation periplasmic fractions 202-F4 <0.5

IU/ml (<1/9) no neutralisation 202-B7 <0.5 IU/ml (<1/9) no neutralisation Anti-rabies glycoprotein G 213-D6 <0.5 IU/ml (<1/9) no neutralisation periplasmic fractions, total 213-E6 5.31 (1/140) strong neutralisation elution 213-B7 0.62 (1/16) neutralisation 213-D7 0.62 (1/16) neutralisation 213-H7 0.83 (1/22) neutralisation Anti-rabies glycoprotein G 214-A8 1.42 (1/38) neutralisation periplasmic fractions, 214-E8 <0.5 IU/ml (1/11) 0.42 = minor neutralisation, monoclonal antibody but below cut-off eluted 214-F8 0.65 (1/17) neutralisation 214-C10 <0.5 IU/ml (<1/9) 0.25 = minor neutralisation, but below cut-off 214-D10 <0.5 IU/ml (<1/9) 0.25 = minor neutralisation, but below cut-off 214-H10 0.67 (1/18) neutralisation Anti-"other viral coat 202-D4 <0.5 IU/ml (<1/9) no neutralisation protein" control 202-F7 <0.5 IU/ml (<1/9) no neutralisation periplasmic fractions 192-D2 <0.5 IU/ml (<1/9) no neutralisation 192-F4 <0.5 IU/ml (<1/9) no neutralisation

TABLE C-2 Binding of selected NANOBODIES ® (V_{HH} sequences) to immobilized F_{TM}-protein in Surface Plasmon Resonance. name clone ka (1/Ms) kd (1/s) KD (M) NB1 192-C4 1.13E+06 8.46E−03 7.47E−09 NB2 191-D3 1.59E+06 3.24E−03 2.05E−09 NB4 192-H1 1.65E+06 6.11E−03 3.72E−09 NB5 192-A8 3.22E+05 9.37E−04 2.91E−09 NB6 191-E4 2.98E+05 2.08E−04 7.00E−10 NB9 192-C6 1.15E+06 8.08E−03 7.00E−09 NB10 192-F2 8.07E+05 5.77E−03 7.14E−09 NB11 191-B9 1.94E+05 4.92E−03 2.54E−03 NB13 192-H2 8.29E+05 1.28E−02 1.54E−08 NB14 192-B1 2.29E+05 1.27E−02 5.55E−08 NB15 192-C10 1.75E+05 6.13E−04 3.49E−09

TABLE C-3 Classification of viral fusion proteins based on the structural motifs of their post-fusion conformations Protein Virus family Virus species database code Class I Orthomyxo- Influenza A virus HA 1HA0, 3HMG, viridae Influenza C virus HEF 1HTM, 1QU1, 1FLC Paramyxo- Simian parainfluenza virus 5 F 2B9B, 1SVF viridae Human parainfluenza virus F 1ZTM Newcastle disease virus F 1G5G Respiratory syncytial F 1G2C Measles F2 Sendai F2 Filoviridae Ebola virus gp2 1EBO, 2EBO Retroviridae Moloney murine leukemia virus TM 1AOL Human immunodeficiency virus 1 gp41 1ENV, 1AIK Simian immunodeficiency virus gp41 2SIV, 2EZO Human T cell leukemia virus 1 gp21 1MG1 Human syncytin-2 TM 1Y4M Visna virus TM 1JEK Coronaviridae Mouse hepatitis virus S2 1WDG SARS corona virus E2 2BEQ, 1WYY Class II Flaviviridae Tick-borne encephalitis virus E 1URZ, 1SVB Dengue 2 and 3 virus E2 1OK8 IUZG, Yellow Fever E 10AN, 1TG8 West Nile E Togaviridae Semliki forest virus E1 1E9W, 1RER Sindbis E1 Class III Rhabdoviridae Rabies virus G 2GUM Vesicular stomatitis virus G Herpesviridae Herpes simplex virus gB 2CMZ

TABLE C-4 Sequence analysis of hRSV Nanobodies from new libraries

TABLE C-5 Characteristics of Nanobodies that bind hRSV F-protein Competition Binding Synagis ® RSV neutralization hRSV Fab kinetic analysis IC50 (nM)(n = 2) Clone Family

Epitope EC50 EC50 ka (1/Ms) kd(1/s) KD Long A-2 B1 191D3 LG 3sub2 II 1.5E−10 5.9E−09 1.5E+06 2.8E−03 1.9E−09 253 227 — 1E4 LG 3sub2 II 6.6E−11 4.5E−09 8.0E+05 1.3E−03 1.6E−09 380 298 ND 7B2 16 II 9.0E−11 1.9E−09 5.7E+05 6.5E−04 1.1E−09 91 177 2690 NC23 34 II 1.0E−10 2.3E−09 8.0E+05 7.4E−04 9.2E−10 144 109 — 15H8 29 II 8.3E−10 3.9E−08 1.2E+06 2.1E−02 1.6E−08 200 218 2340 NC41 29 II 4.1E−10 3.2E−08 8.2E+05 6.7E−03 8.1E−09 58 26 4000 15B3 4sub1 IV-VI 5.8E−11 — 4.1E+05 2.7E−04 6.7E−10 — — 1274 191E4 LG 21 IV-VI 8.3E−11 — 5.7E+05 1.5E−04 2.7E−10 — — 4327 Synagis ® II 2.8E+05 1.8E−04 6.4E−10 4 2.5 1.7

TABLE C-6 Nomenclature for multivalent Nanobodies directed against hRSV F-protein SEQ ID Type Name Construct NO: Bivalent RSV101 191D3-15GS-191D3 2382 RSV102 191D3-25GS-191D3 2383 RSV103 191D3-35GS-191D3 2384 RSV104 191D3-9GS-191D3 2385 RSV105 7B2-9GS-7B2 2386 RSV106 7B2-15GS-7B2 2387 RSV107 15H8-9GS-15H8 2388 RSV108 15H8-15GS-15H8 2389 RSV109 NC23-9GS-NC23 2390 RSV110 NC23-15GS-NC23 2391 RSV113 15B3-15GS-15B3 2392 RSV114 NC39-20GS-NC39 2393 RSV115 191E4-18GS-191E4 2394 RSV116 NC41-15GS-NC41 2395 Biparatope RSV201 191D3-9GS-191E4 2396 RSV202 191D3-15GS-191E4 2397 RSV203 191D3-25GS-191E4 2398 RSV204 7B2-15GS-15H8 2399 RSV205 7B2-15GS-15B3 2400 RSV206 15H8-15GS-15B3 2401 RSV207 15H8-15GS-7B2 2402 RSV301 191E4-9GS-191D3 2403 RSV302 191E4-15GS-191D3 2404 RSV303 191E4-25GS-191D3 2405 RSV305 15B3-15GS-7B2 2406 RSV306 15B3-15GS-15H8 2407 RSV513 7B2-15GS-19E2-15GS-7B2 3584 RSV514 7B2-9GS-19E2-9GS-7B2 3585 RSV515 7B2-15GS-8A1-15GS-7B2 3586 RSV516 7B2-9GS-8A1-9GS-7B2 3587 Trivalent RSV400 7B2-15GS-7B2-15GS-7B2 2408 RSV401 7B2-15GS-7B2-15GS-15B3 2409 RSV402 15B3-15GS-7B2-15GS-7B2 2410 RSV403 7B2-15GS-15B3-15GS-7B2 2411 RSV404 15H8-15GS-15H8-15GS-15H8 2412 RSV405 191D3-15GS-191D3-15GS-191D3 2413 RSV406 NC23-15GS-NC23-15GS-NC23 2414 RSV407 NC41-15GS-NC41-15GS-NC41 2415 RSV408 NC41-AAA-NC41-AAA-NC41 2989 RSV409 NC41-9GS-NC41-9GS-NC41 2990 RSV410 NC41-20GS-NC41-20GS-NC41 2991 RSV411 NC41-15GS-NC41-15GS-15B3 2992 RSV412 15B3-15GS-NC41-15GS-NC41 2993 RSV413 NC41-15GS-15B3-15GS-NC41 2994 RSV414 NC41v03-15GS-NC41v03-15GS- 2996 NC41v03 RSV426 NC41v06-15GS-NC41v06-15GS- 2997 NC41v06 RSV427 NC41v18-15GS-NC41v18-15GS- 2998 NC41v18 RSV502 1E4-15GS-1E4-15GS-1E4 2995

TABLE C-7 Reactivity of monovalent Nanobodies with antigen extracts of HEp-2 cells infected with different escape mutants of the Long strain

TABLE C-8 Reactivity of monovalent and bivalent Nanobodies with antigen extracts of HEp-2 cells infected with different escape mutants of the Long strain

TABLE C-9 Relative viral genomic RNA in lungs of treated mice 3 and 5 days post viral inoculation 3 days post viral inoculation relative gRNA level PBS LGB1 LGB2 Synagis Mouse 1 8.64 6.31 45.80 2.13 Mouse 2 13.09 3.23 45.90 1.97 Mouse 3 43.23 2.94 8.50 4.01 Mouse 4 12.10 1.01 32.99 1.63 Mouse 5 31.79 2.42 60.99 0.00 Average 21.77 3.18 38.84 1.95 SD 13.43 1.74 17.57 1.28 5 days post viral inoculation relative gRNA level PBS RSV101 12D2biv Synagis Mouse 1 170.69 16.96 214.74 4.82 Mouse 2 53.45 10.96 466.40 4.81 Mouse 3 471.42 3.84 350.39 7.20 Mouse 4 404.66 5.60 418.76 6.32 Mouse 5 342.39 2.19 193.26 4.15 Average 288.52 7.91 328.71 5.46 SD 172.47 6.04 121.32 1.25

TABLE C-10 Viral titers in mouse treated with 202-C8, 191-D3 or only PBS, 4 and 6 days post virus inoculation as described in Example 37 Geo. Group Mouse 1 Mouse 2 Mouse 3 Mean StDev Day 4 lung titers (TCID50/ml lung homogenate) PBS (n = 3) 355656 63246 63246 160716 137843 191D3 (n = 3) 112468 112468 632456 285797 245124 202-C8 (n = 3) 0 0 0 0 0 Day 6 lung titers (TCID50/ml lung homogenate) PBS (n = 3) 63426 112468 112468 96121 23119 191-D3 (n = 3) 63246 112468 112468 96061 23203 202-C8 (n = 3) 0 0 0 0 0

TABLE C-11 Animal weight and viral titers after intranasal administration of Nanobody into mice challenged with virus at different time points after inoculation of the Nanobody (see Example 38) Weight Weight Weight Weight Weight Lung titer Day 0 Day 1 Day 2 Day 3 Day 4 Day 4 202-C8 4 h mouse 1 18,15 18,32 17,67 18,5 18,23 0 202-C8 4 h mouse 2 20,67 20,42 20,43 20,94 20,93 0 202-C8 4 h mouse 3 19,72 19,67 18,97 19,68 19,77 0 Average 19,51 19,47 19,02 19,71 19,64 0 St. Dev. 1.27 1.06 1.38 1.22 1.35 0 202-C8 24 h mouse 1 18,76 18,81 18,52 18,83 18,85 0 202-C8 24 h mouse 2 19,48 19,62 18,99 18,96 19,13 0 202-C8 24 h mouse 3 18,73 18,55 18,18 18,34 18,32 0 202-C8 24 h mouse 4 19,19 19,27 18,9 19,48 19,32 0 202-C8 24 h mouse 5 18,95 19,24 18,36 18,96 19,06 0 202-C8 24 h mouse 6 18,99 18,81 18,21 18,66 18,91 0 average 19,02 19,05 18,53 18,87 18,93 0 St. Dev. 0.28 0.39 0.35 0.38 0.34 0 202-C8 48 h mouse 1 17,88 17,5 17,44 17,43 17,81 9355 202-C8 48 h mouse 2 17,29 17,01 16,94 17,11 17,37 355656 202-C8 48 h mouse 3 19,42 19,08 19,2 19,33 19,44 93550 202-C8 48 h mouse 4 19,47 19,53 18,89 19.31 19,51 0 202-C8 48 h mouse 5 19,73 19,55 19,34 19,54 20,02 0 202-C8 48 h mouse 6 18,92 18,84 18,72 18,47 18,91 63250 202-C8 48 h mouse 7 17,94 17,65 17,82 17,74 19,49 0 average 18,66 18,45 18,34 18,42 18,94 74544 St. Dev. 0.95 1.04 0.93 1.00 0.98 129378 PBS 4 h mouse 1 18,97 18,89 18,69 18,05 16,95 3556500 PBS 4 h mouse 2 18,15 18,36 18,13 17,32 15,95 6325000 PBS 4 h mouse 3 19,54 19,9 19,68 18,11 16,87 6325000 Average 18,89 19,05 18,83 17,83 16,59 5402167 St. Dev. 0.70 0.78 0.78 0.44 0.56 1598394 PBS 48 h mouse 1 20,01 19,73 19,59 18,76 17,66 3556500 PBS 48 h mouse 2 21,43 21,68 20,9 20,06 19,39 632500 PBS 48 h mouse 3 18,78 19,02 18,74 17,67 16,8 632500 average 20,07 20,14 19,74 18,83 17,95 1607167 St. Dev. 1.33 1.38 1.09 1.20 1.32 1688172 191-D3 4 h mouse 1 20,3

20,42 20,11 19,72 19,28 6324600 191-D3 4 h mouse 2 18,39 18,54 18,66 18,38 18,33 9355000 191-D3 4 h mouse 3 18,39 18,82 18,44 17,77 16,3 3556500 Average 19,03 19,26 19,07 18,62 17,97 6412033 St. Dev. 1.10 1.01 0.91 1.00 1.52 2900239 191-D3 24 h mouse 1 18,94 18,63 18,62 18,21 18,29 6324600 191-D3 24 h mouse 2 19,46 19,62 19,4 18,48 18,09 63250000 191-D3 24 h mouse 3 19,63 19,58 19,83 19,18 18,51 2000000 191-D3 24 h mouse 4 19,03 18,94 19,07 18,45 17,49 6325000 191-D3 24 h mouse 5 18,91 18,72 19 17,84 17,32 935500 average 19,19 19,10 19,18 18,43 17,94 15767020 St. Dev. 0.33 0.47 0.46 0.49 0.51 26657313 191-D3 48 h mouse 1 19,5 19,39 18,93 19,04 18 3556500 191-D3 48 h mouse 2 19,53 19,3 19,2 18,76 17,94 3556500 191-D3 48 h mouse 3 20,02 20,23 20,46 19,81 19,26 9355000 191-D3 48 h mouse 4 18,21 18,09 18,12 17,75 17,29 935500 191-D3 48 h mouse 5 18,38 18,17 18,32 17,92 16,53 6325000 191-D3 48 h mouse 6 21,19 20,83 20,55 20,34 18,98 632460 average 19,47 19,34 19,26 18,94 18,00 4060160 St. Dev. 1.10 1.09 1.04 1.02 1.02 3322192

TABLE C-12 Test items for use in the study described in Example 42 Alternative Name names Reference RSV NB2 191D3 SEQ ID NO: 159 in present application ALX-0081 12A2H1-3a- SEQ ID NO: 98 in WO 06/122825 12A2H1 RANKL008a SEQ ID NO: 759 in WO 08/142164

TABLE C-13 Study design for study described in Example 42 Single Dose Number of Group Substance Route (mg/kg) animals 1 RSV NB2 i.v. 4 3 2 ALX-0081 i.v. 5 3 3 RANKL008A i.v. 5 3 4 RSV NB2 i.t. 3.6 28 5 ALX-0081 i.t. 3.1 28 6 RANKL008A i.t. 3.2 28 7 — — — 8

TABLE C-14 LLOQ and ULOQ for determination of RSV NB2 in rat plasma and BALF samples as described in Example 42 LLOQ (ng/ml) ULOQ (ng/ml) Plasma/BALF Plasma/BALF PK ELISA Plate level level Plate level level RSV NB2 0.4 4.0 20.0 200.0

TABLE C-15 LLOQ and ULOQ for determination of ALX-0081 in rat plasma and BALF samples as described in Example 42 LLOQ (ng/ml) ULOQ (ng/ml) PK ELISA Plate level Plasma/BALF Plate level Plasma/BALF ALX-0081 0.75 3.75 40.0 200.0

TABLE C-16 LLOQ and ULOQ for determination of RANKL008A in rat plasma and BALF samples as described in Example 42 LLOQ (ng/ml) ULOQ (ng/ml) Plasma/BALF Plasma/BALF PK ELISA Plate level level Plate level level RANKL008A 0.1 1.0 7.5 75.0

TABLE C-17 Individual plasma concentration-time data of RSV NB2, ALX-0081, and RANKL008A after a single i.v. bolus dose of RSV NB2 (4 mg/kg), ALX-0081 (5 mg/kg) and RANKL008A (5 mg/kg), respectively to male Wistar rats Plasma concentration after i.v.

administration (μg/mL) Nominal RSV NB2 ALX-0081 RANKL008A Time ID 1 ID 2 ID 3 ID 4 ID 5 ID 6 ID 7 ID 8 ID 9 3 min 23.6 34.5 32.1 60.4 63.2 NS 94.3 (5 min) 107 100 15 min 5.16 10.7 10.6 9.18 14.1 NS 95.7 94.8 92.8 30 min 3.61 5.91 3 3.15 3.37 4.55 88.4 85.9 74.1 1 hr NS 5.12 2.36 1.09 1.31 1.84 81.5 73.8 NS 2 hr NS NS 0.763 0.498 0.594 NS 58.7 55.9 NS 4 hr NS NS 0.161 0.219 0.315 0.328 35.8 35.1 NS 6 hr NS NS 0.056 0.125 0.161 0.116 / / / 8 hr / / / / / / 17.1 18.8 NS 24 hr BQL NS BQL BQL BQL BQL 3.17 3.94 NS 48 hr / / / / / / 0.902 0.988 NS NS: No sample could be obtained (refer to in vivo report) BQL: Below Quantification Limit

TABLE C-18 Individual plasma concentration-time data of RSV NB2, ALX-0081, and RANKL008A after a single i.t. dose of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg), respectively to male Wistar rats. 6/8 hr time-point: 6 hr for RSV NB2 and ALX-0081, 8 hr for RANKL008A Plasma concentration after i.t. administration (μg/mL) RSV NB2 ALX-0081 RANKL008A Time ID Concentration ID Concentration ID Concentration 3 min 10 0.158 38 0.056 66 0.004 11 0.085 39 0.013 67 0.030 12 0.081 40 0.029 68 0.006 13 0.127 41 0.077 69 0.005 20 min 14 0.204 42 0.102 70 0.072 15 0.167 43 0.102 71 0.081 16 0.131 44 0.097 72 0.151 17 0.267 45 0.070 73 0.083 1 hr 18 0.202 46 0.122 74 0.401 19 0.167 47 0.112 75 0.541 20 0.120 48 0.049 76 0.305 21 0.120 49 0.109 77 1.077 2 hr 22 BQL 50 0.041 78 0.279 23 0.230 51 0.100 79 0.389 24 0.091 52 0.084 80 0.705 25 0.202 53 0.091 81 0.489 4 hr 26 0.113 54 0.069 82 0.965 27 0.150 55 0.077 83 0.601 28 0.080 56 0.053 84 0.934 29 0.129 57 0.085 85 0.672 6/8 hr 30 0.125 58 0.034 86 0.869 31 0.071 59 0.048 87 1.42 32 0.108 60 0.070 88 1.16 33 0.091 61 0.059 89 0.606 24 hr 34 0.024 62 0.014 90 0.493 35 0.024 63 0.022 91 0.450 36 0.025 64 0.014 92 0.434 37 0.036 65 0.020 93 0.342

TABLE C-19 Mean plasma concentration-time data of RSV NB2, ALX-0081, and RANKL008A after a single i.t. dose of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg), respectively to male Wistar rats Plasma concentration after i.t. administration (μg/mL) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Time Average SD Average SD Average SD 3 min 0.113 0.037 0.044 0.028 0.012 0.013 20 min 0.192 0.058 0.093 0.015 0.097 0.037 1 hr 0.152 0.040 0.098 0.033 0.581 0.345 2 hr 0.175 0.074 0.079 0.026 0.465 0.181 4 hr 0.118 0.030 0.071 0.014 0.793 0.184 6 hr 0.099 0.023 0.052 0.015 / / 8 hr / / / / 1.01 0.35 24 hr 0.027 0.006 0.018 0.004 0.430 0.063

TABLE C-20 Individual Basic Pharmacokinetic parameters of RSV NB2, ALX-0081, and RANKL008A after a single i.v. dose of RSV NB2 (4 mg/kg), ALX-0081 (5 mg/kg) and RANKL008A (5 mg/kg) to Wistar Rats. i.v.: RSV NB2 4 mg/kg; ALX-0081/RANKL008A 5 mg/kg ALX-0081 ALX-0081 RANKL008A RANKL008A RSV NB2 Parameter Unit ID 4 ID 5 ID 7 ID 8 ID 3 C(0) ug/mL 96.7 92.0 94.3 110 42.3 Vss mL/kg 255 250 91.5 92.8 250 CL

mL/hr/kg 363 311 9.17 8.82 363 MRT hr 0.702 0.804 9.98 10.5 0.690 t½ λz hr 2.01 2.12 13.2 12.0 0.926 λz Lower hr 2 2 24 24 0.5 λz Upper hr 6 6 48 48 6 AUClast hr * ug/mL 13.4 15.6 528 550 11.0 AUCextrap % 2.51 3.09 3.16 3.03 0.560 AUCinf hr * ug/mL 13.8 16.1 545 567 11.0 AUCinf/D hr * kg/mL 0.0028 0.0032 0.1091 0.1134 0.0028

TABLE C-21 Mean Basic Pharmacokinetic parameters of RSV NB2, ALX-0081, and RANKL008A after a single i.v. dose of RSV NB2 (4 mg/kg), ALX-0081 (5 mg/kg) and RANKL008A (5 mg/kg) to Wistar Rats i.v.: RSV NB2 4 mg/kg; ALX-0081/RANKL008A 5 mg/kg ALX-0081 CV RANKL008A Parameter Unit Average % Average CV % RSV NB2 C(0) ug/mL 94.3 4 102 11 42.3 Vss mL/kg 252 1 92.1 1 250 CL mL/hr/kg 337 11 9.00 3 363 MRT hr 0.753 10 10.2 4 0.690 t½ λz hr 2.06 4 12.6 7 0.926 λz Lower hr 2 0 24 0 0.5 λz Upper hr 6 0 48 0 6 AUClast hr * ug/mL 14.5 10 539 3 11.0 AUCextrap % 2.80 15 3.09 3 0.560 AUCinf hr * ug/mL 14.9 11 556 3 11.0 AUCinf/D hr * kg/mL 0.003 9 0.111 3 0.003

TABLE C-22 Basic Pharmacokinetic parameters of RSV NB2, ALX-0081, and RANKL008A after a single i.v. dose of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to Wistar Rats i.t. administration ALX-0081 RANKL008A RSV NB2 Parameter Unit 3.1 mg/kg 3.2 mg/kg 3.6 mg/kg Vss/F mL/kg 36339 2833 21853 CL/F mL/hr/kg 2407 130 1641 MRT hr 15.1 21.7 13.3 t½ λz hr 10.5 13.0 9.48 λz Lower hr 2 8 4 λz Upper hr 24 24 24 t½ λz 0.979 1.000 0.999 AUClast hr*ug/mL 1.02 16.5 1.83 AUCextrap % 20.8 32.8 16.8 AUCinf hr*ug/mL 1.29 24.6 2.19 tmax hr 1 8 0.330 Cmax ug/ml 0.098 1.01 0.192 AUCinf/D hr*kg/mL 0.0004 0.0077 0.0006 F % 13.9 6.90 22.1 Vss/F = MRT*CL (MRT not corrected for MAT) Estimation F incorrect if CL i.v. and CL i.t. are different; Note dose i.v. ≠ i.t.

TABLE C-23 Individual observed BALF concentrations of RSV NB2, ALX-0081, and RANKL008A after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF concentrations after i.t. administration (μg/mL) RSV NB2 Nominal Concen- ALX-0081 RANKL008A Time ID tration ID Concentration ID Concentration 3 min 10 46.2 38 145 66 32.3 11 65.0 39 57.9 67 56.1 12 23.0 40 69.2 68 27.0 13 36.7 41 115 69 80.2 20 min 14 32.8 42 40.4 70 14.4 15 54.8 43 148 71 87.9 16 70.2 44 93.4 72 43.3 17 68.1 45 55.7 73 22.4 1 hr 18 134 46 179 74 124 19 50.7 47 80.6 75 70.3 20 35.8 48 62.4 76 33.8 21 18.4 49 35.8 77 49.8 2 hr 22 BQL 50 33.7 78 16.1 23 22.1 51 36.9 79 58.3 24 26.1 52 111 80 49.0 25 32.6 53 37.1 81 22.3 4 hr 26 14.9 54 32.7 82 24.8 27 60.9 55 2.44 83 11.4 28 45.0 56 85.1 84 95.0 29 4.81 57 50.5 85 24.9 6/8 hr 30 24.4 58 36.2 86 15.6 31 43.6 59 90.1 87 42.1 32 21.6 60 51.9 88 72.4 33 33.1 61 74.6 89 30.2 24 hr 34 9.53 62 20.9 90 32.7 35 19.1 63 13.2 91 14.6 36 10.7 64 16.5 92 7.48 37 17.0 65 14.6 93 6.91 BQL: below the quantification limit

TABLE C-24 Mean observed BALF concentrations of RSV NB2, ALX-0081, and RANKL008A

after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF concentration after i.t. administration (μg/mL) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Nominal Time Average SD Average SD Average SD 3 min 96.8 40.4 48.9 24.4 42.7 17.6 20 min 84.3 47.9 35.7 32.9 56.5 17.2 1 hr 89.4 62.4 69.4 39.2 59.7 51.1 2 hr 54.6 37.5 36.4 20.4 26.9 5.3 4 hr 42.7 34.6 39 37.9 31.4 26.1 6 hr 63.2 23.9 40.1 24.1 / / 8 hr / / / / 30.7 9.9 24 hr 16.3 3.4 15.4 12.1 14.1 4.7

TABLE C-25 Individual theoretical amount (BALF Concentration × 10 mL) of RSV NB2, ALX-0081, and RANKL008A in BALF after single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF Theoretical Amount after i.t. Administration (μg) RSV NB2 ALX-0081 RANKL008A Nominal Time ID Amount ID Amount ID Amount 4 min 10 462 38 1446 66 323 11 650 39 579 67 561 12 230 40 692 68 270 13 367 41 1155 69 802 20 min 14 328 42 404 70 144 15 548 43 1479 71 879 16 702 44 934 72 433 17 681 45 557 73 224 1 hr 18 1338 46 1788 74 1238 19 507 47 806 75 703 20 358 48 624 76 338 21 184 49 358 77 498 2 hr 22 BQL 50 337 78 161 23 221 51 369 79 583 24 261 52 1109 80 490 25 326 53 371 81 223 4 hr 26 149 54 327 82 248 27 609 55 24.4 83 114 28 450 56 851 84 950 29 48.1 57 505 85 249 6/8 hr 30 244 58 362 86 156 31 436 59 901 87 421 32 216 60 519 88 724 33 331 61 746 89 302 24 hr 34 95.3 62 209 90 327 35 191 63 132 91 146 36 107 64 165 92 74.8 37 170 65 146 93 69.1 BQL: below the quantification limit

TABLE C-26 Mean (+SD) theoretical amount (BALF Concentration × 10 mL) of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) in BALF after intratracheal administration BALF theoretical amount after i.t. administration (μg) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Nominal Time Average SD Average SD Average SD 4 min 427 176 968 404 489 244 20 min 565 172 843 479 420 329 1 hr 597 511 894 624 694 392 2 hr 269 53 546 375 364 204 4 hr 314 261 427 346 390 379 6 hr 307 99 632 239 / / 8 hr / / / / 401 241 24 hr 141.0 47.2 163 34 154 121

TABLE C-27 Individual recovered volume of BALF after two lavages with DPBS (2 × 5 mL) after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats Recovered Volume of BALF after lavages Nominal RSV NB2 ALX-0081 RANKL008A Time ID BALF (mL) ID BALF (mL) ID BALF (mL) 4 min 10 5.5 38 7.5 66 8.0 11 6.5 39 6.5 67 8.0 12 8.5 40 8.5 68 4.0 13 7.5 41 7.5 69 8.5 20 min 14 8.0 42 7.0 70 7.5 15 6.0 43 8.0 71 3.0 16 6.5 44 8.0 72 6.0 17 8.5 45 7.5 73 8.0 1 hr 18 6.5 46 8.0 74 7.0 19 6.5 47 7.5 75 6.0 20 7.5 48 8.0 76 7.5 21 7.5 49 7.0 77 8.0 2 hr 22 5.5 50 8.0 78 6.0 23 6.0 51 8.0 79 7.5 24 6.5 52 6.5 80 8.0 25 7.0 53 7.5 81 8.0 4 hr 26 5.5 54 8.0 82 7.0 27 5.0 55 8.0 83 6.5 28 9.5 56 9.0 84 7.0 29 8.0 57 7.5 85 7.5 6/8 hr 30 7.0 58 8.0 86 7.0 31 7.0 59

9.0 87 6.5 32 7.0 60 6.0 88 7.5 33 8.5 61 8.5 89 9.0 24 hr 34 6.5 62 7.5 90 8.0 35 6.5 63 7.5 91 7.5 36 7.5 64 8.5 92 8.0 37 7.0 65 6.5 93 5.5

TABLE C-28 Individual actual amount (BALF Concentration × recovered volume) of RSV NB2, ALX-0081, and RANKL008A in BALF after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF Actual Amount after i.t. Administration (μg) Nominal RSV NB2 ALX-0081 RANKL008A Time ID Amount ID Amount ID Amount 4 min 10 254 38 1084 66 258 11 422 39 377 67 449 12 195 40 588 68 108 13 275 41 866 69 682 20 min 14 262 42 283 70 108 15 329 43 1183 71 264 16 456 44 747 72 260 17 579 45 418 73 179 1 hr 18 869 46 1430 74 867 19 330 47 605 75 422 20 269 48 499 76 254 21 138 49 250 77 399 2 hr 22 BQL 50 270 78 96.4 23 132 51 295 79 438 24 170 52 721 80 392 25 228 53 278 81 179 4 hr 26 81.9 54 262 82 174 27 305 55 19.5 83 74.3 28 428 56 766 84 665 29 38.5 57 379 85 187 6/8 hr 30 171 58 289 86 109 31 305 59 811 87 274 32 151 60 311 88 543 33 281 61 634 89 272 24 hr 34 62.0 62 157 90 262 35 124 63 98.7 91 110 36 80.0 64 140 92 59.9 37 119 65 95.2 93 38.0 BQL: below the quantification limit

TABLE C-29 Mean actual amount (BALF Concentration × recovered volume) of RSV NB2, ALX-0081, and RANKL008A in BALF after a single intratracheal administration RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF actual amount after i.t. Administration (μg) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Nominal Time Average SD Average SD Average SD 4 min 287 97 729 310 374 248 20 min 406 140 658 401 203 74 1 hr 401 322 696 512 485 265 2 hr 177 48 391 220 276 165 4 hr 213 185 357 311 275 265 6 hr 227 77 512 254 / / 8 hr / / / / 299 180 24 hr 96.5 30.4 123 30 117 101

TABLE C-30 Individual theoretical amount (BALF Concentration × 10 mL) normalized by dose (%) of RSV NB2, ALX-0081, and RANKL008A in BALF after a single intratracheal administration of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) to male rats BALF Theoretical Amount normalized by dose (%) RSV NB2 ALX-0081 RANKL008A Nominal Amount/D Amount/D Amount/D Time ID (%) ID (%) ID (%) 4 min 10 40.5 38 147 66 31.3 11 57.0 39 58.8 67 54.4 12 20.2 40 70.2 68 26.2 13 32.2 41 117 69 77.8 20 min 14 28.7 42 41.0 70 14.0 15 48.1 43 150 71 85.4 16 61.6 44 94.8 72 42.0 17 59.7 45 56.5 73 21.8 1 hr 18 117.3 46 182 74 120 19 44.5 47 81.8 75 68.3 20 31.4 48 63.3 76 32.8 21 16.2 49 36.3 77 48.4 2 hr 22 BQL 50 34.3 78 15.6 23 19.3 51 37.5 79 56.6 24 22.9 52 113 80 47.6 25 28.6 53 37.6 81 21.7 4 hr 26 13.1 54 33.2 82 24.1 27 53.4 55 2.48 83 11.1 28 39.5 56 86.4 84 92.3 29 4.22 57 51.3 85 24.2 6/8 hr 30 21.4 58 36.7 86 15.1 31 38.3 59 91.5 87 40.9 32 18.9 60 52.7 88 70.3 33 29.0 61 75.8 89 29.3 24 hr 34 8.36 62 21.2 90 31.8 35 16.8 63 13.4 91 14.2 36 9.36 64 16.7 92 7.26 37 15.0 65 14.9 93 6.71 BQL:

below the quantification limit

TABLE C-31 Individual actual amount (BALF Concentration × recovered volume) normalized by dose (%) of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) in BALF after intratracheal administration BALF Actual Amount normalized by dose (%) RSV NB2 ALX-0081 RANKL008A Amount/D Amount/D Amount/D Time ID (%) ID (%) ID (%) 4 min 10 22.3 38 110 66 25.1 11 37.0 39 38.2 67 43.6 12 17.1 40 59.7 68 10.5 13 24.1 41 87.9 69 66.2 20 min 14 23.0 42 28.7 70 10.5 15 28.8 43 120 71 25.6 16 40.0 44 75.8 72 25.2 17 50.8 45 42.4 73 17.4 1 hr 18 76.3 46 145 74 84.1 19 28.9 47 61.4 75 41.0 20 23.6 48 50.6 76 24.6 21 12.1 49 25.4 77 38.7 2 hr 22 BQL 50 27.4 78 9.4 23 11.6 51 30.0 79 42.5 24 14.9 52 73.2 80 38.1 25 20.0 53 28.2 81 17.3 4 hr 26 7.19 54 26.6 82 16.9 27 26.7 55 1.98 83 7.21 28 37.5 56 77.8 84 64.6 29 3.37 57 38.5 85 18.1 6/8 hr 30 15.0 58 29.4 86 10.6 31 26.8 59 82.3 87 26.6 32 13.2 60 31.6 88 52.7 33 24.6 61 64.4 89 26.4 24 hr 34 5.44 62 15.9 90 25.4 35 10.9 63 10.0 91 10.6 36 7.02 64 14.2 92 5.81 37 10.5 65 9.66 93 3.69 BQL: below the quantification limit

TABLE C-32 Mean (+SD) theoretical amount (BALF Concentration × 10 mL) normalized by dose (%) of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) in BALF after intratracheal administration BALF theoretical amount/Dose (%) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Time Average SD Average SD Average SD 4 min 37.5 15.5 98.3 41.0 47.5 23.7 20 min 49.5 15.1 85.6 48.6 40.8 32.0 1 hr 52.3 44.8 90.7 63.3 67.4 38.0 2 hr 23.6 4.7 55.5 38.1 35.4 19.8 4 hr 27.6 22.9 43.4 35.1 37.9 36.8 6 hr 26.9 8.7 64.2 24.3 / / 8 hr / / / / 38.9 23.4 24 hr 12.4 4.1 16.5 3.4 15.0 11.7

TABLE C-33 Mean actual amount (BALF Concentration × recovered volume) normalized by dose (%) of RSV NB2 (3.6 mg/kg), ALX-0081 (3.1 mg/kg) and RANKL008A (3.2 mg/kg) in BALF after intratracheal administration BALF actual amount/Dose (%) RSV NB2 ALX-0081 RANKL008A (ID 10-37) (ID 38-65) (ID 66-93) Time Average SD Average SD Average SD 4 min 25.1 8.5 74.0 31.5 36.3 24.1 20 min 35.7 12.3 66.8 40.7 19.7 7.2 1 hr 35.2 28.2 70.7 51.9 47.1 25.7 2 hr 15.5 4.2 39.7 22.3 26.8 16.0 4 hr 18.7 16.2 36.2 31.6 26.7 25.7 6 hr 19.9 6.8 51.9 25.8 / / 8 hr / / / / 29.1 17.5 24 hr 8.46 2.66 12.5 3.1 11.4 9.8

TABLE C-34 Alternative screening of NANOBODIES ® (V_{HH} sequences) described in Example 44 % % Inhibition 101F % SEQ Binding % Binding Fab Inhibition ID Previous RSV-A Hep2-B1 1;100 1;300 Synagis Clone NO: Llama Selection Family screen Epitope Fold blanc 1;50 PE 1;200 PE PE PE 1;1000 PE 1:10 PE PMP8A1 249 206 R1 trypsin 1 101F 3.7 98% 92% nd 55% 20% PMP8B10 342 207 R1 trypsin 11 101F 3.5 94% 84% 56% 31% 6% PMP13A1 274 206 R1 + 2 101F 4sub1 101F 2.9 84% 65% 74% 46% 13% PMP13B4 318

206 R1 + 2 101F 5 101F 2.7 75% 56% 82% 47% 20% PMP13C1 278 206 R1 + 2 101F 4sub1 101F 3.0 104% 86% 57% 37% 9% PMP19E2 301 206 R1 101F; 4sub2 101F 3.5 87% 58% 74% 27% 5% R2 peptide PMP13D1 308 206 R1 + 2 101F 4sub3 101F 3.1 93% 75% 78% 52% 16% PMP13E12 2580 207 R1 + 2 101F 14 101F 3.7 97% 75% 74% 28% 8% PMP23E5 365 212 R1 + 2 23 101F 3.4 103% 82% 37% 16% nd RSV 101F PMP1B2 166 156 R1 RSV LG21 LG191E4 101F 3.8 88% 85% 82% 58% 25% trypsin PMP1A2 389 156 R1 RSV LG34 101F 4.0 86% 66% 82% 27% 5% trypsin PMP7B2 354 212 R1 trypsin 16 Synagis 4.7 61% 41% 70% PMP19C4 371 207 R1 101F; 29 15H8 Synagis 2.5 72% 50% 39% R2 peptide PMP1A6 404 156 R1 RSV LG Synagis 4.2 57% 39% 67% trypsin PMP1G8 2578 156 R1 RSV LG Synagis 3.7 73% 43% 57% trypsin PMP1E4 211 156 R1 RSV LG3-2 Synagis 3.6 55% 55% 55% trypsin PMP1G3 159 156 R1 RSV LG3-2 LG191D3 Synagis 3.4 52% 45% 52% trypsin PMP1E5 167 156 R1 RSV LG3-1 Synagis 3.4 54% 37% 41% trypsin PMP20B2 2576 156 R1 101F LG3-1 Synagis 3.0 32% 32% 33% PMP20C1 2577 156 R1 101F LG40 Synagis 2.7 37% 35% 33%

TABLE C-35 Overview of immunizations, sampling and neutralizing antibody titers of the llamas. Immunisation experiment 75a 75b Cocktail nr RFFIT titer C127 C127 (50% dilution) Date Day Llama 183 Llama 196 Tissue collection Llama 183 Llama 196 Start immunisation Day 25/07/07 0 2.5 IU 2.5 IU 10 ml pre-immune blood <0.50 IU/ml (<1/9) <0.50 IU/ml (<1/9) Day 01/08/07 7 2.5 IU 2.5 IU — Day 21/08/07 27 10 ml immune blood 2 IU/ml (1/66) 6 IU/ml (1/179) Day 22/08/07 28 2.5 IU 2.5 IU — Day 29/08/07 35 2.5 IU 2.5 IU Day 31/08/07 37 10 ml immune blood 22 IU/ml (1/674) 27 IU/ml (1/789) Day 05/09/07 42 150 ml immune blood (PBL1) 37 IU/ml (1/989) 33 IU/ml (1/896) lymph node biopsy: unsuccessful Day 12/09/07 49 150 ml immune blood (PBL2) 22.72 IU/ml (1/674) 14.86 IU/ml (1/441) Day 20/09/07 57 2.5 IU 2.5 IU Day 25/09/07 62 150 ml immune blood (PBL3) 22.25 IU/ml (1/673) 35.35 IU/ml (1/1071)

TABLE C-36 In vitro neutralizing potency of monovalent Nanobody clones with the RFFIT assay CVS-11 neutralizing antibody titer Nanobody ATCC VR 959, sequence G protein: NCBI EU126641 Clone Elusion 50% dilution IU[a]/ml IU/mg IU/μM[b] nM IC_{50}[c] Mab 8-2 Ascites mouse 1/303250 10108.33 nd[d] nd nd Mab RV1C5 100 μg IgG_{2a}/ml PBS (Santa 1/4985 165.15 1651.5 193500 0.17 Cruz sc-57995) 214-C10 trypsin 1st + mab 2d round 1/122 4.24 10.60 0.16 219.67 214-F8 trypsin 1st + mab 2d round 1/33 1.15 7.19 0.11 324.85 214-A8 trypsin 1st + mab 2d round 1/263 9.12 7.93 0.12 292.97 214-E8 trypsinst + mab 2d round 1/140 4.87 9.37 0.14 248.86 213-E6 Mab 1st + trypsin 2d round 1/3238 112.33 170.20 2.54 13.66 213-B7 Mab 1st + trypsin 2d round 1/140 4.87 7.38 0.11 315.86 213-D7 Mab 1st + trypsin 2d round 1/147 5.10 7.61 0.11 305.37 213-D6 Mab 1st + trypsin 2d round <1/9 <0.50 <0.48 <0.01 >7816.67 213-H7 Mab 1st + trypsin 2d round 1/49 1.71 12.21 0.18 191.43 192-C4 Anti HRSV[e] <1/9 <0.50 <0.63 <0.01 >5881.11 192-A8 Anti HRSV <1/9 <0.50

<0.77 <0.02 >4838.89 191-E4 Anti HRSV <1/9 <0.50 <0.63 <0.01 >5955.56 212-A2 Trypsin 1st and 2d round 1/47 1.62 1.72 0.03 1340.00 212-B2 Trypsin 1st and 2d round 1/75 2.60 3.66 0.05 634.27 212-G2 Trypsin 1st and 2d round 1/263 9.12 9.31 0.14 249.66 212-F6 Trypsin 1st and 2d round 1/4057 122.43 114.42 1.71 17.67 212-B12 Trypsin 1st and 2d round 1/1028 31.00 20.00 0.30 101.02 212-C12 Trypsin 1st and 2d round 1/11363 394.26 308.02 4.60 7.55 214-H10 trypsin 1st + mab 2d round 1/330 11.44 8.17 0.12 284.24 [a]International Unit (IU) [b]1 mg nanobody/ml = 67 μM [c]= mg/ml × 50% dilution × 67000 [d]not determined [e]human respiratory syncytial virus

TABLE C-37 Effect of combinations of Nanobodies on the neutralizing potency compared to single Nanobodies. CVS neutralizing antibody titer strain CVS-11, ATCC VR 959, sequence G protein: NCBI EU126641 Combinations of Nanobodies 50% dilution IU[a]/ml IU/mg IU/μM[b] nM IC_{50}[c] 10 μl 212-C12 + 10 μl medium 1/19426 643.58 205.62 3.07 10.80 10 μl medium + 10 μl 213-E6 1/2987 98.64 65.76 0.98 33.65 10 μl 212-C12 + 10 μl 213-E6 1/10757 356.35 153.93 2.30 14.42 10 μl 212-C12 + 10 μl medium 1/8302 232.64 85.85 1.28 21.87 10 μl medium + 10 μl 213-H7 1/150 4.22 30.14 0.45 62.53 10 μl 212-C12 + 10 μl 213-H7 1/4346 122.3 85.52 1.28 22.05 10 μl 212-C12 + 10 μl medium 1/21220 597.18 220.36 3.29 8.56 10 μl medium + 10 μl 214-E8 1/280 7.38 14.19 0.21 124.43 10 μl 212-C12 + 10 μl 214-E8 1/8635 243.01 150.01 2.24 12.57 10 μl 212-C12 + 10 μl medium 1/14380 404.70 149.34 2.23 12.63 10 μl medium + 10 μl 172-B3[d] <1/9 <0.50 <0.14 <0.01 >26948.89 10 μl 212-C12 + 10 μl 172-B3 1/8902 250.54 79.03 1.18 23.86 10 μl 214-E8 + 10 μl medium 1/178 5.26 10.12 0.15 195.73 10 μl medium + 10 μl 213-H7 1/60 1.76 12.57 0.19 156.33 10 μl 214-E8 + 10 μl 213-H7 1/131 3.88 11.76 0.18 168.78 10 μl 214-E8 + 10 μl medium 1/108 3.18 6.12 0.09 322.59 10 μl medium + 10 μl 213-E6 1/5252 155.78 83.75 1.25 23.73 10 μl 214-E8 + 10 μl 213-E6 1/2022 59.96 50.39 0.75 39.43 10 μl 214-H10 + 10 μl medium 1/842 24.96 17.83 0.27 111.40 10 μl medium + 10 μl 213-E6 1/6166 182.84 98.30 1.47 20.21 10 μl 214-H10 + 10 μl 213-E6 1/1611 47.8 29.33 0.44 67.79 [a]International Unit (IU) [b]1 mg Nanobody/ml = 67 μM [c]= mg/ml × 50% dilution × 67000 [d]172-B3 = control Nanobody directed against TLR-3

TABLE C-38 Cross-neutralisation potency of monovalent Nanobody clones: neutralization of the genotype 1 ERA strain ERA neutralizing antibody titer Attenuated vaccine strain, ATCC VR332, complete genome: NCBI EF206707 Interpretation Sample 88% nucleotide identity with G of CVS-11 cross- Clone Elusion 50% dilution EU[a]/ml EU/mg EU/μM[b] nM IC_{50}[c] neutralisation Mab 8-2 Ascites mouse 1/506795 16895.00 nd[d] nd nd Yes OIE 0.5 IU/ml Canine reference serum 1/47 1.56 nd nd nd 3 x stronger compared to CVS WHO 0.5 IU/ml Human reference serum 1/20 0.66 nd nd nd Similar to CVS WHO 6 IU/ml Human reference serum 1/192 6.40 nd nd nd Similar to CVS 192-C4 Anti-HRSV[e] <1/9 <0.50 <0.63 <0.01 >5881.11 No 192-A8 Anti-HRSV <1/9 <0.50 <0.77 <0.02 >4838.89 No 191-E4 Anti-

HRSV <1/9 <0.50 <0.63 <0.01 >5955.56 No 214-C10 Anti-rabies[f] 1/421 14.03 35.08 0.52 63.66 Yes 214-F8 Anti-rabies 1/114 3.81 23.81 0.36 94.04 Yes 214-A8 Anti-rabies <1/9 <0.50 <0.43 <0.01 >8561.11 No 214-E8 Anti-rabies <1/9 <0.50 <0.96 <0.02 >3871.11 No 213-E6 Anti-rabies 1/8635 287.83 154.75 2.31 14.43 Yes 213-B7 Anti-rabies 1/165 5.51 8.35 0.12 268.00 Yes 213-D7 Anti-rabies 1/179 5.97 8.91 0.13 250.78 Yes 213-D6 Anti-rabies <1/9 <0.50 <0.48 <0.01 >7816.67 No 213-H7 Anti-rabies 1/367 12.23 87.36 1.30 25.56 Yes 212-A2 Anti-rabies 1/16 0.52 0.55 0.01 3936.25 Yes 212-B2 Anti-rabies 1/55 1.84 2.59 0.04 864.91 Yes 212-G2 Anti-rabies <1/9 <0.50 <0.51 <0.01 >7295.56 No 212-F6 Anti-rabies 1/30 0.99 0.93 0.01 2389.67 Yes 212-B12 Anti-rabies 1/14 0.45 0.29 <0.01 7417.86 No 212-C12 Anti-rabies 1/27367 912.23 336.62 5.02 6.63 Yes 214-H10 Anti-rabies <1/9 <0.50 <0.36 <0.01 >10422.22 No [a]1 Equivalent Unit (EU) is comparable to the neutralizing potency of 1 International Unit (IU) [b]1 mg nanobody/ml = 67 μM [c]= mg/ml × 50% dilution × 67000 [d]not determined [e]control Nanobody raised against human respiratory syncytial virus [f]Nanobody raised against rabies virus

TABLE C-39 Cross-neutralisation potency of monovalent Nanobody clones: neutralization of wild type genotype 1 strain CB-1 Chien Beersel-1 (CB-1) neutralizing antibody titer Belgian isolate of a genotype 1 canine rabies virus (Le Roux I. & Van Gucht S, WHO Rabies Bulletin 2008, 32(1), Quarter 1) Interpretation cross- Nanobody 50% dilution EU[a]/ml EU/mg EU/μM[b] nM IC_{50}[c] neutralisation Mab 8-2 Ascites mouse 1/881758 29391.92 nd[d] nd nd Very strong OIE 0.5 IU/ml Canine reference serum 1/36 1.18 nd nd nd 2 x stronger compared to CVS WHO 0.5 IU/ml Human reference serum 1/47 1.56 nd nd nd 3 x stronger compared to CVS WHO 6 IU/ml Human reference serum 1/402 13.40 nd nd nd 2 x stronger compared to CVS 192-C4 Anti-HRSV[e] <1/9 <0.50 <0.63 <0.01 >5881.11 Absent 192-A8 Anti-HRSV <1/9 <0.50 <0.77 <0.011 >4838.89 Absent 191-E4 Anti-HRSV <1/9 <0.50 <0.63 <0.01 >5955.56 Absent 214-C10 Anti-rabies[f] 1/653 21.77 54.43 0.81 41.04 Strong 214-F8 Anti-rabies 1/593 19.78 123.63 1.85 18.08 Very strong 214-A8 Anti-rabies 1/2768 92.25 80.22 1.20 27.84 Strong 214-E8 Anti-rabies 1/1906 63.55 122.21 1.82 18.28 Very strong 213-E6 Anti-rabies 1/10610 353.66 535.85 8.00 4.17 Very strong 213-B7 Anti-rabies 1/1263 42.09 63.77 0.95 35.01 Strong 213-D7 Anti-rabies 1/1996 66.52 99.28 1.48 22.49 Strong 213-D6 Anti-rabies 1/73 2.42 2.30 0.034 963.70 Weak 213-H7 Anti-rabies 1/8902 296.74 2119.57 31.64 1.05 Very strong 212-A2 Anti-rabies 1/524 17.48 18.60 0.28 120.19 Strong 212-B2 Anti-rabies 1/1384 46.12 64.96 0.97 34.37 Strong 212-G2 Anti-rabies 1/483 16.09 16.42 0.25 135.94 Strong 212-F6 Anti-rabies 1/1959 65.32 61.05 0.91 36.60 Strong 212-B12 Anti-rabies 1/11364 378.80 244.39 3.65 9.14 Very strong 212-C12 Anti-rabies 1/17635 587.84 459.25 6.85 4.86 Very strong 214-H10 Anti-rabies 1/4985 166.18 118.70 1.77 18.82 Very strong [1]Equivalent Unit (EU) is comparable to the neutralizing potency of 1 International Unit (IU) [b]1 mg nanobody/ml = 67 μM [c]= mg/ml × 50% dilution × 67000 [d]not applicable [e]control Nanobody raised against human respiratory syncytial virus [f]Nanobody raised against rabies virus

TABLE C-40 Cross-neutralisation potency of monovalent and bivalent Nanobody clones: neutralization of EBLV-1 strain EBLV-1 neutralizing antibody titer Genotype 5, strain 8918FRA, complete genome: NCBI EU293112 Interpretation Sample 71% nucleotide identity with G of CVS-11 cross- Clone Elusion 50% dilution EU[b]/ml EU/mg EU/μM[c] nM IC_{50}[d] neutralisation Mab 8-2 Ascites mouse 1/627878 20929.27 na na na Yes OIE 0.5 IU/ml Canine reference serum <1/9 <0.50 na na na No WHO 0.5 IU/ml Human reference serum <1/9 <0.50 na na na No WHO 6 IU/ml Human reference serum 1/37 1.22 na Na na 5x weaker compared to CVS- 11 214-C10 trypsin 1st + mab 2d round <1/9 <0.50 <1.25 <0.02 >2977.78 No 214-F8 trypsin 1st + mab 2d round <1/9 <0.50 <3.13 <0.05 >1191.11 No **214-A8** trypsin 1st + mab 2d round 1/25 0.83 0.72 0.02 3082.00 **Yes 214-E8** trypsinst + mab 2d round 1/67 2.25 4.33 0.06 520.00 **Yes** 213-E6 Mab 1st + trypsin 2d round <1/9 <0.50 <0.76 <0.02 >4913.33 No **213-B7** Mab 1st + trypsin 2d round 1/38 1.27 1.92 0.03 1163.68 **Yes 213-D7** Mab 1st + trypsin 2d round 1/41 1.38 2.06 0.03 1094.88 **Yes** 213-D6 Mab 1st + trypsin 2d round <1/9 <0.50 <0.48 <0.01 >7816.67 No **213-H7** Mab 1st + trypsin 2d round 1/16 0.52 3.71 0.06 586.25 **Yes** 192-C4 Anti HRSV <1/9 <0.50 <0.63 <0.01 >5881.11 No 192-A8 Anti HRSV <1/9 <0.50 <0.77 <0.02 >4838.89 No 191-E4 Anti HRSV <1/9 <0.50 <0.63 <0.01 >5955.56 No **212-A2** Trypsin 1st and 2d round 1/25 0.83 0.88 0.01 2519.20 **Yes** 212-B2 Trypsin 1st and 2d round <1/9 <0.50 <0.70 <0.02 >5285.56 No 212-G2 Trypsin 1st and 2d round <1/9 <0.50 <0.51 <0.01 >7295.56 No 212-F6 Trypsin 1st and 2d round <1/9 <0.50 <0.47 <0.01 >7965.56 No 212-B12 Trypsin 1st and 2d round <1/9 <0.50 <0.32 <0.01 >11538.89 No 212-C12 Trypsin 1st and 2d round <1/9 <0.50 <0.39 <0.01 >9528.89 No **214-H10** trypsin 1st + mab 2d round 1/41 1.36 0.97 0.01 2287.80 **Yes** 212-C12 15GS 212-C12 <1/9 <0.50 <0.50 <0.013 >4166.61 No 213-E6 5GS 213-E6 <1/9 <0.50 <0.53 <0.028 >4001.35 No **213-E6 15GS 213-H7** 1/63 2.04 4.86 0.14 236.70 **Yes 214-E8 15GS 213-H7** 1/2187 70.15 305 8.52 3.76 **Yes (potent) 213-H7 15GS 214-F8** 1/41 1.32 11 0.30 107.74 **Yes** [a]serial dilution with different tips [b]1 Equivalent Unit (EU) can inhibit 50% of $10^{4.54}$ $TCID_{50}$ of EBLV-1 on BHK cells; this is comparable to the neutralizing potency of 1 International Unit (IU) against CVS-11 [c]1 mg Nanobody/ml = 67 μM [d]= mg/ml × 50% dilution × 67000 [e]not applicable

TABLE C-41 Cross-neutralisation potency of monovalent and bivalent Nanobody clones: neutralization of wild type genotype 1 strains and a laboratory CVS strain in suspensions of infected mouse brain using neuroblastoma cells as the susceptible target system [a] Tissue Culture Infectious Dose 50%: this corresponds with the dilution of the infected brain suspension - Nanobody mixture which yields 50% infection in neuroblastoma cells [b] Titers with grey background correspond with a minimum hundredfold reduction of virus infectivity compared to control clone 172-B3 (anti-TLR3)

TABLE C-42 Overview of the neutralisation potency of monovalent and bivalent Nanobody

clones: neutralization profile against different rabies virus strains and isolates. Neutralisation[a] of Genotype 1 9912CBG 9147FRA CVS 9722POL 8740THA 07059IC Dog Fox Strain Raccoon Human Dog Ivory 9009NIG Genotype 5 Nanobody CVS ERA CB-1 Cambodia France IP13 dog Poland Thailand Coast Dog Niger EBLV-1 Mab 8-2 Ascites mouse **Yes**[b] **Yes Yes Yes Yes** No **Yes Yes Yes Yes Yes** OIE 0.5 IU/ml Canine ref. Yes Yes Yes nt[c] nt nt nt nt nt nt No serum WHO 0.5 Human ref. Yes Yes Yes nt nt nt nt nt nt nt No IU/ml serum WHO 6 IU/ml Human ref. Yes Yes Yes nt nt nt nt nt nt nt Yes serum 192-C4 Anti-HRSV[d] No No No nt nt nt nt nt nt nt No 192-A8 Anti-HRSV No No No nt nt nt nt nt nt nt No 191-E4 Anti-HRSV No No No nt nt nt nt nt nt nt No 172-B3 Anti-TLR3[e] No nt nt No No No No No No No nt 214-F8 Anti-rabies Yes Yes **Yes Yes Yes** Yes **Yes Yes Yes Yes** No 213-E6 Anti-rabies **Yes Yes Yes Yes Yes Yes Yes Yes Yes** No No 213-H7 Anti-rabies Yes Yes **Yes** No **Yes** Yes **Yes Yes** No **Yes** Yes 212-C12 Anti-rabies **Yes Yes Yes** No No Yes No **Yes** Yes **Yes** No 214-E8 Anti-rabies Yes No Yes nt nt nt nt nt nt nt Yes 214-C10 Anti-rabies Yes Yes Yes nt nt nt nt nt nt nt No 214-A8 Anti-rabies Yes No Yes nt nt nt nt nt nt nt Yes 213-B7 Anti-rabies Yes Yes Yes nt nt nt nt nt nt nt Yes 213-D7 Anti-rabies Yes Yes Yes nt nt nt nt nt nt nt Yes 213-D6 Anti-rabies No No Yes nt nt nt nt nt nt nt No 212-A2 Anti-rabies Yes Yes Yes nt nt nt nt nt nt nt Yes 212-B2 Anti-rabies Yes Yes Yes nt nt nt nt nt nt nt No 212-G2 Anti-rabies Yes No Yes nt nt nt nt nt nt nt No 212-F6 Anti-rabies **Yes** Yes Yes nt nt nt nt nt nt nt No 212-B12 Anti-rabies Yes No **Yes** nt nt nt nt nt nt nt No 214-H10 Anti-rabies Yes No **Yes** nt nt nt nt nt nt nt Yes 212-C12 15GS **Yes** nt nt **Yes** nt nt nt nt **Yes Yes EBLV-1** 212-C12 213-E6 5GS **Yes** nt nt **Yes** nt nt nt nt **Yes Yes** No 213-E6 213-E6 15GS **Yes** nt nt **Yes** nt nt nt nt **Yes Yes** Yes 213-H7 214-E8 15GS **Yes** nt nt **Yes** nt nt nt nt **Yes Yes Yes** 213-H7 213-H7 15GS **Yes** nt nt **Yes** nt nt nt nt **Yes Yes** Yes 214-F8 [a]Neutralisation is defined as an RFFIT titer of $\geqq$0.50 IU or EU/ml (CVS, ERA, CB-1, EBLV-1), or a minimum hundredfold reduction of virus infectivity of a mixture of infected brain and nanobody in the neuroblastoma assay [b]Yes in bold means a relative strong neutralizing potency: $\geqq$100 IU or EU/mg in the RFFIT assay or $\leqq$100 $TCID_{50}$/ml in the neuroblastoma assay [c]Not tested [d]Control Nanobody raised against human respiratory syncytial virus [e]Control Nanobody raised against Toll-like receptor 3

TABLE C-43 Effect of linking Nanobodies in bivalent or biparatopic combinations on the neutralizing potency. CVS neutralizing antibody titre Potency strain CVS-11, ATCC VR 959, sequence (IU/nM) G protein: NCBI EU126641 increase Nanobodies 50% versus Stock dilution IU[a]/ml IU/mg IU/nM[b] nM IC50[c] monovalent Bivalent 17/09/08 NB6 18GS NB6 10 <0.50 <2.38 <0.07 >725 — 17/09/08 213-H7 15GS 213-H7 12839 412 549 15.38 2.09 34.2 17/09/08 214-E8 15GS 214-E8 14156 454 349 9.78 3.28 31.5 17/09/08 212-C12 15GS 212-C12 10284 330 330 8.57 3.74 4.6 25/02/09 213-E6 5GS 213-E6 41075 1292 1297 36 0.88 27.7 30/10/08 213-E6 25GS 213-E6 674 21 300 8.29 3.76 6.4 30/10/08 214-F8 15GS 214-F8 421 13 650 17.2 1.79 63.7 Biparatopic 17/09/08 213-E6 5GS 212-C12 12006 385 385 10 3.21 6.3 17/09/08 213-E6 25GS 212-C12 40199 1289 248 6.70 4.79 4.2 30/10/08 213-E6 25GS 214-E8 1489 46 657 1.84 1.68 2.3 03/02/09 213-E6 15GS 213-H7 125670

3763 4252 93.7 0.26 107.1 17/09/08 214-E8 5GS 212-C12 5340 171 214 5.68 5.65 5.2 17/09/08 214-E8 15GS 212-C12 31109 998 322 8.70 3.69 8 30/10/08 214-E8 25GS 212-C12 2767 70.5 573 1.60 1.94 1.5 25/02/09 214-E8 15GS 213-H7 59651 1890 8215 230 0.14 605.3 25/02/09 213-H7 15GS 214-F8 13532 429 3575 97.5 0.33 270.8 [a]International Unit (IU) [b]1 mg bihead Nanobody/ml = 35.7 to 38.5 μM [c]= mg/ml × 1/50% dilution × (35700 to 38500)

TABLE C-44 Synthesis of the peak clinical score, mortality and survival time in different groups of mice as described in Example 50 Peak clinical Mean time for Median Nr. of Inoculum score[a] Mortality mice death survival time[b] mice Virus Pre-incubated with (mean/mouse) (%) (days) (days) 7 $10^{1.5}$$TCID_{50}$[c] — PBS 4.3 71 7.4 ± 0.89 7 7 $10^{1.5}$$TCID_{50}$ 1 IU mab 8-2 0 0 Na[d] na 6 $10^{1.5}$$TCID_{50}$ 6.4 μg 191-G2 5.3 100 7.3 ± 0.52 7 7 $10^{1.5}$$TCID_{50}$ 1 IU 212-C12 6 100 7.4 ± 0.53 7 7 $10^{1.5}$$TCID_{50}$ 1 IU 213-E6 3.4 57 6.75 ± 0.96 9 [a]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [b]the median survival time is the time at which half of the mice have died on the Kaplan Meier curve (survival curve) [c]$TCID_{50}$: tissue culture infectious dose 50%, [d]not applicable

TABLE C-45 Synthesis of peak clinical score, mortality and survival time in different groups of mice as described in Example 50 Mean time for Nr. of Peak clinical score[a] Mortality mice death Median survival time[b] mice Inoculum Pre-incubated (mean/mouse) (%) (days) (days) 8 $10^{1.5}$ $TCID_{50}$[c] 191-G2 1IU 5.25 ± 2.12 87.5 7.29 ± 1.25 8 9 $10^{1.5}$ $TCID_{50}$ Mab 8-2 1IU 0 0 0 na[d] 9 $10^{1.5}$ $TCID_{50}$ 212-C12 15GS 212-C12 1IU 1.33 ± 2.65 22.2 9 ± 1.4 na 9 $10^{1.5}$ $TCID_{50}$ 214-E8 15GS 214-E8 1IU 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 213-H7 15GS 213-H7 1IU 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 214-E8 15GS 212-C12 1IU 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 213-E6 25GS 212-C12 1IU 0 0 0 na 8 $10^{1.5}$ $TCID_{50}$ 213-E6 5GS 212-C12 1IU 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 213-E6 15GS 213-H7 1IU 0 0 0 na [a]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [b]the median survival time is the time at which half of the mice have died on the Kaplan Meier curve (survival curve) [c]$TCID_{50}$: tissue culture infectious dose 50%, [d]not applicable

TABLE C-46 Synthesis of peak clinical score, mortality and survival time in different groups of mice as described in Example 52 Antibody/Nanobody Peak clinical Mean time for mice Median survival Nr. of IN injection on Virus IN injection on score Mortality death time mice day −1 day 0 (mean/mouse)[a] (%) (days) (days)[b] 8 191-D3 1IU 10^2 $TCID_{50}$[c] 6.1 ± 2.5 87.5 9.9 ± 1.4 9 8 Mab 8-2 1IU 10^2 $TCID_{50}$ 0 0 0 Na[d] 8 212-C12 1IU 10^2 $TCID_{50}$ 6.1 ± 2.5 87.5 10.2 ± 1.6 12 8 213-E6 1IU 10^2 $TCID_{50}$ 5.25 ± 3.2 75 11.8 ± 1.6 12 [a]clinical scores range from 0 (no disease) to 7 (conjunctivitis, weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [b]the median survival time is the time at which half

of the mice have died on the Kaplan Meier curve (survival curve) [c]$TCID_{50}$: tissue culture infectious dose 50% [d]not applicable

TABLE C-47 Synthesis of peak clinical score, mortality and survival time upon intranasal inoculation of a mix of virus and NANOBODY ® (V_{HH} sequence) or antibody as described in Example 51 Peak clinical Mean time for Median Nr. of score Mortality mice death survival Exp mice Inoculum (mean/mouse)[a] (%) (days) time (days)[b] I 8 CVS 10^3 $TCID_{50}$[c] + 191-D3 6.5 ± 0.53 100 8.75 ± 0.46 9 9 CVS 10^3 $TCID_{50}$ + 212-C12 3.78 ± 3.6 55.6 11.6 ± 1.52 13 9 CVS 10^3 $TCID_{50}$ + 213-E6 3 ± 3.57 44.4 12.5 ± 1 na[d] II 8 CVS 10^2 $TCID_{50}$ + PBS 6.12 ± 2.5 87.5 12 ± 0 12 8 CVS 10^2 $TCID_{50}$ + Mab 8-2 6 ± 2.5 87.5 10.3 ± 1.6 10.5 8 CVS 10^2 $TCID_{50}$ + 212-C12 0 0 0 na 8 CVS 10^2 $TCID_{50}$ + 213-E6 0 0 0 na III 8 CVS 10^2 $TCID_{50}$ + 191-D3 4.22 ± 3.23 66 11.3 ± 3.14 13 8 CVS 10^2 $TCID_{50}$ + Mab8-2 6.11 ± 2.3 89 9.25 ± 0.46 9 8 CVS 10^2 $TCID_{50}$ + 212-C12 2.33 ± 3.5 33 11.7 ± 2.3 na 8 CVS 10^2 $TCID_{50}$ + 213-E6 0 0 0 na 8 CVS 10^2 $TCID_{50}$ + 0 0 0 na 214E8-15GS-213-H7 [a]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis), [b]the median survival time is the time at which half of the mice have died on the Kaplan Meier curve (survival curve), [c]$TCID_{50}$: tissue culture infectious dose 50%, [d]not applicable

TABLE C-48 Synthesis of peak clinical score, mortality and survival time in different groups of mice as described in Example 50.2 Mean time for Nr. for Peak clinical score[b] Mortality mice death Median survival time[c] mice Inoculum Pre-incubated (mean/mouse) (%) (days) (days) 9 $10^{1.5}$ $TCID_{50}$[d] NB6-18GS-NB6 1IU 5.33 ± 2 88.9 7.12 ± 2.42 6 9 $10^{1.5}$ $TCID_{50}$ Mab 8-2 1IU 0 0 0 na[e] 10 $10^{1.5}$ $TCID_{50}$ 214-E8 15GS 212-C12 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 213-E6 25GS 212-C12 1IU 0 0 0 na 7 $10^{1.5}$ $TCID_{50}$ 213-E6 5GS 212-C12 1IU 0.86 ± 2.27 14.3 21 na 9 $10^{1.5}$ $TCID_{50}$ 213-E6 15GS 213-H7 1IU 0 0 0 na 10 $10^{1.5}$ $TCID_{50}$ 213-E6 5GS 213-E6 1IU 0 0 0 na 9 $10^{1.5}$ $TCID_{50}$ 213-E6 15GS 214-E8 1IU 4 ± 3 66.7 12.5 ± 1.22 13 10 $10^{1.5}$ $TCID_{50}$ 214-E8 15GS 213-E6 1IU 0 0 0 na [b]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [c]the median survival time is the time at which half of the mice have died on the Kaplan Meier curve (survival curve) [d]$TCID_{50}$: tissue culture infectious dose 50%, [e]not applicable

TABLE C-49 Synthesis of peak clinical score, mortality and survival time in different groups of mice as described in Example 50.4 Nr. of Peak clinical score[a] Mortality Mean time for mice death Median survival time mice Inoculum Pre-incubated (mean/mouse) (%) (days) (days) 9 10^2 $TCID_{50}$[c] PBS 6 ± 0 100 6.11 ± 0.33 6 8 10^2 $TCID_{50}$ RV1C5 1 IU 0 0 0 na[d] 9 10^2 $TCID_{50}$ 213E6-15GS-213H7 1 IU 0 0 0 na [a]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [b]the median survival time is the time at which half of the mice have died on the

Kaplan Meier curve (survival curve) [c]$TCID_{50}$: Tissue Culture Infectious Dose 50%, [d]not applicable

TABLE C-50 Synthesis of peak clinical score, mortality and survival time upon intranasal or intracerebral inoculation of 10^2 $TCID_{50}$ CVS-11 mixed with 1 IU 212-C12. Mean time Median Peak clinical for mice survival Nr. of Route of score[a] Mortality death time[b] mice Inoculum Pre-incubated inoculation (mean/mouse) (%) (days) (days) 9 10^2 $TCID_{50}$[c] 212-C12 1IU IC 6 ± 0 100 7.22 ± 0.44 7 9 10^2 $TCID_{50}$ 212-C12 1IU IN 0 0 0 na[d] [a]clinical scores range from 0 (no disease) to 6 (weight loss, depression, hunched back, wasp waist, incoordination and hind limb paralysis) [b]the median survival time is the time at which half of the mice have died on the Kaplan Meier curve (survival curve) [c]$TCID_{50}$: tissue culture infectious dose 50% [d]not applicable

TABLE C-51 Concentration (ng) of NANOBODY ® (V_{HH} sequence) RSV101 or 12B2biv in lung homogenatesof mice inoculated with NANOBODY ® (V_{HH} sequence) 3 and 5 days after administering of the NANOBODY ® (V_{HH} sequence) and infection with RSV as described in Example 55. Day 3 Day 5 Mouse RSV101 12B2biv PBS RSV101 12B2biv PBS 1 17.47 36.42 <5 5.8 19.15 6.68 2 14.21 27.07 8.46 <5 10.21 3 29.69 15.92 <5 16.56 4 31.69 45.74 <5 14.86 5 19.55 27.59 <5 21.51

TABLE C-52 Neutralization and kinetic binding parameters for selected NC41 variants Neutralization IC50 (nM) Biacore (F_{tm}-NN) Name Long B-1 Long B-1 ka (1/Ms) kd (1/s) KD (M) NC41 202 4707 122 3291 1.7E+06 6.70E−03 4.00E−09 NC41v03 255 1507 nd nd nd nd NC41v06 111 806 nd nd 2.0E+06 4.80E−03 2.50E−09 NC41v17 249 677 149 346 1.9E+06 5.90E−03 3.20E−09 NC41v18 116 728 98 194 nd nd nd Synagis 7.3 2.1 6.0 2.9

TABLE C-53 Antigens used for llama immunization Virus strain Serotype Amount[a] (μg) Llama 3049 A/Chicken/Italy/1067/1999 H7N1 100 A/Mallard/Netherlands/2/2005 H5N2 100 A/Swan/Netherlands/06003448/2006 H7N7 100 FMDV Asia 1 Shamir Asia 1 50 FMDV A24 Cruzeiro A 15 Llama 3050 A/Ostrich/Netherlands/03006814/2003 H2N3 100 A/Mallard/Netherlands/06026212/2006 H8N4 100 A/Ty/Netherlands /06001571-041Tr/2006 H6N5 100 A/Chearwater/Australia/2576/02 H15N6 100 A/Mallard/Netherlands/06014516/2006 H10N8 100 A/Chicken/Italy/22A/98 H5N9 100 FMDV SAT2 SAT2 50 [a]Amount of antigen for each individual immunization.

TABLE C-54 Analysis of llama antibody response by haemagglutination inhibition test Immunised with H7N1 HI titer 2log H5N7 HI titer 2log H5 and H7 34 34 llama strains 0 DPI DPI 55 DPI 0 DPI DPI 55 DPI 3049 H7N1/H5N2/ — 7 9 — 3 5 H7N7 3050 H5N9 — — — —

7 11

TABLE C-55 Oligonucleotides used for the construction of phage display libraries and sequencing as described in example 61 SEQ ID Primer NO: Sequence (5′-3′) NotI-d(T)18 3057 AACTGGAAGAATTCGCGGCCGCAGGAA TTTTTTTTTTTTTTTTTT VH2B 3058 AGGTSMARCTGCAGSAGTCWGG lam07 3059 AACAGTTAAGCTTCCGCTTGCGGCCGCGGAG CTGGGGTCTTCGCTGTGGTGCG lam08 3060 AACAGTTAAGCTTCCGCTTGCGGCCGCTGGTT GTGGTTTTGGTGTCTTGGGTT BOLI-192 3061 AACAGTTAAGCTTCCGCTTGCGGCCGCTA CTTCATTCGTTCCTGAGGAGACGGT MPE26 3062 GGATAACAATTTCACACAGGA

TABLE C-56 Phage display libraries obtained as described in Example 61 Days post Library Llama immunisation Hinge primer Library Size[a] pAL439 3049 34 lam07 4.7×10^6 pAL440 3049 34 lam08 8.0×10^6 pAL441 3049 34 BOLI-192 6.1×10^6 pAL442 3049 55 lam07 6.7×10^6 pAL443 3049 55 lam08 7.6×10^6 pAL444 3049 55 BOLI-192 1.1×10^7 pAL445 3050 34 lam07 1.0×10^7 pAL446 3050 34 lam08 9.8×10^6 pAL447 3050 34 BOLI-192 8.0×10^6 pAL448 3050 55 lam07 5.4×10^6 pAL449 3050 55 lam08 9.5×10^6 pAL450 3050 55 BOLI-192 5.3×10^6 [a]The number of colonies obtained after transformation of *E. coli* TG1.

TABLE C-57 Influenza strains used for antigen preparation as described in Example 63 Influenza strain Serotype A/PR/8/34 (ATCC VR-1469) H1N1 A/Mallard/Netherlands/2/05 H5N2 A/Mallard/Denmark/75-64650/03 H5N7 A/Turkey/Wisconsin/68 H5N9 A/Chicken /Italy/1067/V99 H7N1 A/Swan/Netherlands/06003448/06 H7N7 A/Ostrich/Netherlands /03006814/03 H2N3 A/Ty/Netherlands/06001571-041Tr/06 H6N5 A/Mallard /Netherlands/06026212-002/06 H8N4 A/Duck/Germany/R113/95 H9N2 A/Mallard /Netherlands/06014516/06 H10N8 A/Chearwater/Australia/2576/02 H15N6

TABLE C-58 Sequence characteristics, panning history and binding to influenza antigens of selected putative H5 binding NANOBODIES ® (V_{HH} sequences) Number of Potential Panning Extinction at 450 nm in identical CDR3 N-glycosylation BstEII site round 1 on Panning round ELISA on AIV antigens[e] Expressed Clone clones[a] Group[b] site[c] in FR4[d] antigen[e] 2 on antigen[e] H1N1 H7N7 H5N2 H5N9 H5N7 in yeast IV121 3 A None present H5N2 HAhis6 H5N1 0.085 0.053 0.101 0.099 0.449 not done IV122 2 A None present H5N2 HAhis6 H5N1 0.06 0.055 0.168 0.129 0.937 not done IV123 1 A None present H5N2 HAhis6 H5N1 0.065 0.06 0.12 0.188 0.487 not done IV126 1 A None present H5N2 HAhis6 H5N1 0.142 0.06 0.202 0.33 0.883 not done IV127 2 A None present H5N2 HAhis6 H5N1 0.113 0.106 0.216 0.443 1.15 not done IV131 1 A None present H5N2 HAhis6 H5N1 0.047 0.046 0.216 0.398 0.936 done IV132 1 A None present H5N2 HAhis6 H5N1 0.048 0.048 0.072 0.113 0.33 not done IV133 1 A None present H5N2 HAhis6 H5N1 0.048 0.051 0.243 0.377 1.206 done IV134 2 A None present H5N2 HAhis6 H5N1 0.049 0.049 0.106 0.194 0.95 not

done IV135 1 A None present H5N2 HAhis6 H5N1 0.053 0.049 0.195 0.169 0.832 not done IV136 1 A None present H5N2 HAhis6 H5N1 0.088 0.123 0.182 0.372 0.953 not done IV140 3 A None present H5N2 HAhis6 H5N1 0.047 0.048 0.117 0.099 0.834 not done IV144 3 A None present H5N2 HAhis6 H5N1 0.12 0.089 0.407 0.656 1.282 done IV156 1 A None present H5N9 H5N7 0.048 0.054 0.401 0.649 1.418 done IV157 1 A None present H5N9 H5N7 0.046 0.049 0.352 0.336 1.375 done IV160 1 A None present H5N9 HAhis6 H5N1 0.052 0.053 0.283 0.312 1.243 not done IV124 2 B None present H5N2 HAhis6 H5N1 0.413 0.063 0.274 0.429 0.868 not done IV125 1 B None present H5N2 HAhis6 H5N1 0.461 0.076 0.272 0.413 0.801 not done IV145 1 B None present H5N2 HAhis6 H5N1 0.204 0.056 0.162 0.183 0.746 not done IV146 1 B None present H5N2 HAhis6 H5N1 0.299 0.051 0.223 0.285 0.744 done IV147 5 B None present H5N2 HAhis6 H5N1 0.216 0.047 0.182 0.197 0.599 not done IV151 1 C None absent H5N2 HAhis6 H5N1 0.172 0.106 0.164 0.181 0.709 not done IV153 1 D None absent H5N7 H5N2 0.045 0.048 0.436 0.05 0.056 not done IV154 1 E None present H5N9 H5N2 0.843 0.961 1.594 0.566 1.35 done IV155 1 F None present H5N9 H5N2 0.759 1.059 1.641 0.449 1.243 done [a]Number of times a clone was isolated that encodes an identical Nanobody. [b]Clones belonging to the same CDR3 group have highly similar CDR3 sequences and identical CDR3 length. [c]Potential N-glycosylation sites (Asn-X-Ser/Thr, where X is not Pro) are either absent or present at the indicated position (IMGT numbering). [d]The presence of a unique BstEII restriction endonuclease cleavage site present in the FR4 encoding region and suitable for subcloning into yeast expression vector pRL188 is indicated. [e]H1N1, H7N7, H5N2, H5N7 and H5N9 refer to authentic influenza antigen produced by MDCK cells; HAhis6 H5N1 was from Abcam (cat. No. ab53938).

TABLE C-59 Sequence characteristics, panning history and binding to influenza antigens of selected putative H7 binding NANOBODIES ® (V_{HH} sequences) Poten- Number tial of N- iden- glycosy- BstEII Panning tical CDR3 lation site in Panning round round 2 on Extinction at 450 nm in ELISA on AIV antigens[e] Expressed Clone clones[a] Group[b] site[c] FR4[d] 1 on antigen[e] antigen[e] H1N1 H5N2 H5N7 H5N9 H7N1 H7N7 in yeast IV1 1 A None present H7N1 or H7N7 HAstr H7N2 0.056 0.051 0.057 0.052 1.277 1.096 done IV2 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.048 0.05 0.048 0.045 1.366 0.814 not done IV3 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.048 0.049 0.048 0.047 1.161 0.832 not done IV4 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.047 0.05 0.048 0.047 1.158 0.945 not done IV6 2 A 84 present H7N1 or H7N7 HAstr H7N2 0.048 0.051 0.05 0.054 0.92 0.724 not done IV7 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.048 0.054 0.05 0.047 1.2 0.806 not done IV9 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.046 0.051 0.047 0.047 1.008 0.939 not done IV10 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.047 0.052 0.047 0.048 1.133 1.078 not done IV11 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.047 0.05 0.053 0.051 0.912 0.762 not done IV12 1 A 84 present H7N1 or H7N7 HAstr H7N2 0.065 0.123 0.195 0.078 0.956 0.984 not done IV16 1 A 84 present H7N1 HA1his H7N7 0.048 0.05 0.05 0.045 1.071 0.789 not done IV24 1 A 84 present H7N7 HA1his H7N7 0.05 0.049 0.051 0.047 1.166 1.032 not done

IV26 1 A 84 present H7N7 HA1his H7N7 0.061 0.109 0.114 0.097 1.127 1.003 done IV30 1 A 84 present H7N1 HA1his H7N7 0.054 0.054 0.072 0.053 0.844 0.32 not done IV34 1 A 84 present H7N1 HA1his H7N7 0.05 0.108 0.076 0.079 1.097 0.95 not done IV14 1 B None present H7N1 HA1his H7N7 0.054 0.05 0.052 0.048 1.191 0.969 not done IV15 1 B None present H7N1 HA1his H7N7 0.046 0.05 0.053 0.05 0.551 0.502 not done IV17 7 B None present H7N1 HA1his H7N7 0.046 0.05 0.048 0.046 0.67 0.593 not done IV18 3 B None present H7N1 HA1his H7N7 0.051 1.503 0.516 0.098 0.927 0.608 not done IV29 1 B None present H7N1 HA1his H7N7 0.053 0.049 0.054 0.048 0.946 1.002 done IV31 1 B None present H7N1 HA1his H7N7 0.045 0.051 0.05 0.049 1.013 1.043 not done IV33 1 B None present H7N1 HA1his H7N7 0.045 0.049 0.047 0.047 0.885 0.762 not done IV35 1 B None present H7N7 HA1his H7N7 0.065 0.054 0.054 0.047 1.121 0.907 not done IV36 1 B None present H7N7 HA1his H7N7 0.048 0.048 0.048 0.047 1.029 0.999 not done IV40 1 B None absent H7N7 HA1his H7N7 0.048 0.05 0.05 0.047 1.021 0.667 not done IV42 1 B None present H7N1 HA1his H7N7 0.06 0.049 0.052 0.048 0.741 0.797 not done IV8 1 C None present H7N1 or H7N7 HAstr H7N2 0.047 0.05 0.049 0.045 1.077 0.456 not done IV21 1 C None present H7N7 HA1his H7N7 0.047 0.047 0.047 0.05 0.945 0.565 done Poten- Number tial of N- iden- glycosy- BstEII Panning tical CDR3 lation site in Panning round round 2 on Extinction at 450 nm in ELISA on AIV antigens[e] Expressed Clone clones[a] Group[b] site[c] FR4[d] 1 on antigen[e] antigen[e] H1N1 H1N1 H1N1 H1N1 H1N1 H1N1 in yeast IV23 1 C None present H7N7 HA1his H7N7 0.047 0.048 0.049 0.046 1.052 0.616 not done IV45 1 C None present H7N1 HA1his H7N7 0.05 0.052 0.05 0.047 0.59 0.217 not done IV47 1 C None present H7N7 HA1his H7N7 0.07 0.055 0.054 0.05 1.077 0.668 not done IV48 1 C None present H7N7 HA1his H7N7 0.061 0.051 0.052 0.048 0.939 0.442 not done IV50 1 C None present H7N7 HA1his H7N7 0.056 0.055 0.052 0.049 0.814 0.32 not done IV22 2 D None present H7N7 HA1his H7N7 0.051 0.05 0.051 0.053 1.001 0.976 not done IV37 1 D None present H7N7 HA1his H7N7 0.048 0.049 0.05 0.048 1.001 0.978 done IV38 1 D None present H7N7 HA1his H7N7 0.047 0.051 0.05 0.047 0.915 0.99 not done IV5 1 E None present H7N1 or H7N7 HAstr H7N2 0.054 0.049 0.05 0.049 1.171 1.092 done IV27 1 E None present H7N1 HA1his H7N7 0.054 0.047 0.051 0.048 1.321 1.165 not done IV25 1 F None present H7N7 HA1his H7N7 0.046 0.05 0.048 0.047 0.706 0.797 done IV28 1 G None present H7N1 HA1his H7N7 0.049 0.049 0.049 0.047 0.704 0.714 failed [a]Number of times a clone was isolated that encodes an identical Nanobody. [b]Clones belonging to the same CDR3 group have highly similar CDR3 sequences and identical CDR3 length. [c]Potential N-glycosylation sites (Asn-X-Ser/Thr, where X is not Pro) are either absent or present at the indicated position (IMGT numbering). [d]The presence of a unique BstEII restriction endonuclease cleavage site present in the FR4 encoding region and suitable for subcloning into yeast expression vector pRL188 is indicated. [e]H1N1, H7N1, H7N7, H5N2, H5N7 and H5N9 refer to authentic influenza antigen produced by MDCK cells; HA1his H7N7 was from Abcam (Abcam, Cat. No. ab61286).

TABLE C-60 Antigen binding characteristics of yeast-produced NANOBODIES ® (V_{HH} sequences) binding to H5 strains ELISA titers[c] (ng/ml) VNT titer[d] CDR3 HA0his6 H5, HA1his6 H7, (ug/ml) HI titer[e] (ug/ml) Clone group H5N9[a] ab53938[b] ab53875[b] H5N7 H5N9 H5N7 H5N9 IV131 A 19.5 36.8 32 >50 >50 >1000 >1000 IV133 A 29.4 39.1 32.5 >50 >50 >1000 >1000 IV144 A 31.6 33.1 34.8 >50 >50 >1000 >1000 IV156 A 14.4 51.9 33 >50 >50 >1000 >1000 IV157 A 14.5 30.6 9.9 >50 >50 >1000 >1000 IV146 B 43.0 161.5 62.9 <0.75 <0.75 >1000 >1000 IV154 E 8.3 >10000 >10000 >50 >50 >1000 >1000 IV155 F 34.3 >10000 >10000 >50 >50 >1000 >1000 [a]ELISA titers were determined on authentic AIV antigens of strains shown in Table C-57 using a peroxidase-conjugated anti-his6 monoclonal antibody. Nanobody concentrations resulting in an extinction of 0.2 were interpolated. [b]ELISA titers were determined on recombinant haemagglutinins derived from two different H5 influenza strains derived from Abcam. Nanobody concentrations resulting in an extinction of 1 were interpolated. [c]>10000 indicates extinctions below the value used for interpolation of titer at the highest Nanobody concentration analysed. [d]>50, no virus neutralization at the highest Nanobody concentration analysed; <0.75, neutralization at the lowest Nanobody concentration analysed. [e]>1000, no inhibition of haemagglutination at the highest Nanobody concentration analysed.

TABLE C-61 Antigen binding characteristics of yeast-produced NANOBODIES ® (V_{HH} sequences) binding to H7 strains ELISA titers (ng/ml) VNT titer[c] CDR3 HA1his6 H7, (μg/ml) HI titer[d] (μg/ml) Clone group H7N1[a] H7N7[a] ab61286[b] H7N1 H7N7 H7N1 H7N7 IV1 A 11.2 66.4 62.2 >50 >50 >600 >600 IV26 A 14.1 147 80.6 >50 >50 >1000 >1000 IV29 B 6.8 9.3 7.2 >50 >50 >1000 >1000 IV21 C 85.8 1969 69 >50 >50 >1000 >1000 IV37 D 46 141 31.4 >50 >50 >1000 >1000 IV5 E 5.0 12.9 30.7 >50 >50 >1000 >1000 IV25 F 18.8 22.8 27.8 >50 >50 >400 >400 [a]ELISA titers were determined on authentic AIV antigens of strains shown in Table C-57 using a peroxidase-conjugated anti-his6 monoclonal antibody. Nanobody concentrations resulting in an extinction of 0.2 were interpolated. [b]ELISA titers were determined on recombinant haemagglutinin derived from Abcam (Cat. No. ab61286). Nanobody concentrations resulting in an extinction of 1 were interpolated. [c]>50, no virus neutralization at the highest Nanobody concentration analysed. [d]>1000, >600 or >400, no inhibition of haemagglutination at the highest Nanobody concentration analysed.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

All references disclosed herein are incorporated by reference, in particular for the teaching that is referenced hereinabove.

Claims

1. A polypeptide comprising an amino acid sequence with the general structure FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 in which FR1-FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementary determining regions 1 to 3 respectively that specifically binds to an F protein of a respiratory syncytial virus (RSV), wherein the polypeptide comprises a combination of CDR1, CDR2, and CDR3 selected from (a), (b), (c), (d), (e), or (f):

(a) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 723; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 723; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 723;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1287; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1287; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1287;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1851; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1851; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1851;

(b) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO:731; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 731; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference the amino acid sequence of SEQ ID NO: 731;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1295; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1295; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference the amino acid sequence of SEQ ID NO: 1295;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1859; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1859; and 3. amino

acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1859;

(c) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 918; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 918; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 918;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1482; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1482; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1482;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2046; 2. amino acid sequences that have at least 80% amino acid identity the amino acid sequence of SEQ ID NO: 2046; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 2046;

(d) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 935; 2. amino acid sequences that have at least 80% amino acid identity the amino acid sequence of SEQ ID NO: 935; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 935;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1499; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1499; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1499;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2063; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 2063; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 2063;

(e) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 936; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 936; and 3.

amino acid sequences that have 3, 2, or 1 amino acid difference the amino acid sequences of SEQ ID NO: 936;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 1500; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 1500; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 1500;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2064; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 2064; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 2064;

(f) a CDR1 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2595; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 2595; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 2595;

a CDR2 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2611; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 2611; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference with the amino acid sequence of SEQ ID NO: 2611;

a CDR3 comprising an amino acid selected from the group consisting of: 1. the amino acid sequence of SEQ ID NO: 2627; 2. amino acid sequences that have at least 80% amino acid identity with the amino acid sequence of SEQ ID NO: 2627; and 3. amino acid sequences that have 3, 2, or 1 amino acid difference the amino acid sequence of SEQ ID NO: 2627.

2. The polypeptide according to claim 1, wherein said amino acid sequence neutralizes RSV.

3. The polypeptide comprising one or more amino acid sequences according to claim 1, and optionally further comprising one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers.

4. The polypeptide according to claim 1, that comprises a domain antibody, a single domain antibody, a VHH sequence, a partially or fully humanized VHH sequence, a camelized VH sequence, or an immunoglobulin single variable domain.

5. A polypeptide according to claim 1, that comprises one or more amino acid sequences having at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, 126 to 407, 2431 to 2448, 2574 to 2581, 2682 to 2717 and 3064 to 3128 in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;

and in which:

optionally one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table B-2.

6. A polypeptide according to claim 1, that comprises one or more amino acid sequences selected from SEQ ID NO's: 159, 167, 181, 190, 193, 224, 354, 371, 372, and 2579 or of an amino acid sequence which has at least 80% amino acid identity, at least 90% amino acid identity, 95% amino acid identity, 99% amino acid identity, or 100% amino acid identity with the at least one of the amino acid sequences of SEQ ID NO's: 159, 167, 181, 190, 193, 224, 354, 371, 372, and 2579.

7. The polypeptide according to claim 1, comprising one or more amino acid sequences that comprise a partially or fully humanized VHH sequence.

8. The polypeptide according to claim 1, further comprising one or more other groups, residues, moieties or binding units selected from the group consisting of a domain antibody, a single domain antibody, a VHH sequence, a partially or fully humanized VHH sequence, a camelized VH sequence, or an immunoglobulin single variable domain.

9. The polypeptide according to claim 1, wherein the polypeptide comprises at least one amino acid sequence directed against a first antigenic determinant, epitope, part or domain of an F protein of RSV virus and at least one amino acid sequence directed against a second antigenic determinant, epitope, part or domain of the F protein of RSV virus different from the first antigenic determinant, epitope, part or domain.

10. The polypeptide according to claim 1, wherein the polypeptide comprises three amino acid sequences that bind the same antigenic determinant, epitope, part or domain of the F protein.

11. The polypeptide according to claim 1, wherein the polypeptide comprises two amino acid sequences that bind a first antigenic determinant, epitope, part or domain of the F protein and one amino acid sequence that binds a second antigenic determinant, epitope, part or domain of the F protein.

12. A polypeptide according to claim 1 that comprises an amino acid sequence from the

group consisting of SEQ ID NO's: 2408 to 2413, 2415, 2989 to 2994, 2996 to 2998, 3049 and 3584 to 3587 or from the group consisting of from amino acid sequences that have more than 80%, more than 90%, more than 95%, or 99% or more sequence identity with at least one of the amino acid sequences of SEQ ID NO's: 2408 to 2413, 2415, 2989 to 2994, 2996 to 2998, 3049 and 3584 to 3587.

13. A composition comprising at least one polypeptide according to claim 1.

14. A composition according to claim 13, further comprising at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and that optionally comprises one or more further pharmaceutically active polypeptides and/or compounds.

15. A pharmaceutical composition comprising a polypeptide according to claim 1 and a carrier suitable for pulmonary delivery.

16. A pharmaceutical device comprising an inhaler for liquids, an aerosol or a dry powder inhaler comprising the polypeptide according to claim 1.

17. The polypeptide according to claim 1, comprising:

(a) a CDR1 comprising the amino acid sequence of SEQ ID NO: 723, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1287; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1851;

(b) a CDR1 comprising the amino acid sequence of SEQ ID NO: 731, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1295; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1859;

(c) a CDR1 comprising the amino acid sequence of SEQ ID NO: 918, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1482; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 2046;

(d) a CDR1 comprising the amino acid sequence of SEQ ID NO: 935, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1499; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 2063;

(e) a CDR1 comprising the amino acid sequence of SEQ ID NO: 936, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1500; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 2064; or

(f) a CDR1 comprising the amino acid sequence of SEQ ID NO: 2595, a CDR2 comprising the amino acid sequence of SEQ ID NO: 2611; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 2627.

18. The polypeptide of claim 4, wherein the immunoglobulin single variable domain has been obtained by affinity maturation.

19. The polypeptide of claim 8, wherein the immunoglobulin single variable domain has been obtained by affinity maturation.

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Assignee: Ablynx N.V. (Zwijnaarde)
Inventors: Anna Hultberg (Vleuten), Bram Maassen (De Bilt), Peter Vanlandschoot (Bellem), Erik Depla (Destelbergen), Catelijne Stortelers (Ghent), Cornelis Theodorus Verrips (Besse sur Issole), Steven Van Gucht (Denderleeuw), Jose Melero (Madrid), Michael John Scott Saunders (Brussels), Johannes Joseph Wilhelmus De Haard (Oudelande), Robert Anthony Weiss (London), Nigel J. Temperton (Tonbridge), Xavier Saelens (Ypres), Bert Schepens (Drongen), Alexander Szyroki (Ghent), Michael Marie Harmsen (AM Weesp)
Primary Examiner: Shanon A Foley
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