

ANTIGEN BINDING PROTEINS

FIELD OF THE INVENTION

The invention is directed to an antigen binding protein that binds to the Human Immunodeficiency Virus (HIV) envelope and its use in treating or preventing HIV infection. The antigen binding protein of the invention binds to at least two different epitopes on the HIV envelope protein, in particular the V3 loop region (V3/glycan) and the CD4 binding site (CD4bs) of HIV envelope surface glycoprotein 120 (gp120).

BACKGROUND TO THE INVENTION

HIV, the virus that over time may result in Acquired Immunodeficiency Syndrome (AIDS), continues to be a serious public health challenge and has claimed 40.1 million lives so far. HIV attacks the body's immune system, targeting CD4-positive white blood cells, and leaves those infected vulnerable to opportunistic infections such as tuberculosis and fungal infections, severe bacterial infections and some cancers. Globally, 38.4 million people were living with HIV at the end of 2021, with 1.5 million people becoming newly infected (WHO, Key Facts HIV, July 2022).

Whilst there is currently no cure for HIV infection, it can be treated with antiretroviral therapy (ART), which includes a number of different types of drugs that prevent the virus from multiplying (nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors and integrase inhibitors), allowing the body's immune system to recover sufficiently for the infected patient to be asymptomatic. 75% of people living with HIV in 2021 received some form of ART. However, ART often requires taking medication every day for life and has the risk of serious and debilitating side effects. Further, increased use of ART has also been accompanied by the emergence of drug resistance, the levels of which have steadily increased in recent years.

Broadly neutralizing antibodies (bNAbs) could potentially provide longer-term HIV suppression, but individual bNAbs have only had limited success in previous studies. This is in part because antibody-resistant virus either already existed in the patient or emerged soon after treatment began (NIH Research Matters, 14 June 2022). Combinations of bNAbs are currently being investigated in the presence or absence of ART (Nature, 606, 368-374, 2022).

Further treatment options are needed for HIV infection, in particular drugs that are long-acting and effective against a wide spectrum of HIV strains so that patients taking them are less susceptible to drug resistance.

SUMMARY OF THE INVENTION

In a first aspect of the invention, an anti-HIV gp120-binding protein that binds to at least two different epitopes on human immunodeficiency virus (HIV) surface glycoprotein 120 (gp120) is provided.

5 In a second aspect of the invention, a bispecific anti-HIV gp120-binding protein comprising an anti-V3 bNAb and two copies of a CD4 domain is provided, wherein the C-terminus of one CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb heavy chains and the C-terminus of the other copy of the CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb heavy chain.

10 In another aspect of the invention, a bispecific molecule that binds to human immunodeficiency virus (HIV) glycoprotein gp120 and human CD4 is provided, wherein the bispecific molecule comprises: (i) a first antigen-binding domain comprising an anti-V3 bNAb; (ii) a second antigen-binding domain comprising a CD4 domain, and (iii) a third antigen-binding domain comprising a CD4 domain.

15 In a third aspect of the invention, an anti-HIV gp120-binding protein having two identical heavy chains and two identical light chains is provided, comprising or consisting of: a heavy chain that is at least 95% identical to SEQ ID NO:121 and a light chain that is at least 95% identical to SEQ ID NO:63.

In a fourth aspect of the invention, an anti-HIV gp120-binding protein consisting of two
20 identical heavy chains of SEQ ID NO:121 and two identical light chains of SEQ ID NO:63 is provided.

In a fifth aspect of the invention, an anti-HIV gp120-binding protein comprising or consisting of a sequence that is at least 95% identical to any one of SEQ ID NOs:152-157 is provided.

In a sixth aspect of the invention an anti-HIV gp120-binding protein consisting of SEQ ID NO:155 is provided.

25 In further aspects of the invention, pharmaceutical compositions comprising anti-HIV gp120-binding proteins of the invention, methods of preventing HIV infection and methods of treating HIV infection with anti-HIV gp120-binding proteins of the invention, uses of anti-HIV gp120-binding proteins of the invention, methods of manufacturing anti-HIV gp120-binding proteins of the invention and kits comprising anti-HIV gp120-binding proteins of the invention are also provided.

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DESCRIPTION OF DRAWINGS/FIGURES

FIG. 1 shows schematic designs of bispecific molecules of the invention. Human CD4 domains or variants thereof are fused, either directly or via linkers, to the N-termini of either the heavy chains (A), the light chains (B) or both chains (C) of anti-V3 bNAbs. Such designs facilitate

concomitant binding of the human CD4 domain of the bispecific molecule and the V3 glycan binding domain of the bispecific molecule to HIV-1 gp120 and prevent HIV-1 virions from binding to and fusing with the cell membrane (D).

FIG. 2 shows IC50 values (nM) of soluble CD4 domains (SEQ ID NOs:4-15) against a panel of HIV-1 envelopes in a PSV assay (ACTOne), together with the Tm for each soluble CD4 domain. The horizontal bars indicate geometric mean IC50.

FIG. 3 shows that linker length between the CD4 domain and bNAb1 heavy chain N-terminus does not particularly affect anti-viral activity in a PSV assay (ACTOne) (A) but does change the PK of the resultant bispecific molecules in a humanized mouse model (Tg32-hFcRn strain) (B). Thermal stability of the CD4 domain also affects the PK of the bispecific molecules (B).

FIG. 4 shows IC50 values (nM) of two bispecific molecules (SEQ ID NO:121 and SEQ ID NO:63; and SEQ ID NO:102 and SEQ ID NO:63) of the invention having a variant human CD4 domain (D1m-K8C-G99C, SEQ ID NO:11; and D1m, SEQ ID NO:4 respectively) fused to each of the heavy chain N-termini of bNAb1 via a GGGGS (1xG4S) (SEQ ID NO:90) linker, and control molecules, against a panel of HIV-1 envelopes in a PSV assay (ACTOne) (A) and a different panel of HIV-1 envelopes from bNAb1-resistant strains in a PSV assay (ACTOne) (B). Each dot represents one HIV envelope. The horizontal bars indicate geometric mean IC50.

FIG. 5 shows IC50 values (nM) of single ORF versions of the most potent bispecific format (*i.e.* fusing CD4 D1 to the N-terminus of bNAb1 heavy chain), also referred to as scFv-Fc molecules (SEQ ID NOs:152-157), in PSV assays (ACTOne cells). The horizontal bars indicate geometric mean IC50.

FIG. 6 shows IC50 values (nM) of two bispecific molecules (SEQ ID NO:151 and SEQ ID NO:89; and SEQ ID NO:150 and SEQ ID NO:89) of the invention having variant human CD4 domains (D1m, SEQ ID NO:4 and D1mD2, SEQ ID NO:2, respectively) fused to each of the heavy chain N-termini of bNAb6 (SEQ ID NO:88 and 89) via a 4xG4S linker (SEQ ID NO:93), and control molecules, against a panel of HIV-1 envelopes in a PSV assay (ACTOne). Each dot represents one HIV envelope. The horizontal bars indicate geometric mean IC50.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

"Affinity", also referred to as "binding affinity", is the strength of binding at a single interaction site, *i.e.*, of one molecule, *e.g.*, an antigen binding protein, to another molecule, *e.g.*, its target antigen, at a single binding site. The binding affinity of an antigen binding protein to its target

may be determined by equilibrium methods (*e.g.*, enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (*e.g.*, BIAcore analysis).

5 **"Alternative antibody formats"** include alternative scaffolds in which one or more CDRs of the antigen binding protein can be arranged onto a suitable non-immunoglobulin protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an avimer (see, *e.g.*, U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301) or an EGF domain.

10 **"Antibody"** is used herein to refer to a heterotetrameric glycoprotein with an approximate molecular weight of 150,000 daltons. An intact antibody is composed of two identical heavy chains (HCs) and two identical light chains (LCs) linked by covalent disulphide bonds. This H2L2 structure folds to form a 'Y' shape with three functional domains comprising two antigen-binding fragments, known as 'Fab' fragments (the 'top' of the 'Y'), and a fragment crystallisable 'Fc' (the 'bottom' of the 'Y'). The Fab fragment is composed of the variable domain at the amino-terminus, variable heavy (VH) or variable light (VL), and the constant domain at the carboxyl terminus, CH1 (heavy) and CL (light). The Fc fragment is composed of two domains formed by dimerization of paired CH2 and CH3 regions. The Fc may elicit effector functions by binding to receptors on immune cells or by binding C1q, the first component of the classical complement pathway. The five classes of antibodies IgM, IgA, IgG, IgE and IgD are defined by distinct heavy chain amino acid sequences, which are called μ , α , γ , ϵ and δ respectively; each heavy chain can pair with either a K or λ light chain. The majority of antibodies in the serum belong to the IgG class, there are four isotypes of human IgG (IgG1, IgG2, IgG3 and IgG4), the sequences of which differ mainly in their hinge region. In an embodiment, an anti-CD4bs antibody, as used herein, refers to an antibody that binds to a CD4 binding site

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25 **"Antigen binding antibody fragments" or "antigen binding fragments" or "antibody fragments"** as used herein include Fab, F(ab')₂, Fv, disulphide linked Fv, single chain Fv (scFv), disulphide-linked scFv, diabodies, TANDABS, *etc.* and modified versions of any of the foregoing (for a summary of alternative "antibody" formats see Holliger and Hudson, Nature Biotechnology, 23(9), 1126-1136, 2005).

30 **"Antigen binding protein" and "anti-gp120 binding protein"** are used interchangeably herein and refer to antibodies and fragments thereof, alternative antibody formats, and other protein constructs, such as domains, that are capable of binding to HIV gp120. Envelope glycoprotein gp120 (or gp120) is a 120 kDa glycoprotein that is part of the outer layer of HIV. It presents itself as viral membrane spikes consisting of three molecules of gp120 linked together and anchored to the membrane by gp41 protein. Gp120 is essential for viral infection as it facilitates HIV entry into the host cell through its interaction with cell surface receptors. Gp120 is encoded by the

HIV env gene. The env gene encodes a gene product of around 850 amino acids. The primary env product is the protein gp160, which gets cleaved into gp120 (about 480 amino acids) and gp41 (about 345 amino acids) in the endoplasmic reticulum by the cellular protease furin. The amino acid sequence of an exemplary gp160 from HIV clone WITO is provided below (SEQ ID NO: 363; the V3 loop is boldened and the potential N332 N-linked glycosylation site is boldened and underlined):

10 MKVMGTTKKNYQHLWRWGIMLLGMLMMSSAAEQLWVTVYVGVPVWREANTTLFCASDAKAYDTEVHNWVWAT
HACVPTDPNPQEVMGNVTEDFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLHCTNVTISSTNGSTA
NVTMREEMKNCSFNNTTIVIRDKIQKEYALFYKLDIVPIEGKNTNTSYRLINCNTSVITQACPKVSFEPIPIHYCAPA
15 GFAILKCNKTFNGKGPCRNVSTVQCTHGIKPVVSTQLLNGSLAEEDIIIRSENFTNNGKNIIVQLKEPVKIN**CT**
RPGNNTRRSINIGPGRFYATGAIIGDIRKAHCNISTEQWNNLTQIVDKLREQFGNKTIIFNQSSGGDP
EVMHTFNCGGEFFYCNSTQLFNSTWFNNGTSTWNSTADNITLPCRIKQVINMWQEVGKAMYAPPIRGQIDCS
SNITGLILTRDGGSNSSQNETFRPGGGMKDNWRSELYKYKVVKIEPLGIAPTRAKRRVVQREKRAVTLGAVFLG
FLGAAGSTMGAASLTTLVQARLLLSGIVQQQSNLLRAIEAQQHMLQLTVWGKQLQARVLAIERYLKDQQLLGI
15 WGCSGKLICTTTVPWNTSWSNKSVDYIWNMTWMQWEREIDNYTGFIYTLIEESQNNQKEKNELELLELDKWA
SLWNWFNITNWLWYIKLFIMIIGGLVGLRIVCAVLSIVNRVRQGYSPLSFQTRLNPNRGPDRPEETEGEGGERDR
DRSARLVNGFLAIWDDLRLSLCLFSYHRLRDLILLIVARVVEILGRRGWEILKYWWNLLKYWSQELKNSAVSLLNV
TAIAVAEGTDRVIEIVQRAVRILHIPTRIRQGFERALL

The amino acid of an exemplary gp120 is provided below (SEQ ID NO: 364; the V3 loop is boldened and the potential N332 N-linked glycosylation site is boldened and underlined):

25 AEQLWVIVYVGVPVWREANTTLFCASDAKAYDTEVHNWVWATHACVPTDPNPQEVMGNVTEDFNMWKNMVE
EQMHEDIISLWDQSLKPCVKLTPLCVTLHCTNVTISSTNGSTANVTMREEMKNCSFNNTTIVIRDKIQKEYALFYK
LDIVPIEGKNTNTSYRLINCNTSVITQACPKVSFEPIPIHYCAPAGFAILKCNKTFNGKGPCRNVSTVQCTHGIKPV
VSTQLLNGSLAEEDIIIRSENFTNNGKNIIVQLKEPVKIN**CTRPGNNTRRSINIGPGRFYATGAIIGDIR**
KAHCNISTEQWNNLTQIVDKLREQFGNKTIIFNQSSGGDPVVMHTFNCGGEFFYCNSTQLFNSTWFNNGTS
TWNSTADNITLPCRIKQVINMWQEVGKAMYAPPIRGQIDCSSNITGLILTRDGGSNSSQNETFRPGGGMKDN
WRSELYKYKVVKIEPLGIAPTRAKRRVVQREKR

30 **"Antigen binding site"** and **"paratope"** are used interchangeably herein and refer to a particular site on an antigen binding protein that makes contact with and is capable of specifically binding to a site (*i.e.*, epitope) on an antigen, *e.g.*, HIV gp120. The antigen binding site may be formed by a single variable domain, or paired VH/VL domains as can be found on a standard antibody. Single-chain Fv (ScFv) domains can also provide antigen binding sites.

35 **"Avidity"** also referred to as functional affinity, is the cumulative strength of binding at multiple interaction sites, *e.g.*, the sum total of the strength of binding of two molecules (or more) to one another at multiple sites, *e.g.*, taking into account the valency of the interaction.

A **"bispecific molecule"** as used herein is an antigen binding protein that is capable of binding to two different epitopes on the same antigen, *i.e.*, HIV gp120 protein. In particular, one

epitope comprises part of or the whole of the V3 loop region of gp120 and the other epitope comprises part of or the whole of the CD4 binding site of gp120.

5 **"Broadly neutralizing antibody"** or **"bNAb"** as used herein, is meant an antibody that neutralizes more than one HIV-1 virus species (from diverse clades and different strains within a clade) in a neutralization assay. A broad neutralizing antibody may neutralize at least 2, 3, 4, 5, 6, 7, 8, 9 or more different strains of HIV-1, the strains belonging to the same or different clades.

10 **"CD4 binding site" or "CD4-binding site" or "CD4bs"** refers to a site on the HIV envelope protein gp120 that binds to CD4. (Cluster of differentiation factor 4). CD4 is a T-cell surface protein that serves as the primary receptor site for HIV during HIV infection. The CD4 binding site on gp120 is a highly conserved, discontinuous and conformational that comprises residues on either side of the HIV V4 loop (Curr HIV/AIDS Rep, 9(1): 52-63, 2021) that binds to CD4.

15 A **"CD4 domain"** as used herein is a soluble recombinant form of human CD4 (Cluster of differentiation factor 4, a transmembrane glycoprotein found on T-cells), or a fragment thereof, that mimics the activity of native membrane-anchored human CD4 in its binding interactions with the HIV envelope protein. A CD4 domain of the present invention binds to the CD4-binding site of HIV gp120 and may block the ability of HIV gp120 to bind membrane-anchored CD4, *e.g.*, on CD4+ T cells. A CD4 domain of the invention may induce a structural rearrangement in gp120 upon binding, including a structural rearrangement of part or all of the V3 region of gp120. This structural rearrangement in gp120 results in a high affinity binding site for a chemokine coreceptor (CXCR4 and/or CCR5) being exposed. Native CD4 comprises four domains that are exposed on the extracellular surface of the cell, D1, D2, D3 and D4; a transmembrane domain; and a cytoplasmic tail domain. D1 and D3 resemble Ig variable domains and D2 and D4 resemble Ig constant domains. CD4 domains of the invention include one or more of domains D1 to D4 of CD4, or variants thereof.

20 Examples of CD4 domains of the invention include wild-type D1 (SEQ ID NO:3); "mD1.22" (SEQ ID NO:4), which is a variant of D1 of CD4 (Chen *et al*, JVI 88(2): 1125-39, 2014); wild-type D1D2 (SEQ ID NO:1); "mD1.22-D2" (SEQ ID NO:2), which is a variant of D1D2 (Fetzer *et al*, Journal of Virology, 92(12), 2018); and further variants of mD1.22 (SEQ ID NOs:5-21).

30 **"CDRs"** are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. In one embodiment, the CDRs are defined based on the Kabat definition. In another embodiment, the CDRs are defined based on the Chothia definition. In a further embodiment, the Chothia definition is from Discovery Studio which uses the definitions from

Chothia and Lesk, J Mol Biol. 196(4):901-17 (1987) and Morea et al, Methods, 20:267-279 (2000). In another embodiment, the Chothia definition is based on the Chothia from Abysis definition. In a further embodiment, the CDRs are defined based on the IMGT definition. In another embodiment, the CDRs are defined based on the Honegger definition. In another embodiment, the CDRs are defined based on the contact definition. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

"Domain" refers to a folded polypeptide structure that retains its tertiary structure independent of the rest of the polypeptide. Generally, domains are responsible for discrete functional properties of polypeptides and in many cases may be added, removed or transferred to other polypeptides without loss of function of the remainder of the protein and/or of the domain.

"Effector Function" as used herein refers to one or more of antibody-mediated effects including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-mediated complement activation including complement-dependent cytotoxicity (CDC), complement-dependent cell-mediated phagocytosis (CDCP), antibody dependent complement-mediated cell lysis (ADCML), and Fc-mediated phagocytosis or antibody-dependent cellular phagocytosis (ADCP).

"Epitope" as used herein refers to the portion of an antigen (*e.g.*, gp120) that makes contact with and is capable of specifically binding to a particular site (paratope) on an antigen binding protein. An epitope may be linear or conformational/discontinuous. A conformational/discontinuous epitope comprises amino acid residues that are separated by other sequences, *i.e.*, it does not comprise a continuous sequence in the antigen's primary amino acid sequence, but instead relies on the tertiary folding of the polypeptide. Although the residues within a conformational/discontinuous epitope may be from different regions of the polypeptide chain, they are in close proximity in the three-dimensional structure of the antigen.

In the case of multimeric antigens, a conformational or discontinuous epitope may include residues from different polypeptide chains. Particular residues comprised within an epitope can be determined through computer modelling programs or via three-dimensional structures obtained through methods known in the art, such as X-ray crystallography.

Epitope mapping can be carried out using various techniques known to persons skilled in the art as described in publications such as Methods in Molecular Biology 'Epitope Mapping Protocols', by Mike Schutkowski and Ulrich Reineke (volume 524, 2009) and Johan Rockberg and Johan Nilvebrant (volume 1785, 2018). Exemplary methods include peptide-based approaches such as pepscan whereby a series of overlapping peptides are screened for binding using techniques such as ELISA or by in vitro display of large libraries of peptides or protein mutants, *e.g.*, on phage. Detailed epitope information can be determined by structural techniques including X-ray crystallography,

solution nuclear magnetic resonance (NMR) spectroscopy and cryogenic-electron microscopy (cryo-EM). Mutagenesis, such as alanine scanning, is an effective approach whereby loss of binding analysis is used for epitope mapping. Another method is hydrogen/deuterium exchange (HDX) combined with proteolysis and liquid-chromatography mass spectrometry (LC-MS) analysis to
5 characterize discontinuous or conformational epitopes.

"Half-life" or **" $t_{1/2}$ "** refers to the time required for the serum concentration of an antigen binding protein to reach half of its original value. The serum half-life of proteins can be measured by pharmacokinetic studies according to the method described by Kim *et al.*, 1994, Eur. J. of Immuno.
24: 542-548. According to this method, radio-labelled protein is injected intravenously into mice and
10 its plasma concentration is periodically measured as a function of time, for example, at about 3 minutes to about 72 hours after the injection. Other methods for pharmacokinetic analysis and determination of the half-life of a molecule will be familiar to those skilled in the art.

"HIV envelope protein" or **"ENV"** refers to a trimeric viral membrane-associated glycoprotein (gp) or 'spike'. It is found on both the viral membrane and the cell membrane of
15 infected host cells. The *env* gene encodes the gp160 polypeptide which forms a homotrimer and is cleaved into gp120 and gp41 polypeptides. Gp120 is a surface (SU) glycoprotein responsible for binding to receptor molecules and the transmembrane (TM) glycoprotein, gp41, mediates fusion of the viral membrane with the plasma cell membrane. Over half of the mass of the trimeric envelope 'spike' is an N-linked glycan shield that hides most amino acid-based epitopes on gp120. Binding of
20 the cell surface receptor CD4 to HIV gp120 induces a structural rearrangement creating a high affinity binding site for a chemokine coreceptor (CXCR4 and/or CCR5), on gp120. Following gp120 binding to CXCR4 or CCR5 further conformational changes are triggered which results in gp120 disengaging from gp41, allowing for the fusion peptide of gp41 to be inserted into the cell membrane, which in turn triggers a sequence of structural changes resulting in membrane fusion
25 (Dimitrov *et al.*, Biochemistry 44(37): 12471-12479, 2005).

"Human immunodeficiency virus (HIV)" has been characterized into two types: HIV-1 and HIV-2. HIV-1 is more virulent and more infective than HIV-2 and is the cause of the majority of HIV infections globally, whereas HIV-2 is limited to a much smaller number of people, mostly in West Africa (Gilbert *et al.*, Statistics in Medicine 22(4): 573-593). Herein, when reference is made to
30 "HIV" this is intended to mean "HIV-1". HIV virions are spherical with viral glycoprotein "spikes", the HIV envelope protein, protruding outwards. A conical capsid exists within the virion, enclosing a ribonucleoprotein complex comprising two copies of positive-sense single stranded RNA tightly bound to nucleocapsid proteins and enzymes needed for viral replication.

A **"linker"** is an amino acid sequence that links one domain in a polypeptide to another domain in a polypeptide. For example, a linker within the meaning of the invention includes an amino acid sequence that joins a CD4 domain to a bNAb heavy chain or a bNAb light chain. In an embodiment, the linker is not cleavable under intracellular conditions.

5 **"Multi-specific antigen binding protein"** or **"MSABP"** refers to an antigen binding protein that comprises at least two different antigen binding sites. Each of these antigen-binding sites is capable of binding to a different epitope, which may be present on the same antigen or different antigens. In an embodiment, the multi-specific antigen binding proteins of the invention are bispecific molecules capable of binding to two different epitopes on the HIV envelope protein. In
10 particular, one epitope may comprise part of or the whole of the V3 loop region of gp120 and the other epitope may comprise part of or the whole of the CD4 binding site of gp120.

Symmetric formats of MSABPs combine multiple binding specificities in a single polypeptide chain or single HL pair including Fc-fusion proteins of fragment-based formats and formats whereby antibody fragments are fused to regular antibody molecules. Examples of symmetric formats may
15 include DVD-Ig, TVD-Ig, CODV-Ig, (scFv)₄-Fc, IgG-(scFv)₂, Tetravalent DART-Fc, F(ab)₄CrossMab, IgG-HC-scFv, IgG-LC-scFv, mAb-dAb *etc.*

"Neutralizes" as used throughout the present specification means that the biological activity of HIV is reduced in the presence of an antigen binding protein as described herein in comparison to the biological activity of HIV in the absence of the antigen binding protein, *in vitro* or
20 *in vivo*. For example, a neutralizing antigen binding protein of the invention may inhibit HIV entry into a target cell and reduce viral load in a patient infected with HIV.

"Percent identity" or **"% identity"** between a query amino acid sequence and a subject amino acid sequence is the "Identities" value, expressed as a percentage, that is calculated using a suitable algorithm (*e.g.*, BLASTP, FASTA, Needleman-Wunsch, Smith-Waterman, LALIGN, or
25 GenePAST/KERR) or software (*e.g.*, DNASTAR Lasergene, GenomeQuest, EMBOSS needle or EMBOSS infoalign), over the entire length of the query sequence after a pair-wise global sequence alignment has been performed using a suitable algorithm (*e.g.*, Needleman-Wunsch or GenePAST/KERR) or software (*e.g.* DNASTAR Lasergene or GenePAST/KERR). Importantly, a query amino acid sequence may be described by an amino acid sequence disclosed herein, in particular in
30 one or more of the claims.

The query sequence may be 100% identical to the subject sequence, or it may include up to a certain integer number of amino acid alterations as compared to the subject sequence such that the % identity is less than 100%. For example, the query sequence is at least 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical to the subject sequence. In the case of amino acid sequences,

such alterations include at least one amino acid residue deletion, substitution (including conservative and non-conservative substitutions), or insertion, wherein said alterations may occur at the amino- or carboxy-terminal positions of the query sequence or anywhere between those terminal positions, interspersed either individually among the amino acid residues in the query sequence or in one or more contiguous groups within the query sequence.

For antibody sequences, the % identity may be determined across the entire length of the query sequence, including the CDRs. Alternatively, the % identity may exclude one or more or all of the CDRs, for example all of the CDRs are 100% identical to the subject sequence and the % identity variation is in the remaining portion of the query sequence, *e.g.*, the framework sequence, so that the CDR sequences are fixed and intact.

"Protein scaffold" as used herein includes, but is not limited to, an immunoglobulin (Ig) scaffold, for example an IgG scaffold, which may be a four chain or two chain antibody, or which may comprise only the Fc region of an antibody, or which may comprise one or more constant regions from an antibody, which constant regions may be of human origin.

The protein scaffold may be an Ig scaffold, for example an IgG, or IgA scaffold. The IgG scaffold may comprise some or all the domains of an intact antibody (*i.e.*, CH1, CH2, CH3, VH, VL). The antigen binding protein may comprise an IgG scaffold selected from IgG1, IgG2, IgG3, IgG4 or IgG4PE. For example, the scaffold may be IgG1. The scaffold may consist of, or comprise, the Fc region of an antibody, or is a part thereof.

The protein scaffold may be a non-Ig scaffold. The protein scaffold may be a derivative of a scaffold selected from the group consisting of CTLA-4, lipocalin, Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); heat shock proteins such as GroEl and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin kunitz type domains of human protease inhibitors; and fibronectin/adnectin; which has been subjected to protein engineering in order to obtain binding to an antigen, such as gp120.

"Single variable domain" refers to a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains such as VH, VHH and VL and modified antibody variable domains, for example, in which one or more loops have been replaced by sequences that are not characteristic of antibody variable domains, or antibody variable domains that have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains that retain at least the binding activity and specificity of the full-length domain. A single variable domain as defined herein is capable of binding an antigen or epitope independently of a different variable region or domain. A "domain

antibody" or "DAB" may be considered the same as a human "single variable domain". A single variable domain may be a human single variable domain, but also includes single variable domains from other species such as rodent (for example, as disclosed in WO 00/29004), nurse shark and Camelid VHHs. Camelid VHHs are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain only antibodies naturally devoid of light chains. Such VHH domains may be humanised according to standard techniques available in the art, and such domains are considered to be "single variable domains".

"Stabilizing mutation" refers to a change of an amino acid residue in a polypeptide sequence that increases the thermal thermostability of said polypeptide. Increased thermostability may be reflected in a melting temperature (T_m) increase of, for example, between 1 and 50 °C. CD4 domains with stabilizing mutations include SEQ ID NOs:5-21.

A **"variant sequence"** substantially retains the biological characteristics of the unmodified protein. In the case of an antibody sequence disclosed herein, the VH or VL (or HC or LC) sequence may be a variant sequence with up to 10 amino acid substitutions, additions or deletions. For example, the variant sequence may have up to 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitution(s), addition(s) or deletion(s). The sequence variation may exclude one or more or all of the CDRs, for example the CDRs are the same as the VH or VL (or HC or LC) sequence and the variation is in the remaining portion of the VH or VL (or HC or LC) sequence, so that the CDR sequences are fixed and intact.

"V3 loop region", "V3/glycan" or "V3" as used herein refers to the third variable region (V3) of HIV gp120. Comparison of predicted amino acid sequences from several different isolates has shown that sequence heterogeneity of gp120 is clustered in five variable regions (designated V1, V2, V3, V4, and V5.) The V3 region contains post-translational modifications, such as glycosylation, and is essential for viral infectivity. The V3 region, although only 35 amino acids long, exhibits considerable sequence variability. Additionally, variability in potential N-linked glycosylation sites allow for further variability in the variable regions of gp120. Together, the V3 region and the N-linked glycosylation sites within and adjacent to the region are understood to comprise the "V3 loop region," "V3/glycan" or "V3" as used herein. For example, one site of glycosylation (e.g., oligomannose such as Man-5 to Man-9) is centered on amino acid residue N332 of gp120. Other sites of potential N-linked glycosylation within and adjacent to the V3 loop region include K295, N301, N386, N392 of gp120. The V3 loop is generally considered to be in the region between cysteine residues C296 and C331 of gp120, while some N-linked glycosylation sites are located directly adjacent to the V3 loop. The V3 loop comprises a highly conserved tetrapeptide sequence,

GPGR (residues 312 to 315) (Ivanhoff *et al.*, Virology, 187(2) 1992). HIV-1 cellular entry depends on the interaction of the V3 loop region with an HIV co-receptor, commonly CCR5 or CXCR4. The V3 loop comprises: (i) the base (residues 296–299), (ii) the stem (residues 300–303 and 321–326), and (iii) the crown (residues 304–320) (Friedrich *et al.*, Nature Communications 12, 6705 (2021)). A consensus sequence of the V3 region of gp120 (Milich *et al.*, *J Virol.*, 67(9):5623-5634 (1993)) is provided below:

CTRPNNNTRKSIHIGPGRAFYTTGEIIGDIRQAHC (SEQ ID NO: 361)

It is understood that the consensus sequence describes the highest frequency of residues emerging on each position of this region across multiple subtypes, but that the V3 loop region of a particular strain may exhibit sequence variability.

A **"V3-bNAb"** or **"anti-V3 bNAb"** is a bNAb that binds within the V3 loop region. A V3-bNAb may also be referred to herein as an anti-V3 antibody. A V3-bNAb may bind the N332 glycan in the V3 loop region and/or other N-linked glycosylation sites within and adjacent to the V3 loop region.

STATEMENT OF THE INVENTION

An antigen binding protein of the invention binds to the Human Immunodeficiency Virus (HIV) envelope protein. In particular, the antigen binding protein binds to HIV envelope surface glycoprotein 120 (gp120) and is, therefore, also referred to herein as an anti-gp120 binding protein. The anti-gp120 binding protein of the invention binds to at least two different epitopes on gp120, including the V3 loop region (V3) and the CD4 binding site (CD4bs) of gp120.

Bispecific molecules of the invention that bind to the V3 loop region and the CD4bs of gp120 have been shown to effectively neutralize HIV and exhibit significantly better anti-viral activity than monospecific molecules that only bind to the V3 loop region or the CD4bs of gp120, and mixtures of these monospecific molecules. Without being bound by any particular theory, we postulate that the bispecific molecules of the invention bind the two different epitopes in the same or neighboring HIV envelope protein trimers at the same time, such that the bispecific molecules achieve stronger binding (increased avidity) to the HIV envelope proteins. This may be as a result of the high local concentration of the bispecific molecules' binding sites (paratopes) being "pre-positioned" around their target binding sites (epitopes) on the HIV envelope compared to their monospecific counterparts, which in turn leads to stronger anti-viral activity.

Binding to the CD4 binding site (CD4bs) of HIV gp120

The antigen binding protein of the invention comprises one or more paratopes that bind to the

CD4bs of HIV gp120. Binding domains comprising such paratopes may be include by CD4 domains, as well as other anti-CD4bs domains, including those of anti-CD4bs antibodies and CD4bs-binding fragments thereof. Non-Ig constructs that bind to CD4bs are also part of the invention, such as single chain variable fragments (scFvs). In particular, non-Ig constructs such as scFv comprising one
5 or more CDRs, preferably the three light chain CDRs or the three heavy chain CDRs, or a set of six CDRs of such anti-CD4bs antibodies are also part of the invention.

In an embodiment of the invention, the antigen binding protein of the invention comprises an anti-CD4bs antibody or CD4bs-binding fragment thereof, wherein such antibody or fragment thereof comprises a paratope that binds to the CD4bs of HIV gp120. In a further embodiment, the
10 anti-CD4bs antibody is selected from the group consisting of: b12, HJ16, CH103-106, VRCO1-03, VRC-PG04, VRC-PG04b, VRC-CH30-34, 3BNC117, 3BNC60, NIH45-46, 12A12, 12A21, 8ANC131, 8ANC134, 1NC9, and 1B2530.

In an alternative or additional embodiment of the invention, a paratope that binds to the CD4bs of HIV gp120 is formed by a polypeptide domain that binds to the CD4bs of HIV gp120. In a
15 more particular embodiment, the polypeptide domain is a CD4 domain.

CD4 Domains

CD4 domains of the invention include SEQ ID NOs:1-21.

In an embodiment of the invention, the CD4 domain is a CD4 D1 domain. In an embodiment, the CD4 domain is a human CD4 domain. CD4 D1 domains include human wild-type
20 D1 (SEQ ID NO:3), mD1.22 (SEQ ID NO:4) also known as D1m, and further variants of mD1.22 (SEQ ID NOs:5-21).

In an embodiment of the invention, the CD4 domain is a CD4 D1D2 domain. In an embodiment, the CD4 domain is a human CD4 D1D2 domain. CD4 D1D2 domains include human wild-type D1D2 (SEQ ID NO:1) and mD1.22-D2 (SEQ ID NO:2).

25 In an aspect of the invention, a stabilized CD4 domain is provided. In an embodiment of the invention, a stabilized CD4 D1 domain is provided. In an embodiment, the CD4 domain is thermally stable, *i.e.*, thermostable. In an embodiment, the CD4 domain is a thermostable CD4 D1 domain.

In an embodiment of the invention, the CD4 domain comprises one or more stabilizing mutations. In an embodiment, the stabilizing mutations are in the CD4 D1 domain. In an
30 embodiment, the CD4 D1 domain comprises one or more mutations selected from the group consisting of: K8C, K8I, K8V, T11C, E13C, K21C, Q25E, H27C, H27D, G38C, N52W, R58N, R58T, R58V, L61M, G65C, I70C, K72C, E87G, E91H, E91Q, and G99C. In an embodiment, the CD4 D1 domain comprises K8I. In an embodiment, the CD4 D1 domain comprises K8V. In an embodiment,

the CD4 D1 domain comprises T1C and K72C. In an embodiment, the CD4 D1 domain comprises K8C and G99C.

CD4 domains of the invention comprising novel and inventive stabilizing mutations include SEQ ID NOS:5-21.

5 Increased thermostability may be reflected in a melting temperature (T_m) increase of, for example, between 1 and 50 °C; in particular between 1 and 30 °C; in particular between 1 and 25 °C, in particular between 1 and 21 °C, more particularly between 5 and 21 °C. The T_m increase is determined by measuring the T_m of the CD4 domain(s) comprising one or more stabilizing mutations and subtracting the T_m of the corresponding CD4 domain(s) without said mutation(s). For
10 example, measuring the T_m of a stabilized CD4 D1 domain and subtracting the T_m of the wild-type CD4 D1 domain. In an embodiment, the T_m increase is about 8 °C. In an embodiment, the T_m increase is about 9 °C. In an embodiment, the T_m increase is about 12 °C. In an embodiment, the T_m increase is about 21 °C.

In an embodiment, the T_m of the CD4 domain is above 70 °C. In an embodiment, the T_m of
15 the CD4 domain is between 70 °C and 95 °C. In an embodiment, the T_m of the CD4 domain is between 75 °C and 95 °C. In an embodiment, the T_m of the CD4 domain is between 75 °C and 91 °C. In an embodiment, the T_m of the CD4 domain is about 76 °C, about 77 °C, about 78 °C, about 79 °C, about 80 °C, about 81 °C, about 82 °C, about 83 °C, about 84 °C, about 85 °C, about 86 °C, about 87 °C, about 88 °C, about 89 °C, or about 90 °C. In an embodiment, the T_m of the
20 CD4 domain is about 90 °C. In an embodiment, the T_m of the CD4 domain is about 89 °C.

T_m may be determined by routine methods known in the art or as set out in the Examples. In an embodiment, T_m is determined using the Prometheus System (NanoTemper, München Germany).

Binding to the V3 loop region of HIV gp120

25 The antigen binding protein of the invention comprises one or more paratopes that bind to the V3 loop region of HIV gp120. Binding domains comprising such paratopes include an anti-V3 bNAb or a V3-binding fragment thereof, as well as a non-Ig construct that binds to V3.

An antigen binding protein of the invention may comprise heavy chain CDRs (CDRH1, CDRH2, and CDRH3) as set out in any row of Table 1. An antigen binding protein of the invention
30 may comprise light chain CDRs (CDRL1, CDRL2, and CDRL3) as set out in any row of Table 1. An antigen binding protein of the invention may comprise a set of six CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set out in any row of Table 1.

An antigen binding protein of the invention may comprise heavy chain CDRs (CDRH1, CDRH2, and CDRH3) of any one of PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-

1074LS, PGT121.414.LS and 2G12. An antigen binding protein of the invention may comprise light chain CDRs (CDRL1, CDRL2, and CDRL3) of any one of PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12. An antigen binding protein of the invention may comprise a set of six CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) of any one of PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12.

An antigen binding protein of the invention may comprise a VH domain as set out in Table 2. An antigen binding protein of the invention may comprise a VL domain as set out in Table 2. An antigen binding protein of the invention may comprise a pair of variable domains (a VH and a VL) as set out in any row of Table 2.

Anti-V3 bNAbs

An antigen binding protein of the invention may comprise an anti-V3 bNAb or a V3-binding fragment thereof. An anti-V3 antibody includes an antibody comprising a set of CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set out in any row of Table 1.

Table 1: SEQ ID NOs for the complementarity determining regions (CDRs) of broadly neutralizing antibodies (bNAbs) 1-6

	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
bNAb1	22	23	24	25	26	27
bNAb2	28	29	30	31	32	33
bNAb3	34	35	36	37	38	39
bNAb4	40	41	42	43	44	45
bNAb5	46	47	48	49	50	51
bNAb6	52	53	54	55	56	57
bNAb7	159	160	161	162	163	164
bNAb8	165	166	167	168	169	170
bNAb9	171	172	173	174	175	176
bNAb10	177	178	179	180	181	182
bNAb 11	183	184	185	186	187	188
bNAb 12	189	190	191	192	193	194
bNAb13	195	196	197	198	199	200
bNAb14	201	202	203	204	205	206
bNAb15	207	208	209	210	211	212

bNAb16	213	214	215	216	217	218
bNAb17	219	220	221	222	223	224
bNAb18	225	226	227	228	229	230
bNAb19	231	232	233	234	235	236
bNAb20	237	238	239	240	241	242
bNAb21	243	244	245	246	247	248
bNAb23	249	250	251	252	253	254

In a particular embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises the CDRs of bNAb1. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a CDRH1 of SEQ ID NO:22, a CDRH2 of SEQ ID NO:23, a CDRH3 of SEQ ID NO:24, a CDRL1 of SEQ ID NO:25, a CDRL2 of SEQ ID NO:26 and a CDRL3 of SEQ ID NO:27.

An anti-V3 bNAb may be an antibody comprising a pair of variable domains (a VH and a VL) as set out in any row of Table 2.

An anti-V3 bNAb may be an antibody comprising a heavy chain (HC), with or without M428L/N434S (EU numbering) 'LS' mutations, and a light chain (LC) as set out in any row of Table 2. In an embodiment, the HC comprises LS. [#TH to add additional sequences]

Table 2: SEQ ID NOs for the variable regions (VH and VL) and the heavy chains (HC) and light chains (LC) of bNAbs 1-6. 'LS' refers to M428L/N434S (EU numbering) mutations in the Fc portion of the bNAb.

	VH	VL	HC without 'LS'	HC with 'LS'	LC
bNAb1	58	59	61	62	63
bNAb1*		60*			64*
bNAb2	65	66	67	68	69
bNAb3	70	71	72	73	74
bNAb4	75	76	77	78	79
bNAb5	80	81	82	83	84
bNAb6	85	86	87	88	89
bNAb7	255	256	257	258	259
bNAb8	260	261	262	263	264
bNAb9	265	266	267	268	269
bNAb10	270	271	272	273	274
bNAb11	275	276	277	278	279

bNAb12	280	281	282	283	284
bNAb13	285	286	287	288	289
bNAb14	290	291	292	293	294
bNAb15	295	296	297	298	299
bNAb16	300	301	302	303	304
bNAb17	305	306	307	308	309
bNAb18	310	311	312	313	314
bNAb19	315	316	317	318	319
bNAb20	320	321	322	323	324
bNAb21	325	326	327	328	329
bNAb22 [#]	330		331	332	
bNAb 23	334	335	336	337	338

* a light chain variant with F32Y in the VL and LC

a heavy chain variant with {~TC to inserts definition}

- 5 In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59 or 60. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:65 and a VL domain of SEQ ID NO:66. In an embodiment, the
- 10 anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:70 and a VL domain of SEQ ID NO:71. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:75 and a VL domain of SEQ ID NO:76. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:80 and a VL domain of SEQ ID NO:81. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof,
- 15 comprises a VH domain of SEQ ID NO:85 and a VL domain of SEQ ID NO:86. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:225 and a VL domain of SEQ ID NO:226. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:260 and a VL domain of SEQ ID NO:261. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ
- 20 ID NO:265 and a VL domain of SEQ ID NO:266. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:270 and a VL domain of SEQ ID NO:271. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH

domain of SEQ ID NO:275 and a VL domain of SEQ ID NO:276. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:280 and a VL domain of SEQ ID NO:281. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:285 and a VL domain of SEQ ID NO:286. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:290 and a VL domain of SEQ ID NO:291. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:295 and a VL domain of SEQ ID NO:296. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:300 and a VL domain of SEQ ID NO:301. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:305 and a VL domain of SEQ ID NO:306. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:310 and a VL domain of SEQ ID NO:311. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:320 and a VL domain of SEQ ID NO:321. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:225 or SEQ ID NO:330 and a VL domain of SEQ ID NO:326. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises a VH domain of SEQ ID NO:334 and a VL domain of SEQ ID NO:335.

In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:61 or 62 and a LC of SEQ ID NO:63 or 64. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:62 and a LC of SEQ ID NO:63. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:67 or 68 and a LC of SEQ ID NO:69. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:72 or 73 and a LC of SEQ ID NO:74. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:77 or 78 and a LC of SEQ ID NO:79. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:82 or 83 and a LC of SEQ ID NO:84. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:87 or 88 and a LC of SEQ ID NO:89. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:257 or 258 and a LC of SEQ ID NO:259. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:262 or 263 and a LC of SEQ ID NO:264. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:267 or 268 and a LC of SEQ ID NO:269. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:272 or 273 and a LC of SEQ ID NO:274. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:277 or 278 and a LC of SEQ ID NO:279. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:282 or 283 and a LC of SEQ ID NO:284. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:292 or 293 and a LC of SEQ ID NO:294. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:297 or 298 and a LC of SEQ ID NO:299. In an embodiment, the anti-

V3 antibody comprises a HC of SEQ ID NO:302 or 303 and a LC of SEQ ID NO:304. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:307 or 308 and a LC of SEQ ID NO:309. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:312 or 313 and a LC of SEQ ID NO:314. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO: 317 or 318 and a LC of SEQ ID NO:319. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:322 or 323 and a LC of SEQ ID NO:324. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:327, 328, 331 or 332 and a LC of SEQ ID NO:329. In an embodiment, the anti-V3 antibody comprises a HC of SEQ ID NO:336 or 337 and a LC of SEQ ID NO:329.

Anti-V3 bNAbs known in the art include PGT121-123, PGT125-131, PGT135-137, DH270.6, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12, 438-B11, 447-52D, BG18, DH270.6, ePGT121v1, ePGT121v2, ePGT121v3, EPTC112, and F425-B4e8. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises the six CDRs of any one of PGT121-123, PGT125-131, PGT135-137, DH270.6, QA013.2, 10-1074, 2G12, 438-B11, 447-52D, BG18, DH270.6, ePGT121v1, ePGT121v2, ePGT121v3, EPTC112, and F425-B4e8. In an embodiment, the anti-V3 antibody or V3-binding fragment thereof, comprises the VH domain and the VL domain any one of PGT121-123, PGT125-131, PGT135-137, DH270.6, QA013.2, 10-1074, 2G12, 438-B11, 447-52D, BG18, DH270.6, ePGT121v1, ePGT121v2, ePGT121v3, EPTC112, and F425-B4e8.

An antigen binding protein of the invention may comprise an anti-V3 scFv of any one of the aforementioned anti-V3 bNAbs. In an embodiment, the scFv comprises a VH and VL pair as set out in Table 2. In an embodiment, the scFv comprises a VH and VL pair of any one of PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12. In an embodiment, the C-terminus of the VH domain is attached directly or via a linker to the N-terminus of the VL domain. In an embodiment, the C-terminus of the VL domain is attached directly or via a linker to the N-terminus of the VH domain. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:65 and a VL domain of SEQ ID NO:66. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:70 and a VL domain of SEQ ID NO:71. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:75 and a VL domain of SEQ ID NO:76. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:80 and a VL domain of SEQ ID NO:81. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:85 and a VL domain of SEQ ID NO:86.

An anti-V3 scFv may be fused to an Fc domain. In an embodiment, the scFv is fused to a human Fc domain directly or via a linker (scFv-Fc).

Linkers

Examples of suitable linkers include amino acid sequences that are from 1 amino acid to 150 amino

acids in length. In particular, from 1 to 140 amino acids, from 1 to 130 amino acids, from 1 to 120 amino acids, from 1 to 110 amino acids, from 1 to 100 amino acids, from 1 to 90 amino acids, from 1 to 80 amino acids, from 1 to 70 amino acids, from 1 to 60 amino acids, from 1 to 50 amino acids, from 1 to 40 amino acids, from 1 to 30 amino acids, from 1 to 20 amino acids, from 1 to 10 amino acids, from 5 to 30 amino acids.

In an embodiment, the linker is an amino acid sequence from 5 to 30 amino acids in length. In an embodiment, the linker is an amino acid sequence as set forth in any one of SEQ ID NOs:90 to 95. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:90. In an embodiment, the linker is a multimer of the amino acid sequence as set forth in SEQ ID NO:90. In an embodiment, the linker is [SEQ ID NO:90]ⁿ, wherein n is an integer from 1 to 6. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:91. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:92. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:93. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:94. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:95.

Any of the aforementioned linkers may be incorporated into an antigen binding protein of the invention. In particular, any of the aforementioned linkers may be used to join a domain within the antigen binding protein to another domain within the antigen binding protein. In particular, any of the aforementioned linkers may be used to join a domain within the antigen binding protein that binds to the CD4-binding site of HIV gp120 to another domain within the antigen binding protein that binds to the V3 loop region of HIV gp120. Further, any of the aforementioned linkers may be used to join a CD4 domain as disclosed herein to a bNAb as disclosed herein. In an embodiment, the linker is an amino acid sequence as set forth in any one of SEQ ID NOs:90 to 95. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:90.

In an embodiment, a linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb heavy chain variable domain. In an embodiment, a linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb light chain variable domain. In an embodiment, a linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb heavy chain variable domain and a linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb light chain variable domain. In an embodiment, a linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb heavy chain variable domain and an identical linker is used to join the C-terminus of a CD4 domain to the N-terminus of a bNAb light chain variable domain. In an embodiment, the linker is an amino acid sequence as set forth in any one of

SEQ ID NOs:90 to 95. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:90.

In an embodiment, a linker is used to join the N-terminus of a CD4 domain to the C-terminus of a bNAb heavy chain. In an embodiment, a linker is used to join the N-terminus of a CD4 domain to the C-terminus of a bNAb heavy chain variable domain. In an embodiment, a linker is used to join the N-terminus of a CD4 domain to the C-terminus of a bNAb light chain. In an embodiment, a linker is used to join the N-terminus of a CD4 domain to the C-terminus of a bNAb light chain variable domain. In an embodiment, a linker is used to join the N-terminus of a CD4 domain to the C-terminus of an Fc domain. In an embodiment, the linker is an amino acid sequence as set forth in any one of SEQ ID NOs:90 to 95. In an embodiment, the linker is an amino acid sequence as set forth in SEQ ID NO:90.

In an embodiment of the invention, the domain of the antigen binding protein that binds to the CD4-binding site of HIV gp120 is joined directly to another domain within the antigen binding protein that binds to the V3 loop region of HIV gp120, *i.e.*, a linker is not used. In an embodiment, a CD4 domain as disclosed herein is joined directly to a bNAb as disclosed herein.

Any of the aforementioned linkers may be used to join a VH and VL pair as disclosed herein to form a scFv. In an embodiment, the linker between the VH domain and the VL domain of the scFv is selected from the group consisting of SEQ ID NOs:90-95. In a particular embodiment, the linker between the VH domain and the VL domain of the scFv is SEQ ID NO:93.

Any of the aforementioned linkers may be used to join a scFv as disclosed herein to an Fc domain. In an embodiment, the scFv is fused to a human Fc via a linker selected from the group consisting of SEQ ID NO:90-95. In an embodiment, the scFv is fused to a human Fc via a linker of SEQ ID NO:91.

Bispecific molecules

A bispecific molecule of the invention comprises one or more paratopes that bind to the CD4bs of HIV gp120 and one or more paratopes that bind to the V3 loop region of HIV gp120.

Paratopes that bind to the CD4bs of HIV gp120 may be formed by CD4 domains disclosed herein, as well as other CD4bs-binding domains disclosed herein, including those of anti-CD4bs antibodies and CD4bs-binding fragments thereof, and non-Ig constructs that bind to CD4bs.

Paratopes that bind to the V3 loop region of HIV gp120 may be formed by anti-V3 antibodies and V3-binding fragments thereof disclosed herein, as well as non-Ig constructs that bind to V3 disclosed herein.

In an embodiment, the bispecific molecule comprises a paratope that binds to the CD4bs of HIV gp120 that is formed by an anti-CD4bs antibody or CD4bs-binding fragment thereof and a

paratope that binds to the V3 loop region of HIV gp120 that is formed by an anti-V3 antibody or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises an anti-CD4bs antibody or CD4bs-binding fragment thereof and an anti-V3 antibody or a V3-binding fragment thereof.

5 In an embodiment, the bispecific molecule comprises a CD4 domain and a paratope that binds to the V3 loop region of HIV gp120 that is formed by an anti-V3 antibody or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain and an anti-V3 antibody or a V3-binding fragment thereof.

10 In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody or a V3-binding fragment thereof.

15 In an embodiment, the bispecific molecule comprises a CD4 domain and an anti-V3 antibody, selected from the group consisting of: PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody selected from the group consisting of: PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12, or a V3-binding fragment
20 thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody selected from the group consisting of: PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12, or a V3-binding fragment thereof.

25 In an embodiment, the bispecific molecule comprises a CD4 domain and an anti-V3 antibody comprising a set of CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set out in any row of Table 1, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a set of CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set out in any row of Table 1, or a V3-binding fragment thereof.

30 In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a set of CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set out in any row of Table 1 or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a CDRH1 of SEQ ID NO:22, a CDRH2 of SEQ ID NO:23, a CDRH3 of

SEQ ID NO:24, a CDRL1 of SEQ ID NO:25, a CDRL2 of SEQ ID NO:26 and a CDRL3 of SEQ ID NO:27, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain and an anti-V3 antibody comprising a pair of variable domains (a VH and a VL) as set out in any row of Table 2, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a pair of variable domains (a VH and a VL) as set out in any row of Table 2, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a pair of variable domains (a VH and a VL) as set out in any row of Table 2, or a V3-binding fragment thereof.

In an embodiment, the bispecific molecule comprises a CD4 domain and an anti-V3 antibody or a V3-binding fragment thereof comprising a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59 or 60.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59 or 60.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59 or 60.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:65 and a VL domain of SEQ ID NO:66.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:65 and a VL domain of SEQ ID NO:66.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:70 and a VL domain of SEQ ID NO:71.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:70 and a VL domain of SEQ ID NO:71.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:75 and a VL domain of SEQ ID NO:76.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:75 and a VL domain of SEQ ID NO:76.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:80 and a VL domain of
5 SEQ ID NO:81.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:80 and a VL domain of SEQ ID NO:81.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:85 and a VL domain of
10 SEQ ID NO:86.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a VH domain of SEQ ID NO:85 and a VL domain of SEQ ID NO:86.

An anti-V3 antibody as described above may be an antibody comprising a heavy chain (HC), with or without M428L/N434S (EU numbering) 'LS' mutations. In an embodiment, the HC comprises
15 LS.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:61 or 62 and a LC of SEQ ID NO:63 or 64.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:61 or 62 and a LC of SEQ ID NO:63 or 64.
20

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:62 and a LC of SEQ ID NO:63.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:62 and a LC of SEQ ID NO:63.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:67 or 68 and a LC of SEQ ID NO:69.
25

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:67 or 68 and a LC of SEQ ID NO:69.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:72 or 73 and a LC of SEQ ID NO:74.
30

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:72 or 73 and a LC of SEQ ID NO:74.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:77 or 78 and a LC of SEQ ID NO:79.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:77 or 78 and a LC of SEQ ID NO:79.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:82 or 83 and a LC of SEQ ID NO:84.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:82 or 83 and a LC of SEQ ID NO:84.

In an embodiment, the bispecific molecule comprises a CD4 domain of any one of SEQ ID NOs:1-21 and an anti-V3 antibody comprising a HC of SEQ ID NO:87 or 88 and a LC of SEQ ID NO:89.

In an embodiment, the bispecific molecule comprises a CD4 domain of SEQ ID NO:11 and an anti-V3 antibody comprising a HC of SEQ ID NO:87 or 88 and a LC of SEQ ID NO:89.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain as disclosed herein, wherein the C-terminus of one CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb heavy chains and the C-terminus of the other copy of the CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain as disclosed herein, wherein the C-terminus of one CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb light chains and the C-terminus of the other copy of the CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb light chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and four copies of a CD4 domain as disclosed herein, wherein the C-terminus of the first CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb heavy chains, the C-terminus of the second CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb heavy chains, the third CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb light chains, and the fourth CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb light chains.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain as disclosed herein, wherein the N-terminus of the first CD4 domain is attached directly or by a linker to the C-terminus of one of the anti-V3 bNAb heavy chains and the N-terminus of the other copy of the CD4 domain is attached directly or by a linker to the C-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of one CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb heavy chains and the C-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of one CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb light chains and the C-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb light chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and four copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of the first CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb heavy chains, the C-terminus of the second CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb heavy chains, the third CD4 domain is by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb light chains, and the fourth CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb light chains.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb as disclosed herein and two copies of a CD4 domain of SEQ ID NO:11, wherein the N-terminus of the first CD4 domain is attached by a linker of SEQ ID NO: 90 to the C-terminus of one of the anti-V3 bNAb heavy chains and the N-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the C-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb comprising a VH of SEQ ID NO:58 and a VL of SEQ ID NO:59, and two copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of one CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb heavy chains and the C-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb comprising a VH of SEQ ID NO:58 and a VL of SEQ ID NO:59, and two copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of one CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb light chains and the C-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb light chain.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb comprising a VH of SEQ ID NO:58 and a VL of SEQ ID NO:59, and four copies of a CD4 domain of SEQ ID NO:11, wherein the C-terminus of the first CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb heavy chains, the C-terminus of the second CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb heavy chains, the third CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of one of the anti-V3 bNAb light chains, and the fourth CD4 domain is attached by a linker of SEQ ID NO: 90 to the N-terminus of the other anti-V3 bNAb light chains.

In an embodiment, the bispecific molecule comprises an anti-V3 bNAb comprising a VH of SEQ ID NO:58 and a VL of SEQ ID NO:59, and two copies of a CD4 domain of SEQ ID NO:11, wherein the N-terminus of the first CD4 domain is attached by a linker of SEQ ID NO: 90 to the C-terminus of one of the anti-V3 bNAb heavy chains and the N-terminus of the other copy of the CD4 domain is attached by a linker of SEQ ID NO: 90 to the C-terminus of the other anti-V3 bNAb heavy chain.

In an embodiment, the bispecific molecule comprises a HC of any one of SEQ ID NOs:96-107, 116, 117 or 119-135; and a LC of SEQ ID NO:63.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:62; and a LC of any one of SEQ ID NOs:108-115 and 118.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:68; and a LC of SEQ ID NO:142 or 143.

In an embodiment, the bispecific molecule comprises a HC of any one of SEQ ID NOs:136-141; and a LC of SEQ ID NO:69.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:144 or 145; and a LC of SEQ ID NO:74.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:146 or 147; and a LC of SEQ ID NO:79.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:148 or 149; and a LC of SEQ ID NO:84.

In an embodiment, the bispecific molecule comprises a HC of SEQ ID NO:150 or 151; and a

LC of SEQ ID NO:89.

In an embodiment, the bispecific molecule consists of two heavy chains and two light chains, wherein the heavy chain is at least 95% identical to SEQ ID NO:121 and the light chain that is at least 95% identical to SEQ ID NO:63.

5 In an embodiment, the bispecific molecule consists of two heavy chains and two light chains, wherein the heavy chain is at least 96% identical to SEQ ID NO:121 and the light chain that is at least 96% identical to SEQ ID NO:63.

In an embodiment, the bispecific molecule consists of two heavy chains and two light chains, wherein the heavy chain is at least 97% identical to SEQ ID NO:121 and the light chain that is at least 97% identical to SEQ ID NO:63.

10 In an embodiment, the bispecific molecule consists of two heavy chains and two light chains, wherein the heavy chain is at least 98% identical to SEQ ID NO:121 and the light chain that is at least 98% identical to SEQ ID NO:63.

In an embodiment, the bispecific molecule consists of two heavy chains and two light chains, wherein the heavy chain is at least 99% identical to SEQ ID NO:121 and the light chain that is at least 99% identical to SEQ ID NO:63.

In an embodiment, the bispecific molecule consists of two heavy chains of SEQ ID NO:121 and two light chains of SEQ ID NO:63.

An antigen binding protein of the invention may comprise an anti-V3 scFv of any one of the aforementioned anti-V3 bNAbs. In an embodiment, the scFv comprises a VH and VL pair as set out in Table 2. In an embodiment, the scFv comprises a VH and VL pair of any one of PGT121-123, PGT125-131, PGT135-137, QA013.2, 10-1074, 10-1074LS, PGT121.414.LS and 2G12. In an embodiment, the C-terminus of the VH domain is attached directly or via a linker to the N-terminus of the VL domain. In an embodiment, the C-terminus of the VL domain is attached directly or via a linker to the N-terminus of the VH domain. In an embodiment, the linker between the VH domain and the VL domain of the scFv is selected from the group consisting of SEQ ID NOs:90-95. In an embodiment, the linker between the VH domain and the VL domain of the scFv is SEQ ID NO:93.

25 In an embodiment, the scFv comprises a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:65 and a VL domain of SEQ ID NO:66. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:70 and a VL domain of SEQ ID NO:71. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:75 and a VL domain of SEQ ID NO:76. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:80 and a VL domain of SEQ ID NO:81. In an embodiment, the scFv comprises a VH domain of SEQ ID NO:85 and a VL domain of SEQ ID NO:86. In an embodiment, a linker of SEQ ID

NO:93 joins the VH domain and the VL domain of the scFv. In an embodiment, a linker of SEQ ID NO:93 joins the C terminal of the VH domain to the N terminal of the VL domain to form the scFv. In an embodiment, a linker of SEQ ID NO:93 joins the C terminal of the VL domain to the N terminal of the VH domain to form the scFv.

5 An anti-V3 scFv may be fused to an Fc domain. In an embodiment, the scFv is fused to a human Fc domain directly or via a linker (scFv-Fc). In an embodiment, the C-terminus of the scFv is fused to the N-terminus of a human Fc domain via a linker selected from the group consisting of SEQ ID NOs:90-95. In an embodiment, the N-terminus of the scFv is fused to the C-terminus of a human Fc domain via a linker selected from the group consisting of SEQ ID NOs:90-95. In an
10 embodiment, the scFv is fused to a human Fc domain via a linker of SEQ ID NO:91. In an embodiment, the Fc domain comprises a half-life extending mutation. In an embodiment the half-life extending mutation is LS.

 A scFv-Fc may be fused directly or via a linker to a CD4 domain. In an embodiment, the scFv-Fc is fused via a linker selected from the group consisting of SEQ ID NOs:90-95 to a CD4
15 domain.

 In an embodiment, the antigen binding protein comprises or consists of: (1) a scFv comprising a VH and VL pair as set out in any row of Table 2, wherein the VH and VL domain are joined to form a scFv via a linker selected from the group consisting of SEQ ID NOs:90-95; (2) a CD4 domain selected from the group consisting of SEQ ID NOs:1-21; and (3) and Fc domain
20 comprising LS half-life extending mutations; wherein (1), (2) and (3) are joined together in any order directly or via a linker, and wherein each linker is selected from the group consisting of SEQ ID NOs:90-95.

 In an embodiment, the antigen binding protein comprises or consists of: (1) a scFv comprising a VH and VL pair as set out in any row of Table 2, wherein the VH and VL domain are
25 joined to form a scFv via a linker of SEQ ID NO:93; (2) a CD4 domain selected from the group consisting of SEQ ID NOs:1-21; and (3) and Fc domain comprising LS half-life extending mutations; wherein (1), (2) and (3) are joined together in any order via a linker between each domain, and wherein the linker is SEQ ID NOs:90.

 In an embodiment, the bispecific molecule of the invention comprises a sequence that is at
30 least 95%, 96%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs:152-157. In an embodiment, an antigen binding protein of the invention consists of a sequence that is at least 95%, 96%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs:152-157. In an embodiment, an antigen binding protein of the invention comprises or consists of SEQ ID NO:152. In an embodiment, an antigen binding protein of the invention comprises or consists of SEQ ID NO:153.

In an embodiment, an antigen binding protein of the invention comprises or consists of SEQ ID NO:154. In an embodiment, an antigen binding protein of the invention comprises or consists of SEQ ID NO:155. In an embodiment, an antigen binding protein of the invention comprises or consists of SEQ ID NO:156. In an embodiment, an antigen binding protein of the invention
5 comprises or consists of SEQ ID NO:157.

Production methods

Antigen binding proteins may be prepared by any of a number of conventional techniques. For example, antigen binding proteins may be purified from cells that naturally express them (*e.g.*, an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression
10 systems.

A number of different expression systems and purification regimes can be used to generate the antigen binding proteins of the invention. Generally, host cells are transformed with a recombinant expression vector encoding the desired antigen binding protein. The expression vector may be maintained by the host as a separate genetic element or integrated into the host
15 chromosome depending on the expression system. A wide range of host cells can be employed, including Prokaryotes (including Gram-negative or Gram-positive bacteria, for example *Escherichia coli*, *Bacilli sp.*, *Pseudomonas sp.*, *Corynebacterium sp.*), Eukaryotes including yeast (for example *Saccharomyces cerevisiae*, *Pichia pastoris*), fungi (for example *Aspergillus sp.*), or higher Eukaryotes including insect cells and cell lines of mammalian origin (for example, CHO, NS0, PER.C6, HEK293,
20 HeLa).

The host cell may be an isolated host cell. The host cell is usually not part of a multicellular organism (*e.g.*, plant or animal). The host cell may be a non-human host cell.

Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian host cells are known in the art.

25 The cells can be cultured under conditions that promote expression of the antigen binding protein using a variety of equipment such as shake flasks, spinner flasks, and bioreactors. The polypeptide(s) is(are) recovered by conventional protein purification procedures. Protein purification procedures typically consist of a series of unit operations comprised of various filtration and chromatographic processes developed to selectively concentrate and isolate the antigen binding
30 protein. The purified antigen binding protein may be formulated in a pharmaceutically acceptable composition.

Fc modifications

Fc engineering methods can be applied to modify the functional or pharmacokinetics properties of an antigen binding protein, in particular an antibody. Effector function may be altered by making mutations in the Fc region that increase or decrease binding to C1q or Fcγ receptors and modify CDC or ADCC activity respectively. Modifications to the glycosylation pattern of an antibody can also be made to change the effector function.

The interaction between the Fc region of an antigen binding protein or antibody and various Fc receptors (FcR), including FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), FcRn, C1q, and type II Fc receptors is believed to mediate the effector functions of the antigen binding protein or antibody. Significant biological effects can be a consequence of effector functionality. Usually, the ability to mediate effector function requires binding of the antigen binding protein or antibody to an antigen and not all antigen binding proteins or antibodies will mediate every effector function.

Effector function can be assessed in a number of ways including, for example, evaluating ADCC effector function of antibody coated to target cells mediated by Natural Killer (NK) cells via FcγRIII, or monocytes/macrophages via FcγRI, or evaluating CDC effector function of antibody coated to target cells mediated by complement cascade via C1q. For example, an antigen binding protein of the present invention can be assessed for ADCC effector function in a Natural Killer cell assay. Examples of such assays can be found in Shields *et al.*, 2001, The Journal of Biological Chemistry, Vol. 276, p. 6591-6604; Chappel *et al.*, 1993, The Journal of Biological Chemistry, Vol 268, p. 25124-25131; Lazar *et al.*, 2006, PNAS, 103; 4005-4010.

Examples of assays to determine CDC function include those described in J Imm Meth, 1995, 184: 29-38.

The effects of mutations on effector functions (*e.g.*, FcRn binding, FcγRs and C1q binding, CDC, ADCML, ADCC, ADCP) can be assessed, *e.g.*, as described in Grevys *et al.*, J Immunol. 2015 Jun 1; 194(11): 5497-5508, or Tam *et al.*, Antibodies 2017, 6(3); Monnet *et al.*, 2014 mAbs, 6:2, 422-436.

Throughout this specification, amino acid residues in Fc regions, in antibody sequences or full-length antigen binding protein sequences, are numbered according to the EU index numbering convention.

The long half-life of IgG antibodies is reported to be dependent on their binding to FcRn. Therefore, substitutions that increase the binding affinity of IgG to FcRn at pH 6.0 while maintaining the pH dependence of the interaction with target, by engineering the constant region, have been extensively studied (Ghetie *et al.*, Nature Biotech. 15: 637-640, 1997; Hinton *et al.*, JBC 279: 6213-6216, 2004; Dall'Acqua *et al.*, 10 J Immunol 117: 1129-1138, 2006). The *in-vivo* half-life of antigen

binding proteins of the present invention may be altered by modification of a heavy chain constant domain or an FcRn binding domain therein.

In adult mammals, FcRn, plays a key role in maintaining serum antibody levels by acting as a protective receptor that binds and salvages antibodies of the IgG isotype from degradation. IgG molecules are endocytosed by endothelial cells and, if they bind to FcRn, are recycled out of the cells back into circulation. In contrast, IgG molecules that enter the cells and do not bind to FcRn and are targeted to the lysosomal pathway where they are degraded.

FcRn is believed to be involved in both antibody clearance and the transcytosis across tissues (see Junghans R.P (1997) *Immunol.Res* 16. 29-57 and Ghetie *et al* (2000) *Annu. Rev. Immunol.* 18, 739-766). Human IgG1 residues determined to interact directly with human FcRn include Ile253, Ser254, Lys288, Thr307, Gln311, Asn434 and His435. Mutations at any of these positions may enable increased serum half-life and/or altered effector properties of antigen binding proteins of the invention.

Antigen binding proteins of the present invention may have amino acid modifications that increase the affinity of the constant domain or fragment thereof for FcRn. Increasing the half-life (*i.e.*, serum half-life) of therapeutic and diagnostic IgG antibodies and other bioactive molecules has many benefits including reducing the amount and/or frequency of dosing of these molecules. In one embodiment, an antigen binding protein of the invention comprises all or a portion (an FcRn binding portion) of an IgG constant domain having one or more of the following amino acid modifications.

For example, with reference to IgG1, M252Y/S254T/T256E (commonly referred to as "YTE" mutations) and M428L/N434S (commonly referred to as "LS" mutations) increase FcRn binding at pH 6.0 (Wang *et al.* 2018). In an embodiment, an antigen binding protein of the invention comprises an Fc domain with the LS mutations. In an embodiment, an antigen binding protein of the invention comprises a bNAb in which the LS mutations are present in both of the heavy chain Fc domains.

Half-life and FcRn binding can also be extended by introducing H433K and N434F mutations (commonly referred to as "HN" or "NHance" mutations) (with reference to IgG1) (WO2006/130834).

Additionally, various publications describe methods for obtaining physiologically active molecules with modified half-lives, either by introducing an FcRn-binding polypeptide into the molecules (WO97/43316, US5869046, US5747035, WO96/32478 and WO91/14438) or by fusing the molecules with antibodies whose FcRn-binding affinities are preserved, but affinities for other Fc receptors have been greatly reduced (WO99/43713), or fusing with FcRn binding domains of antibodies (WO00/09560, US4703039).

Post-translational modifications

The skilled person will appreciate that, upon production of an antigen binding protein, such as a bispecific molecule of the invention in a host cell, post-translational modifications may occur. For example, this may include the cleavage of certain leader sequences, the addition of various sugar
5 moieties in various glycosylation patterns, non-enzymatic glycation, deamidation, oxidation, disulfide bond scrambling and other cysteine variants such as free sulfhydryls, racemized disulfides, thioethers and trisulfide bonds, isomerisation, C-terminal lysine clipping, and N-terminal glutamine cyclisation. The present invention encompasses the use of antigen binding proteins that have been subjected to, or have undergone, one or more post-translational modifications. Thus an antigen
10 binding protein of the invention includes an "antigen binding protein" as defined earlier that has undergone a post-translational modification such as described herein.

Glycation is a post-translational non-enzymatic chemical reaction between a reducing sugar, such as glucose, and a free amine group in the protein, and is typically observed at the epsilon amine of lysine side chains or at the N-Terminus of the protein. Glycation can occur during
15 production and storage only in the presence of reducing sugars.

Deamidation can occur during production and storage, is an enzymatic reaction primarily converting asparagine (N) to iso-aspartic acid (iso-aspartate) and aspartic acid (aspartate) (D) at approximately 3:1 ratio. This deamidation reaction is therefore related to isomerization of aspartate (D) to iso-aspartate. The deamidation of asparagine and the isomerisation of aspartate, both involve
20 the intermediate succinimide. To a much lesser degree, deamidation can occur with glutamine residues in a similar manner. Deamidation can occur in a CDR, in a Fab (non-CDR region), or in the Fc region.

Oxidation can occur during production and storage (*i.e.*, in the presence of oxidizing conditions) and results in a covalent modification of a protein, induced either directly by reactive
25 oxygen species or indirectly by reaction with secondary by-products of oxidative stress. Oxidation happens primarily with methionine residues, but may occur at tryptophan and free cysteine residues. Oxidation can occur in a CDR, in a Fab (non-CDR) region, or in the Fc region.

Disulfide bond scrambling can occur during production and basic storage conditions. Under certain circumstances, disulfide bonds can break or form incorrectly, resulting in unpaired cysteine
30 residues (-SH). These free (unpaired) sulfhydryls (-SH) can promote shuffling.

The formation of a thioether and racemization of a disulphide bond can occur under basic conditions, in production or storage, through a beta elimination of disulphide bridges back to cysteine residues via a dehydroalanine and persulfide intermediate. Subsequent crosslinking of

dehydroalanine and cysteine results in the formation of a thioether bond or the free cysteine residues can reform a disulphide bond with a mixture of D- and L-cysteine.

Trisulfides result from insertion of a sulfur atom into a disulphide bond (Cys-S-S-S-Cys) and are formed due to the presence of hydrogen sulphide in production cell culture.

5 N-terminal glutamine (Q) and glutamate (glutamic acid) (E) in the heavy chain and/or light chain is likely to form pyroglutamate (pGlu) via cyclization. Most pGlu formation happens in the production bioreactor, but it can be formed non-enzymatically, depending on pH and temperature of processing and storage conditions. Cyclization of N-terminal Q or E is commonly observed in natural human antibodies.

10 C-terminal lysine clipping is an enzymatic reaction catalyzed by carboxypeptidases, and is commonly observed in recombinant and natural human antibodies. Variants of this process include removal of lysine from one or both heavy chains due to cellular enzymes from the recombinant host cell. Upon administration to the human subject/patient is likely to result in the removal of any remaining C-terminal lysines.

15 Pharmaceutical compositions

Antigen binding proteins as described herein may be incorporated into pharmaceutical compositions for use in the treatment or prevention of HIV infection. In one embodiment, the pharmaceutical composition comprises an antigen binding protein in combination with one or more pharmaceutically acceptable carriers and/or excipients.

20 Such compositions comprise a pharmaceutically acceptable carrier as known and called for by acceptable pharmaceutical practice.

Pharmaceutical compositions may be administered by injection or continuous infusion (examples include, but are not limited to, intravenous, intraperitoneal, intradermal, subcutaneous, intramuscular, intraocular, and intraportal). In one embodiment, the composition is suitable for
25 intravenous administration. In one embodiment, the composition is suitable for subcutaneous administration.

Pharmaceutical compositions may be suitable for topical administration (which includes, but is not limited to, epicutaneous, inhaled, intranasal or ocular administration) or enteral administration (which includes, but is not limited to, oral, vaginal, or rectal administration).

30 The pharmaceutical composition may be included in a kit containing the antigen binding protein together with other medicaments, for example dolutegravir or cabotegravir, and/or with instructions for use. For convenience, the kit may comprise the reagents in predetermined amounts with instructions for use. The kit may also include devices used for administration of the pharmaceutical composition.

The terms "individual", "subject" and "patient" are used herein interchangeably. In one embodiment the subject is a human.

The antigen binding proteins described herein may be used in methods of treatment or prevention of HIV infection and AIDs. The antigen binding proteins described herein may be used in the manufacture of medicaments for the treatment or prevention of HIV infection and AIDs. The antigen binding proteins described may be used in an effective amount for therapeutic, prophylactic or preventative treatment. A therapeutically effective amount of the antigen binding protein described herein is an amount effective to ameliorate or reduce one or more symptoms of HIV infection. A prophylactically effective amount of the antigen binding protein described herein is an amount effective to prevent one or more symptoms of HIV infection.

Combinations

Antigen binding proteins of the present invention may be employed alone or in combination with other therapeutic agents, or a prodrug thereof. Combination therapies according to the present invention thus comprise the administration of an antigen binding protein and the administration of at least one other agent which may be useful in the treatment or prevention of HIV infection and/or AIDS. An antigen binding protein of the present invention and the other therapeutic agent may be formulated and administered together in a single pharmaceutical composition or may be formulated and administered separately. When formulated and administered separately, administration may occur simultaneously or sequentially in any order.

Antigen binding proteins as described herein may be combined with, for example, one or more of an antiretroviral agent, an anti-infective agent, an immunomodulator, and other HIV entry inhibitors.

Antiretroviral agents include Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTIs), Protease Inhibitors (PIs), Entry Inhibitors (EI), Integrase Strand Transfer Inhibitors (INSTI), Maturation Inhibitors (MIs), and Capsid Inhibitors (CIs).

NRTIs may include, but are not limited to: abacavir, adefovir, adefovir dipivoxil, alovudine, amdoxovir, apricitabine, calanolide A, censavudine, didanosine, elvucitabine, emtricitabine, fozivudine, lamivudine, racivir, stampidine, stavudine, tenofovir disoproxil fumerate, tenofovir alafenamide, todoxil, zalcitabine, and zidovudine.

NNRTIs may include, but are not limited to, HBY 097 (Hoechst/Bayer), capravirine, delaviridine, doravirine, efavirenz, etravirine, immunocal, lersivirine, loviride, nevirapine, oltipraz, and rilpivirine.

NRTTIs include, but are not limited to, islatravir.

PIs may include, but are not limited to, amprenavir, atazanavir, brexanavir, cobicistat, darunavir, fosamprenavir, indinavir, lasinavir, lopinavir, palinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

EIs are discussed in DRUGS OF THE FUTURE 1999, 24(12), 1355-1362; CELL, Vol. 9, 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194; and Meanwell *et al.*, Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461. In particular, the antigen binding proteins of the invention can be utilized in combination with attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor. HIV attachment inhibitors are also set forth in US 7,354,924 and US 7,745,625. EIs may include, but are not limited to, cenicriviroc, enfuvirtide, fostemsavir, ibalizumab, leronlimab, maraviroc, vicriviroc and VIR-576.

INSTIs may include, but are not limited to, bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir. In an embodiment, the INSTI is dolutegravir or cabotegravir. In an embodiment, the INSTI is cabotegravir.

Maturation inhibitors may include, but are not limited to, bevirimat, BMS-955176, GSK3640254, GSK3739937, PA-344 and PA-457. It will be understood that GSK3640254 is a compound as described in Dicker I, Jeffrey JL, Protack T, *et al.*, Antimicrob Agents Chemother. 2022;66(1). GSK3739937, also known as VH3739937, is the compound of clinical trial NCT04493684.

Capsid inhibitors may include, but are not limited to, GSK4004280, GSK4011499, and lenacapavir.

Anti-infective agents include, but are not limited to, clindamycin with primaquine, daunorubicin, fluconazole, intraconazole, nystatin pastille, ornidyl eflornithine, megestrol acetate, pentamidine isethionate, piritrexim, trimethoprim, trimetrexate, recombinant human erythropoietin, recombinant human growth hormone, spiramycin, testosterone and total enteral nutrition,

Immunomodulators include, but are not limited to, acemannan, alpha-2-interferon, AS-101, broprimine, CL246,738, FP-21399, gamma interferon, granulocyte macrophage colony stimulating factor, HIV core particle immunostimulant, interleukin-2, immune globulin, IMREG-1, IMREG-2, imuthiol diethyl dithio carbamate, methionine enkephalin, MTP-PE muramyl tripeptide, remune, recombinant soluble human CD4, rCD4-IgG hybrids, SK&F106528, thymopentin, and tumour necrosis factor (TNF).

The antigen binding proteins of the present invention may also be used in combination with agents that induce HIV expression, such as latency reversing agents. Several latency reversing agents include, but are not limited to, the following: histone deacetylase inhibitors (*e.g.*, vorinostat,

panobinostat, romidepin), histone crotonyl transferase inhibitors (sodium crotonate), protein kinase C agonists (*e.g.*, bryostatin, ingenol B), disulfiram, TLR7 agonists (*e.g.*, GS-9620), and bromodomain inhibitors (*e.g.*, JQ1, iBET151).

5 The antigen binding proteins of the present invention may also be used in combination with other agents that induce HIV expression, such as agents for clearance therapy. Several examples of agents for clearance therapy, or of immunological combinations for clearance, include, but are not limited to, the following: bNAbs, CD4-Ig, eCD4-Ig, and dual-affinity re-targeting (DART) proteins.

10 Antigen binding proteins of the invention may be used in combination with broadly neutralizing HIV-1 antibodies, including 1NC9, 1B2530, 2F5, 2G12, 3NBC60, 3BNC117, 4E10, 8ANC131, 8ANC134, 10-1074, 10-1074LS, 10E8, 12A12, 12A21, b12, CAP206-CH12, CH01-04, CH103-106, elipovimab (formerly known as GS-9722), HJ16, M66.6, N6LS (also known as VRC-HIVMAB091-00-AB and the compound of clinical trial NCT03538626), NIH45-46, PG9, PG16, PGT121-123, PGT125-131, PGT135-137, PGT141-145, PGT121.414.LS, PGT151 2G12, QA013.2, VRC01-03, VRC-PG04, VRC-PG04b, VRC-CH30-34.

15 Other agents that may be combined with antigen binding proteins of the invention include BIT225, GSK4000422/VH4000422, and S-648414 (the compound of clinical trial NCT04147715).

The scope of combinations of compounds of this invention with HIV agents is not limited to those mentioned above but includes in principle any combination with any pharmaceutical composition useful for the treatment and/or prevention of HIV infection and/or AIDS.

20

The invention is illustrated by the following clauses:

1. An anti-HIV gp120-binding protein that binds to at least two different epitopes on human immunodeficiency virus (HIV) surface glycoprotein 120 (gp120).
- 25 2. The anti-HIV gp120-binding protein of clause 1, wherein one of the at least two epitopes comprises one or more amino acid residues of the CD4-binding site of HIV gp120.
3. The anti-HIV gp120-binding protein of clause 1 or clause 2, wherein one of the at least two epitopes comprises one or more amino acid residues of the V3 loop region (V3) of HIV gp120.
- 30 4. The anti-HIV gp120-binding protein of clause 3, wherein one of the at least two epitopes comprises a cluster of mannose glycans centered on N332 of HIV gp120.
5. The anti-HIV gp120-binding protein of any one of the preceding clauses that binds to the CD4-binding site of HIV gp120 and the V3 loop region of HIV gp120.

6. The anti-HIV gp120-binding protein of any one of the preceding clauses, comprising a CD4-domain.
7. The anti-HIV gp120-binding protein of clause 6, wherein the CD4 domain is a CD4 D1 domain or CD4 D1D2 domain.
- 5 8. The anti-HIV gp120-binding protein of clause 6 or clause 7, wherein the CD4 domain comprises one or more stabilizing mutations.
9. The anti-HIV gp120-binding protein of clause 8, wherein the CD4 domain has a T_m of between 70 °C and 95 °C.
- 10 10. The anti-HIV gp120-binding protein of any one of clauses 6 to 9, wherein the CD4 D1 domain comprises one or more mutations selected from the group consisting of: K8C, K8I, K8V, T11C, E13C, K21C, Q25E, H27C, H27D, G38C, N52W, R58N, R58T, R58V, L61M, G65C, I70C, K72C, E87G, E91H, E91Q, and G99C.
11. The anti-HIV gp120-binding protein of clause 9, wherein the CD4 domain has a T_m of about 90 °C.
- 15 12. The anti-HIV gp120-binding protein of clause 10 or clause 11, wherein the CD4 domain comprises K8C and G99C.
13. The anti-HIV gp120-binding protein of clause 6, comprising any one of SEQ ID NOs:1-21.
14. The anti-HIV gp120-binding protein of any one of clauses 6 to 13, comprising SEQ ID NO:11.
- 20 15. The anti-HIV gp120-binding protein of any one of clauses 3 to 14, comprising a set of 6 CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3) as set forth in any row of Table 1.
16. The anti-HIV gp120-binding protein of clause 15, comprising a CDRH1 of SEQ ID NO:22, a CDRH2 of SEQ ID NO:23, a CDRH3 of SEQ ID NO:24, a CDRL1 of SEQ ID NO:25, a CDRL2 of SEQ ID NO:26 and a CDRL3 of SEQ ID NO:27.
- 25 17. The anti-HIV gp120-binding protein of any one of the preceding clauses, comprising an immunoglobulin (Ig) scaffold.
18. The anti-HIV gp120-binding protein of clause 15, clause 16 or clause 17, comprising a heavy chain variable (VH) domain and a light chain variable (VL) domain pair as set forth in any row of Table 2.
- 30 19. The anti-HIV gp120-binding protein of clause 18, comprising a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59 or SEQ ID NO:60.

20. The anti-HIV gp120-binding protein of any one of clauses 17 to 19, comprising an Fc domain.
21. The anti-HIV gp120-binding protein of clause 20, wherein the Fc domain comprises a mutation that increases the half-life of the anti-HIV gp120-binding protein compared to the same anti-HIV gp120-binding protein without said mutation.
22. The anti-HIV gp120-binding protein of clause 21, wherein the Fc domain comprises any one of the following sets of mutations (EU numbering):
- M428L and N434S (LS);
- L309D, Q311H and N434S (DHS);
- M252Y, S254T and T256E (YTE); and
- H433K and N434F (HN).
23. The anti-HIV gp120-binding protein of clause 22, wherein the Fc domain comprises LS.
24. The anti-HIV gp120-binding protein of any one of the preceding clauses comprising a broadly neutralizing antibody (bNAb).
25. The anti-HIV gp120-binding protein of clause 24, wherein the bNAb is an anti-V3 bNAb.
26. The anti-HIV gp120-binding protein of clause 25, wherein the anti-V3 bNAb comprises a heavy chain (HC) and a light chain (LC) pair as set forth in any row of Table 2.
27. The anti-HIV gp120-binding protein of clause 26, wherein the HC comprises SEQ ID NO:61 or SEQ ID NO:62 and the LC comprises SEQ ID NO: 63 or SEQ ID NO:64.
28. The anti-HIV gp120-binding protein of clause 27, wherein the HC comprises SEQ ID NO:62 and the LC comprises SEQ ID NO:63.
29. The anti-HIV gp120-binding protein of any one of clauses 17 to 19, comprising an anti-V3 bNAb scFv.
30. The anti-HIV gp120-binding protein of clause 29, wherein the scFv comprises a VH domain of SEQ ID NO:58 and a VL domain of SEQ ID NO:59.
31. The anti-HIV gp120-binding protein of clause 29 or clause 30, wherein the C-terminus of the VH domain is fused directly or via a linker to the N-terminus of the VL domain.
32. The anti-HIV gp120-binding protein of clause 29 or clause 30, wherein the C-terminus of the VL domain is fused directly or via a linker to the N-terminus of the VH domain.
33. The anti-HIV gp120-binding protein of clause 31 or clause 32, wherein the linker between the VH domain and the VL domain of the scFv is selected from the group consisting of SEQ ID NOs:90-95.
34. The anti-HIV gp120-binding protein of clause 33, wherein the linker between the VH domain and the VL domain of the scFv is SEQ ID NO:93.

35. The anti-HIV gp120-binding protein of any one of clauses 29 to 34, wherein the scFv is fused to a human Fc domain directly or via a linker (scFv-Fc).
36. The anti-HIV gp120-binding protein of clause 35, wherein the scFv is fused to a human Fc via a linker selected from the group consisting of SEQ ID NO:90-95.
- 5 37. The anti-HIV gp120-binding protein of clause 35, wherein the scFv is fused to a human Fc via a linker of SEQ ID NO:91.
38. The anti-HIV gp120-binding protein of any one of clauses 35 to 37, wherein the Fc domain is as defined in any one of claims 21 to 23.
39. The anti-HIV gp120-binding protein of any one of clauses 35 to 38, comprising any one of SEQ ID NOs:152-157.
- 10 40. A bispecific anti-HIV gp120-binding protein comprising an anti-V3 bNAb and two copies of a CD4 domain, wherein the C-terminus of one CD4 domain is attached directly or by a linker to the N-terminus of one of the anti-V3 bNAb heavy chains and the C-terminus of the other copy of the CD4 domain is attached directly or by a linker to the N-terminus of the other anti-V3 bNAb heavy chain.
- 15 41. The bispecific protein according to clause 40, wherein each CD4 domain is attached via a linker to each of the heavy chains.
42. The bispecific protein according to clause 41, wherein the linker is selected from the group consisting of SEQ ID NOs:90 to 95.
- 20 43. The bispecific protein according to clause 42, wherein the linker is SEQ ID NO:90.
44. The bispecific protein according to any one of clauses 40 to 43, wherein the CD4 domain is selected from the group consisting of SEQ ID NO:1-21.
45. The bispecific protein according to clause 44, wherein the CD4 domain is SEQ ID NO:11.
46. The bispecific protein according to any one of clauses 40 to 45, wherein the anti-V3 bNAb is selected from the group consisting of bNAb1, bNAb1*, bNAb2, bNAb3, bNAb4, bNAb5 and bNAb6 as set forth in Table 2.
- 25 47. The bispecific protein as claimed in claim 46, wherein the anti-V3 bNAb is bNAb1.
48. The bispecific protein as claimed in any one of claims 40 to 47, wherein the anti-V3 bNAb Fc comprises LS.
- 30 49. An anti-HIV gp120-binding protein having two identical heavy chains and two identical light chains, comprising or consisting of:
- a heavy chain that is at least 95% identical to SEQ ID NO:121 and
 - a light chain that is at least 95% identical to SEQ ID NO:63.

50. An anti-HIV gp120-binding protein consisting of two heavy chains of SEQ ID NO:121 and two light chains of SEQ ID NO:63.
51. An anti-HIV gp120-binding protein comprising or consisting of a sequence that is at least 95% identical to any one of SEQ ID NOs:152-157.
52. An anti-HIV gp120-binding protein consisting of SEQ ID NO:155.
53. A pharmaceutical composition comprising the anti-HIV gp120-binding protein as defined in any one of the preceding clauses and a pharmaceutically acceptable excipient.
54. A method of treating or preventing an HIV infection in a human comprising administering to the human an anti-HIV gp120-binding protein according to any one of clauses 1 to 52, or a pharmaceutical composition according to clause 53, whereby viral load in the human is decreased.
55. An anti-HIV gp120-binding protein according to any one of clauses 1 to 52, or a pharmaceutical composition according to clause 53, for use in treating or preventing an HIV infection in a human.
56. Use of an anti-HIV gp120-binding protein according to any one of clauses 1 to 52, or a pharmaceutical composition according to clause 53, in the manufacture of a medicament for treating or preventing an HIV infection in a human.
57. A kit comprising in separate containers: an anti-HIV gp120-binding protein according to any one of clauses 1 to 52 and an anti-viral drug that inhibits cellular entry, replication, or transcription of HIV in a human.
58. The kit according to clause 57, wherein the antiviral drug is selected from the group consisting of: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Entry Inhibitors, Integrase Strand Transfer Inhibitors (INSTI), Maturation Inhibitors (MIs), Capsid Inhibitors (CIs) and Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTIs).
59. The kit according to clause 58, wherein the antiviral drug is an INSTI.
60. The kit according to clause 59, wherein the INSTI is dolutegravir or cabotegravir.
61. A nucleic acid sequence that encodes an anti-HIV gp120-binding protein according to any one of clauses 1 to 52.
62. An expression vector that comprises the nucleic acid sequence of clause 61.
63. A host cell that comprises the nucleic acid sequence of clause 61 or the expression vector of clause 62.
64. A host cell that comprises two expression vectors:
a first expression vector comprising a nucleic acid sequence encoding a heavy chain

of SEQ ID NO:121; and

a second expression vector comprising a nucleic acid sequence encoding a light chain of SEQ ID NO:63.

- 5 65. A method of producing an anti-HIV gp120-binding protein, comprising culturing the host cell as defined in clauses 63 or 64 under conditions suitable for expression of said nucleic acid sequence or vector, whereby an anti-HIV gp120-binding protein is produced.
66. A soluble CD4 domain having a T_m above 70 °C.
67. A soluble CD4 domain comprising one or more stabilizing mutations selected from the group consisting of K8C, K8I, K8V, T11C, E13C, K21C, Q25E, H27C, H27D, G38C, N52W,
10 R58N, R58T, R58V, L61M, G65C, I70C, K72C, E87G, E91H, E91Q, and G99C.
68. The soluble CD4 domain of clause 66 or clause 67 having a T_m of between 70 °C and 95 °C.
69. The soluble CD4 domain of clause 68 having a T_m of about 90 °C.
70. The soluble CD4 domain of any one of clauses 66 to 69, comprising K8C and G99C.
- 15 71. The soluble CD4 domain of any one of clauses 66 to 68, comprising K8I.
72. The soluble CD4 domain of any one of clauses 66 to 68, comprising K8V.
73. The soluble CD4 domain of any one of clauses 66 to 68, comprising T11C and K72C
74. The soluble CD4 domain of any one of clauses 66 to 68, comprising any one of SEQ ID NOs:5-21.
- 20 75. The soluble CD4 domain of clause 74, comprising SEQ ID NO:11.
76. The soluble CD4 domain of any one of clauses 66 to 75, wherein the CD4 domain is fused directly or via a linker to a human Fc domain.
77. The soluble CD4 domain of clause 76, wherein the Fc domain comprises LS.
- 25 78. The soluble CD4 domain of clause 76 or clause 77, wherein the linker is selected from the group consisting of SEQ ID NOs:90-95.

EXAMPLES

Example 1 – Antigen Binding Protein Production

Plasmids encoding the antigen binding proteins of the invention were expressed in EXP1293 or
30 FREESTYLE 293-F cells using the manufacturer's standard protocol (ThermoFisher Scientific, Waltham, MA). The expressed medium was harvested by centrifugation (4000 rpm for 10 min) and the antigen binding proteins were purified by filtration through a 0.22 µm filter (Millipore Sigma, Burlington, MA) and fast protein liquid chromatography (FPLC) (ÄKTATM Pure, Cytiva, Marlborough

MA). The medium was then passed through a Mabselect SuRe column (Cytiva, Marlborough MA) to capture the antigen binding proteins and the column was washed sequentially with phosphate-buffered saline (PBS) before elution.

5 The antigen binding proteins were then exchanged into a final buffer by using dialysis, a desalting column and preparative size exclusion column (SEC). The purity of the antigen binding proteins was evaluated by using sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS-PAGE) and on a size exclusion column on a high-performance liquid chromatography system (SEC-HPLC).

10 Antigen binding protein concentrations were determined by measuring absorbance at 280 nm wavelength (A280) on a NanoDrop machine (ThermoFisher Scientific, Waltham, MA), and their molecular mass was measured by using liquid chromatography - mass spectrometry (LC-MS) to confirm their identity.

The endotoxin level in the final purified products was measured on an ENDOSAFE system (Charles River Labs, Wilmington MA) to make sure it was sufficiently low (usually < 1 EU (Endotoxin Unit) / mg of protein) for downstream anti-viral studies.

Example 2 – Anti-Viral Activity

The anti-viral activity of the antigen binding proteins was measured in a pseudotyped virus (PSV) assay. Pseudotyped HIV-1 virus (PSV) contains deletions in the genome that make it unable to produce infectious virions, but it can be used to measure the activity of cell entry inhibitors (*i.e.*, molecules that prevent the binding of HIV-1 virions to the target cell membrane and/or prevent entry of HIV-1 into target cells), which include the antigen binding proteins of the invention.

25 PSV was produced in HEK-293T cells (ATCC, Manassas VA) by co-transfecting expression plasmids encoding the HIV-1 gp160 envelope gene and an HIV-1 backbone plasmid using TRANSIT-2020 transfection reagent (Mirus Bio, Madison WI). A panel of HIV-1 PSVs expressing different gp160 envelope trimers was generated to evaluate the effectiveness of the antigen binding proteins of the invention against a wide spectrum of HIV-1 strains.

i. ACTOne cells

30 The genome of PSV used in this assay contains a luciferase gene that is expressed once the virus enters cells. Accordingly, the luminescence signal (after adding a substrate of luciferase) can be used to determine the level of viral infection.

The 50% tissue culture infectious dose (TCID) of a single thawed aliquot of each batch of PSV was determined in ACTOne cells. The ACTOne cell-line used in this assay was derived in-house

from a genetically engineered 293T cell clone that expresses CD4, CXCR4, and CCR5. Cells were maintained in growth medium composed of Dulbecco's modified Eagle's medium (DMEM, Life Technologies) at 37 °C in a humidified 5% CO₂–95% air environment. Cell monolayers were split by treatment with Trypsin-EDTA (0.05%).

- 5 To run the anti-viral assay, ACTOne cells were detached by treating the cell culture flask with trypsin (trypsinization) and resuspended in growth medium containing 2% of DMSO to a density of 2.5×10^5 cells/ml. One hundred μ l of such cells was added to 10 μ l of antigen binding protein pre-loaded in a 96-well plate. Ninety μ l of PSV was then added to each well. The assay plates were incubated at 37°C in a humidified incubator at 5% CO₂ level. Plates were developed
10 after 72 hours of incubation by adding 50 μ l of BRIGHTGLO luciferase reagent (Promega, Madison WI) to each well, and transferring the plates to an ENVISION multilabel plate reader (PerkinElmer, Waltham MA) to measure the luminescence and determine the level of virus that had infected the cells. The higher the luminescence signal, the higher the level of infection.

- Raw data were analyzed using an in-house template in an IDBS system to calculate half-
15 maximal inhibitory concentration (IC₅₀) values which reflects the activity of the antigen binding proteins of the invention at inhibiting viral entry (the smaller the number is, the more active the molecule is).

ii. TZM.bl cells

- Alternatively, the PSV assay was carried out using a luciferase-based assay in a TZM.bl cell line. The
20 TZM-bl cell line is derived from a HeLa cell clone that was engineered to express CD4, CCR5 and CXCR4 and to contain integrated reporter genes for firefly luciferase and *E. coli* β -galactosidase under the control of an HIV-1 long terminal repeat (Wei *et al.*, Antimicrobial agents and chemotherapy 46:1896–905(2002)) permitting sensitive and accurate measurements of infection.

- The detailed materials and methodology have been described elsewhere (Mentefiori, Curr.
25 Protoc. Immunol., 2005, Chapter 12; Seaman *et al.*, Journal of Virology, Feb. 2010, 84(3), p. 1439-1452). In brief, the assay measures the reduction in luciferase reporter gene expression in TZM.bl cells following a single round of virus infection.

- Five-fold serial dilutions of the antigen binding proteins of the invention, from 50 μ g/ml to 3.2 ng/ml, were performed in duplicate in 10% DMEM growth medium (100 μ /well). An amount of
30 200 TCID₅₀ (50% tissue culture infectious dose) of virus was added to each well in a volume of 50 μ l, and the plates were incubated for 1 h at 37°C.

TZM.bl cells were then added (1×10^4 /well in a 100- μ l volume) in 10% D-MEM growth medium containing DEAE-dextran (Sigma, St. Louis, MO) at a final concentration of 11 μ g/ml. Assay

controls included TZM.bl cells alone (cell control) and TZM.bl cells with virus (virus control).

Following a 48-hour incubation at 37°C, 150 µl of assay medium was removed from each well and 100 µl of BRIGHTGLO luciferase reagent (Promega, Madison, WI) was added. The cells were allowed to lyse for 2 min, and then 150 µl of the cell lysate was transferred to a 96-well black solid plate, and luminescence was measured using a Victor 3 luminometer (Perkin Elmer).

The 50% and 80% inhibitory concentration (IC₅₀ and IC₈₀) values were calculated as the serum dilution that caused a 50% and 80% reduction respectively, in relative luminescence units (RLU) compared to the level in the virus control wells after subtraction of cell control RLU. All data were analyzed with 5-parameter curve fitting using neutralizing antibody analysis software provided by the CAVD Vaccine Immunology Statistical Center.

Example 3 – Stability of soluble CD4 domains

All soluble human CD4 domains tested contain a set of “base” mutations in human CD4 domain 1 (D1) over the wild-type sequence (SEQ ID NO:3) that enable the folding of human CD4 D1 on its own. Soluble CD4 D1 with this set of mutations is known as mD1.22 (Chen *et al.*, J Virol. 2014 Jan;88(2):1125-39) and the mutations therein consist of: L5Y, S23N, A55V, I76P, L96V, and F98V (SEQ ID NO:4, also referred to as D1m herein).

To achieve better developability and pharmacokinetics, further mutations were introduced into mD1.22 (SEQ ID NO:4) to enhance its thermal stability. The additional stabilizing mutations were designed based on several methodologies: 1) computational simulation by using Free Energy Perturbation (FEP+, Schrodinger, New York, NY USA); 2) computational simulation by using disulfide-bond scan in Molecular Operating Environment program (MOE, Chemical Computing Group, Montreal Canada); and 3) panning a library of human CD4 D1 with each residue mutated, one by one, to the other 19 types of amino acids (site saturation mutagenesis, TWIST BioScience, San Francisco, CA USA) using phage display under thermally challenging conditions (*i.e.*, incubating the phage at room temperature, 70 °C, and 80 °C, then selecting the CD4 domain variants that can still bind to recombinant HIV-1 gp120 (CN54 strain, Acro Biosystems, Beijing China)).

The best performing variants (SEQ ID NOs: 5-21) were fused with 6xHis tag at their C-termini, expressed and purified from mammalian cells using methods as described in Example 1, except that purification was via a Ni-NTA resin (Cytiva, Marlborough MA) instead of Mabselect SuRe column, with standard protocol from the vendor.

These purified CD4 D1 variants (with C-terminal 6xHis tag) were then evaluated to determine their melting temperature (T_m, using Prometheus System, NanoTemper, München

Germany)), which indicates thermal stability, as well as their anti-viral activity against HIV-1 pseudotyped virus (see Example 2 above for methods using ACTOne cells).

As shown in Table 3 below and in Figure 2, several CD4 D1 variants (SEQ ID NO:5-15) showed dramatically improved thermal stability over the "baseline" or "control" CD4 D1 (D1m, SEQ ID NO:4), while maintaining similar anti-viral activity.

Table 3: Melting temperature of soluble CD4 domains

CD4 Domain	SEQ ID NO	Tm (°C)
D1m	4	68.2
D1m-E91Q	6	72.4
D1m-E91H	7	72.6
D1m-E87G	8	71.9
D1m-N52W	9	72
D1m-K8V	5	77.1
D1m-K8I	10	75.9
D1m-K8C-G99C	11	88.8
D1m-T11C-K72C	12	79.9
D1m-E13C-I70C	13	78.8
D1m-H27C-G38C	14	90.1
D1m-K21C-G65C	15	80.1

Example 4 – Antigen Binding Protein Format and Linker Length

The fusion position of the CD4 domain in the anti-V3 bNAbs (*e.g.*, whether to fuse the CD4 domain to the light chain or heavy chain or both, whether to fuse the CD4 domain to the N-terminus or C-terminus of these chains, or whether to fuse the CD4 domain in the middle of the heavy chain (in between CH1 and CH2 domains)) has an effect on the anti-viral potency of the resulting bispecific as shown in Table 4.1 and Table 5 below.

We observed that the most potent bispecific molecule resulted from fusing CD4 D1 to the N-terminus of the heavy chain of bNAb1 (molecule 1 in Table 4.1, which neutralized 6 envelopes with IC50 < 160 pM and 1 envelope with IC50 about 3 nM in PSV assay). In this bispecific format, the linker length between the CD4 domain and bNAb1 heavy chain N-terminus does not particularly affect anti-viral activity (Figure 3A), but changes the pharmacokinetics (PK) of the resultant

bispecific molecules dramatically (Figure 3B).

As shown in Figure 3B, the shorter-linker bispecific (D1m_1xG4S_bNAb1, SEQ ID NOs:102 and 63) showed much better PK (longer half-life and lower clearance rate) than the longer-linker bispecific (D1m_4xG4S_bNAb1, SEQ ID NOs:105 and 63)) in a humanized mouse model (Tg32 strain where human neonatal Fc receptor (hFcRn) replaced the corresponding mouse gene (mFcRn), The Jackson Laboratory, Bar Harbor, Maine USA).

Table 4.1: (see also Fig. 7) IC50 (nM) of different bNAb1-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in a PSV assay (ACTOne cells)

Envelope	bNAb1-Derived Molecules										
	1	2	3	4	5	6	7	8	9	10	11
42368	0.16	0.91	1.49	4.90	1.24	15.73	5.60	1.44	4.32	1.58	>500
CC1/85	0.04	0.05	0.49	0.01	0.01	0.03	0.04	0.07	7.02	1.98	0.03
NL4-3	0.05	0.17	0.17	0.10	0.14	0.52	0.45	0.22	0.31	0.31	131.20
T278.50	0.12	0.12	1.29	0.04	0.02	0.06	0.13	0.11	3.99	1.43	0.17
X2088.C ₉	0.07	0.86	0.72	13.28	1.50	67.68	18.25	5.25	17.49	9.20	402.35
ZM106.9	0.05	0.18	0.38	0.04	0.03	0.05	0.07	0.09	26.02	15.14	0.07
CAP45.2.00.G3	3.73	2.68	2.53	13.89	2.13	20.44	102.16	20.41	131.43	20.48	>500

5

Table 4.1 (Fig 7.) Molecule Key:

- 1 = D1m-K8C-G99C_1xG4S_bNAb1 (SEQ ID NOs:121+63)
 - 2 = D1m-K8C-G99C_1xG4S_bNAb1-LC (SEQ ID NOs:62+115)
 - 3 = D1m_1xG4S_bNAb1-BothChains (SEQ ID NOs:102+109)
 - 4 = bNAb1-mid_1xG4S_D1m-K8C-G99C (SEQ ID NOs:116+63)
 - 5 = bNAb1-HC_1xG4S_D1m-K8C-G99C (SEQ ID NOs:117+63)
 - 6 = bNAb1-LC_1xG4S_D1m-K8C-G99C (SEQ ID NOs:62+118)
 - 7 = D1m_His (SEQ ID NO:4*) + bNAb1(SEQ ID NOs:62+63) (combo)
 - 8 = D1m-K8C-G99C_Fc (SEQ ID NO:158) + bNAb1 (SEQ ID NOs:62+63) (combo)
 - 9 = D1m_His (SEQ ID NO:4*)
 - 10 = D1m-K8C-G99C_Fc (SEQ ID NO:158)
 - 11 = bNAb1 (SEQ ID NOs:62+63)
- * plus a 6xHis tag (six C-terminal histidine residues)

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Table 4.2: IC₅₀ (nM) of a bNAb1-derived bispecific against entry inhibitor resistant envelopes in a PSV assay (ACTOne cells)

Type	Envelope	bNAb1-derived bispecific
10E8-insensitive	KER2008.12	0.05
	T266-60	0.06
	ZM106.9	0.05
	X2088.c9	0.07
	MB539.2B7	0.04
	JR2 with W680R and K683Q	0.03
N6-insensitive	BL01	0.07
	T278-50	0.12
	6471_V1_C16	0.06
	CH0219_E4	0.08
Temsavir- and Ibalizumab-insensitive	21-116102	0.36
	21-116108	0.01
Maraviroc-insensitive	MP5.7	0.13
	MP11.38	0.05
	MP35.2	0.13
	MP49.20	0.02
	MP53.36	0.04

Table 4.2 Molecule Key:

1 = D1m-K8C-G99C_1xG4S_bNAb1 (SEQ ID NOs:121+63)

Table 5: IC₅₀ (nM) of different bNAb2-, bNAb3- and bNAb4-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb2-Derived Molecules							bNAb3-Derived Molecules					bNAb4-Derived Molecules				CD4 Controls	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
42368	1.79	0.75	1.24	269.20	4.59	2.03	>500	0.37	0.17	5.01	2.12	>500	0.50	8.78	3.42	>500	4.32	1.58
CC1/85	0.64	0.46	0.33	107.46	9.44	1.98	>500	0.29	0.07	4.07	1.15	38.33	0.10	1.39	0.77	2.36	7.02	1.98
NL4-3	0.44	0.26	0.42	8.44	0.80	0.22	150.32	0.08	0.07	0.11	0.06	0.15	0.19	0.86	0.48	327.61	0.31	0.31
T278.50	0.16	0.10	0.09	0.48	0.30	0.14	0.43	0.02	0.03	0.02	0.02	0.01	0.13	0.23	0.41	0.47	3.99	1.43
X2088.C9	0.06	0.05	0.05	0.07	0.02	0.09	0.09	0.06	0.03	0.05	0.03	0.03	0.03	0.01	0.04	0.02	17.49	9.20
ZM106.9	0.05	0.02	0.02	0.04	0.01	0.02	0.03	0.03	0.03	0.01	0.03	0.03	0.03	0.02	0.03	0.03	26.02	15.14
CAP45.2.00.G3	0.10	0.10	0.11	2.49	12.51	3.63	36.53	1.69	0.25	96.75	61.81	>500	13.18	469.16	42.98	>500	131.43	20.48
HIV-2-AID	14.16	19.13	20.28	136.88	>500	*	>500	*	*	*	*	*	*	*	*	*	103.54	24.35
HIV-2-ATM88	1.34	1.22	2.28	2.06	70.58	*	>500	*	*	*	*	*	*	*	*	*	3.93	2.72
HIV-2-HCC-01	35.94	17.47	24.36	>500	>500	*	>500	*	*	*	*	*	*	*	*	*	>500	>300

* not tested

Table 5 Molecule Key:

- 5 1 = D1m-K8C-G99C_2xG4S_bNAb2 (SEQ ID NOs:137+69)
 2 = D1m-K8C-G99C_3xG4S_bNAb2 (SEQ ID NOs:138+69)
 3 = D1m-K8C-G99C_4xG4S_bNAb2 (SEQ ID NOs:139+69)
 4 = bNAb2-LC_1xG4S_D1m-K8C-G99C (SEQ ID NOs:68+143)
 5 = bNAb2 (SEQ ID NOs:68+69) + D1m_His (SEQ ID NO:4*) (combo)
 10 6 = bNAb2 (SEQ ID NOs:68+69) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)
 7 = bNAb2 (SEQ ID NOs:68+69)
 8 = D1m-K8C-G99C_1xG4S_bNAb3 (SEQ ID NOs:144+74)
 9 = D1m-K8C-G99C_4xG4S_bNAb3 (SEQ ID NOs:145+74)
 10 = bNAb3 (SEQ ID NOs:73+74) + D1m_His (SEQ ID NO:4*) (combo)

11 = bNAb3 (SEQ ID NOs:73+74) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

12 = bNAb3 (SEQ ID NOs:73+74)

13 = D1m-K8C-G99C_4xG4S_bNAb4 (SEQ ID NOs:147+79)

14 = bNAb4 (SEQ ID NOs:78+79) + D1m_His (SEQ ID NO:4*) (combo)

5 15 = bNAb4 (SEQ ID NOs:78+79) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

16 = bNAb4 (SEQ ID NOs:78+79)

17 = D1m_His (SEQ ID NO:4*)

18 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

* plus a 6xHis tag (six C-terminal histidine residues)

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Thermal stabilization of CD4 D1 (see Example 3 above) further enhanced the PK of the bispecific molecules (D1m-K8C-G99C_1xG4S_bNAb1, SEQ ID NOs:121 and 63; D1m-T11C-K72C_1xG4S_bNAb1, SEQ ID NOs:122 and 63; D1m-K8I_1xG4S_bNAb1, SEQ ID NOs:119 and 63; and D1m-K8V_1xG4S_bNAb1, SEQ ID NOs:120 and 63) as shown in Table 6 below.

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Table 6: The effect of (1) linker length between the CD4 domain and bNAb1 heavy chain, and (2) thermal stability of CD4 D1, on the PK of bispecific molecules in hFcRn mice (Tg32)

Molecule (SEQ ID NOs)	T _m of CD4 D1 (°C)	Half-life (days)	Clearance (ml/day/kg)
bNAb1 (62+63)	-	5.8	21.6
D1m_4xG4S_bNAb1 (105+63)	68.2	2.2	144
D1m_1xG4S_bNAb1 (102+63)	68.2	4.1	31.7
D1m-K8C-G99C_1xG4S_bNAb1 (121+63)	88.8	10.2	7.4
D1m-T11C-K72C_1xG4S_bNAb1 (122+63)	79.9	8.9	12.9
D1m-K8I_1xG4S_bNAb1 (119+63)	75.9	9.3	12
D1m-K8V_1xG4S_bNAb1 (120+63)	77.1	7.3	12.8

Accordingly, the best molecules for further development contain shorter linker lengths between the CD4 domain and bNAb (1xG4S) and contain a thermally stable CD4 domain(s).

Example 5 – Anti-Viral Activity of bNAb1-derived Bispecific Molecules

As shown in Figure 4A, bispecific molecules (D1m_1xG4S_bNAb1 bispecific having SEQ ID NOs:102 and 63; and D1m-K8C-G99C_1xG4S_bNAb1 bispecific having SEQ ID NOs:121 and 63) with human CD4 domains (CD4 D1m, SEQ ID NO:4, and a K8C and G99C variant thereof, SEQ ID NO:11, respectively) fused to the N-termini of each of the heavy chains of bNAb1 (SEQ ID NOs:62 and 63) via a GGGGS linker (SEQ ID NOs:90) showed dramatically and consistently higher activity (fully neutralized all envelopes tested with geometric mean IC₅₀ ~ 0.1 nM) than the two individual components (human CD4 domain and bNAb1) alone and their mixture (did not neutralize all envelopes tested, geometric mean IC₅₀ much higher than the bispecific molecules). This clearly shows that the fusion strategy provides strong anti-viral synergy.

Interestingly, soluble CD4 has been considered to have negative synergy with bNAb1 (Ivan *et al.*, Plos Biol. 17(1), Jan 2019), based on the result that mixing soluble CD4 with bNAb1 can weaken its anti-viral activity. We found that when soluble CD4 is fused with bNAb1 instead of being mixed, the anti-viral activity is enhanced dramatically.

Figure 4B shows the anti-viral activity of the bispecific molecules (SEQ ID NOs:102 and 63; and SEQ ID NOs:121 and 63) and control molecules against a panel of PSV strains insensitive to bNAb1. It can be seen that the bispecific molecules (fully neutralized all envelopes tested with geometric IC₅₀ ~ 0.2 nM) are much more potent than the individual components alone and their mixture (did not neutralize all envelopes tested, geometric mean IC₅₀ > 10 nM), indicating strong anti-viral synergy. Such synergy is most obvious against the strains that are insensitive to both CD4 and bNAb1, where only the bispecific molecules showed complete inhibition of viral entry with good activity, while neither soluble CD4 domain nor bNAb1 nor their mixture exhibited significant activity.

As shown in Table 4.1 above, although all of the bispecific molecules tested are able to inhibit viral entry, the most consistent and potent bispecific molecule is when the CD4 domain is fused to the N-termini of each of the heavy chains of bNAb1, which correlates well with the structure-based design (Figure 1D).

Furthermore, as shown in Table 4.2 above, when tested in PSV assay against the HIV-1 envelopes insensitive to several entry inhibitors (10E8, N6, Temsavir, Ibalizumab, and Maraviroc), the bispecific molecule (SEQ ID NOs:121 and 63) fully neutralized all these envelopes with IC₅₀s < 400 pM.

In addition, the most potent bispecific format (*i.e.* fusing CD4 D1 to the N-terminus of bNAb1 heavy chain) was converted to a single open-reading-frame (ORF) version, by replacing the Fab arm with a scFv fragment of bNAb1. As shown in Figure 5, several such single-ORF molecules, also referred to as scFv-Fc molecules (SEQ ID NOs:152-157), showed equivalent potency as the leading bispecific format in PSV assays (ACTOne cells).

Given that these single-ORF molecules are each encoded by a single <2kb gene and contain an Fc domain for an increased half-life, they can be readily delivered by gene therapy vehicles, such as adeno-associated virus (AAV), enabling them to be constantly secreted into circulation at a therapeutic concentration. Such a strategy would result in an 'ultra-long' acting therapy against HIV-1.

Example 6 – Anti-Viral Activity of bNAb6-derived Bispecific Molecules

Figure 6 and Table 7 below show the anti-viral activity of bNAb6-derived bispecific molecules and control molecules.

The plot of IC₅₀ values (Figure 6) from PSV assays (ACTOne) clearly shows that when CD4 domain 1 (D1m, SEQ ID NO:4) or domains 1 and 2 (D1mD2, SEQ ID NO:2) is fused to the N-termini of the bNAb6 (SEQ ID NOs:88 and 89) heavy chain, the resultant molecule is much more active than a simple mixture of soluble CD4 domain and bNAb6 antibody, indicating strong synergy.

Table 7 shows the anti-viral activity of the bispecific molecules (D1m_4xG4S_bNAb6, SEQ ID NOs:151 and SEQ ID NOs:89; D1mD2_4xG4S_bNAb6, SEQ ID NO:150 and SEQ ID NO:89; and D1m-K8C-G99C_1xG4S_bNAb6 (SEQ ID NOs: 362+89)) and control molecules against HIV-1 strains resistant to bNAb6 antibody. As can be seen, the bNAb6-derived bispecific molecules are much more potent than the mixtures against double-resistant or insensitive strains.

Table 7: IC₅₀ (nM) of bNAb6-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb6-Derived Molecules						
	1	2	3	4	5	6	7
CAP45.2.00.G3	17.79	>500	5.90	>500	131.43	>500	>500
CH119	8.30	93.62	2.60	49.76	90.66	119.94	>500
BJOX2000	17.27	45.23	3.10	16.96	70.87	33.40	>500

X1632_S2_B10	1.38	20.26	0.75	19.70	16.25	14.94	>500
TRO11	1.99	16.55	1.14	14.64	68.43	17.27	>500
T278.50	0.71	9.26	1.08	9.51	3.99	16.02	>500
LAI	1.52	6.76	0.93	7.46	8.79	5.41	>500
42368	1.30	6.05	0.54	5.75	4.32	7.29	>500
NL4-3	0.17	1.31	0.11	0.75	0.31	0.74	>500
HXB2	0.06	0.08	0.03	0.06	0.11	0.07	>500

Envelope	bNAb6-Derived Molecules			
	8	9	7	10
X2088.C9	0.17	0.15	0.15	9.20
ZM106.9	0.10	0.10	0.08	15.14
3637_V5_C3	103.00	328.50	>500	>500
3468_V1_C12	20.85	47.70	>500	64.15
Q461_E2	4.00	12.70	>500	11.76
3326_V4_C3	72.10	483.00	>500	>500
42368	0.92	2.13	>500	1.58
NL4-3	0.27	*	>500	0.31
T278.50	1.33	*	>500	1.43
CAP45.2.00.G3	9.64	*	>500	20.48
CC1/85	0.42	*	*	1.98
HIV-2-HCC-01	175.65	*	*	>300

* not tested

5 Table 7 Molecule Key:

1 = D1m_4xG4S_bNAb6 (SEQ ID NOs:151+89)

2 = D1m_His (SEQ ID NO:4*) + bNAb6 (SEQ ID NOs:88+89)

3 = D1mD2_4xG4S_bNAb6 (SEQ ID NOs:150+89)

- 4 = D1mD2_His (SEQ ID NO:2*)+ bNAb6 (SEQ ID NOs:88+89)
 5 = D1m_His (SEQ ID NO:4*)
 6 = D1mD2_His (SEQ ID NO:2*)
 7 = bNAb6 (SEQ ID NOs:88+89)
 5 8 = D1m-K8C-G99C_1xG4S_bNAb6 (SEQ ID NOs: 362+89)
 9 = bNAb6 (SEQ ID NOs:88+89) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)
 10 = D1m-K8C-G99C_Fc (SEQ ID NO:158)
 * plus a 6xHis tag (six C-terminal histidine residues)

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Example 7 – Anti-Viral Activity of further anti-V3 bNAb-derived Bispecific

Molecules

Additional bispecific molecules comprising CD4 domains fused to other anti-V3 bNAbs (bNAb2, bNAb3, bNAb4,) were tested, with the results shown in Table 5 above and Tables 8-23 below, a
 15 similar synergistic anti-viral activity was observed against one or more envelopes.

Accordingly, the strategy of fusing a soluble CD4 domain to anti-V3 loop bNAb can be generally applied to enhance the potency and spectrum of these bNAbs.

Conclusions

On the free HIV-1 virus, the V3 loop of gp120 is in its native “closed” state. The V3 loop is
 20 known to adopt various conformations (from different structures in Protein Databank), indicating its flexibility. During HIV-1 infection, the binding of gp120 to cell surface CD4 triggers conformational changes of the V3 loop to “open” itself to bind co-receptors such as CXCR4 or CCR5.

Anti-V3 bNAbs mainly recognizes a pattern of glycans on the V3 loop of gp120, along with the backbone atoms of a few amino acid residues in the V3 loop (Krumm *et al.*, Retrovirology 13(8),
 25 2016). Such “plasticity” of the V3 loop may facilitate the binding of anti-V3 loop bNAbs to this loop when it is “opened” by CD4 binding.

We hypothesize that when soluble CD4 and anti-V3 bNAbs are simply mixed together, the conformational change of the V3 loop triggered by soluble CD4 may be too transient for the anti-V3 bNAb to capture, therefore no synergistic activity is observed. But, in the context of bispecific
 30 molecules, when CD4 binds to the CD4 binding site (CD4bs) on gp120, the anti-V3 bNAb is at such high local concentration that it can immediately capture the exposed V3 loop glycans; this in turn could stabilize the binding of soluble CD4 to gp120 and form a positive feedback loop.

Table 8: IC50 (nM) of different bNAbs-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAbs-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	1.11	2.35	>500	1.58
CC1/85	0.67	2.53	>500	1.98
NL4-3	0.26	0.26	2.62	0.31
T278.50	3.21	1.59	96.06	1.43
X2088.C9	0.54	0.14	0.17	9.20
ZM106.9	0.94	1.09	2.04	15.14
CAP45.2.00.G3	44.41	63.82	>500	20.48
25710	0.51	0.49	8.10	1.32
TRO11	0.91	0.58	0.39	146.64
398F1	4.85	1.35	1.83	90.47
CNE8	134.25	240.63	51.37	346.64
X2278	0.60	5.46	9.53	44.56
BJOX2000	1.11	1.86	126.82	2.34
X1632	2.32	2.38	>500	1.82
CE1176	1.04	2.59	57.07	4.22
246F3	7.18	5.27	40.90	4.28
CH119	2.63	3.22	63.54	3.25

CE0217	2.42	2.19	409.83	2.53
CNE55	20.92	36.59	3300.62	41.82
JR-CSF	0.31	0.45	0.64	5.47
JRFL	0.42	1.16	58.23	1.12

Table 8 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb5 (SEQ ID NOs: 148+84)

Combo = bNAb5 (SEQ ID NOs:83+84) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb5 (SEQ ID NOs:83+84)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 9: IC50 (nM) of different bNAb7-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAb7-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	1.38	2.40	>500	1.58
X2088.C9	0.09	0.19	0.22	9.20
ZM106.9	0.03	0.03	0.04	15.14
3326_V4_C3	17.63	>500	>500	>500
3637_V5_C3	260.71	388.10	>500	>500
3468_V1_C12	2.50	32.37	>500	64.15
620345_C1	4.03	5.83	>500	99.28
0260.v5.c36	0.16	0.22	0.75	119.29

TH976_17	70.02	35.04	>500	39.05
Q461_E2	14.61	20.92	>500	11.76
928_28	0.43	0.57	32.73	0.77
YU-2	0.07	0.16	0.58	0.20
6471_V1_C16	0.59	0.50	>500	5.07
93UG065	50.99	40.15	>500	142.61
CC1/85	0.21	*	*	1.98
NL4-3	0.33	*	*	0.31
T278.50	1.79	*	*	1.43
CAP45.2.00.G3	0.22	*	*	20.48
HIV-2-HCC-01	183.57	*	*	>300

* not tested

Table 9 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAbs7 (SEQ ID NO: 338 + 259)

Combo = bNAbs7 (SEQ ID NOs: 258+ 259) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAbs7 (SEQ ID NOs: 258 + 259)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 10: IC50 (nM) of different bNAbs-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAbs-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
X2088.C9	0.11	0.22	0.23	9.20
ZM106.9	0.02	0.03	0.03	15.14
3637_V5_C3	104.00	305.50	>500	>500
3468_V1_C12	0.06	0.81	1.70	64.15
Q461_E2	7.06	6.59	>500	11.76
3326_V4_C3	75.70	367.00	>500	>500
42368	0.97	1.35	>500	1.58
CC1/85	0.14	*	*	1.98
NL4-3	0.14	*	*	0.31
T278.50	1.20	*	*	1.43
CAP45.2.00.G3	2.72	*	*	20.48
HIV-2-HCC-01	33.29	*	*	>300

* not tested

5 **Table 10 Molecule Key:**

Bispecific = D1m-K8C-G99C_1xG4S_bNAbs (SEQ ID Nos: 339 + 264)

Combo = bNAbs (SEQ ID Nos: 263 +264) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

mAb = bNAbs (SEQ ID Nos: 263 + 264)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 11: IC50 (nM) of different bNAb9-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAb9-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	0.15	1.35	>500	1.58
X2088.C9	0.18	9.50	>500	9.20
ZM106.9	0.08	16.28	>500	15.14
3326_V4_C3	3.87	>500	>500	>500
3637_V5_C3	6.74	>500	>500	>500
3468_V1_C12	1.51	23.22	>500	64.15
620345_C1	1.02	3.25	>500	99.28
0260.v5.c36	0.19	0.14	0.26	119.29
TH976_17	20.42	27.24	>500	39.05
Q461_E2	0.55	18.54	>500	11.76
928_28	0.20	0.42	>500	0.77
YU-2	0.12	0.09	0.36	0.20
6471_V1_C16	0.11	1.17	>500	5.07
93UG065	0.18	31.44	>500	142.61
CC1/85	0.03	*	*	1.98
NL4-3	0.07	*	*	0.31

T278.50	0.14	*	*	1.43
CAP45.2.00.G3	1.03	*	*	20.48
HIV-2-HCC-01	1.68	*	*	>300

* not tested

Table 11 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAbs (SEQ ID NOs: 340 + 269)

Combo = bNAbs (SEQ ID NOs: 268 + 269) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAbs (SEQ ID NOs: 268 + 269)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 12: IC50 (nM) of different bNAbs10-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

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	bNAbs10-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	0.17	2.29	189.62	1.58
X2088.C9	0.17	9.94	233.05	9.20
ZM106.9	0.09	24.96	71.31	15.14
3326_V4_C3	14.28	>500	>500	>500
3637_V5_C3	0.36	439.54	>500	>500
3468_V1_C12	0.21	38.64	258.28	64.15
620345_C1	0.33	0.85	>500	99.28
0260.v5.c36	0.17	0.29	0.48	119.29

TH976_17	18.49	31.63	>500	39.05
Q461_E2	0.41	15.03	>500	11.76
928_28	0.17	0.42	320.41	0.77
YU-2	0.12	0.23	0.81	0.20
6471_V1_C16	0.12	1.23	91.84	5.07
93UG065	0.13	0.12	0.21	142.61
CC1/85	0.04	*	*	1.98
NL4-3	0.08	*	*	0.31
T278.50	0.16	*	*	1.43
CAP45.2.00.G3	4.55	*	*	20.48
HIV-2-HCC-01	0.95	*	*	>300

* not tested

Table 12 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb10 (SEQ ID Nos: 341 + 274)

Combo = bNAb10 (SEQ ID Nos: 273 + 274) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb10 (SEQ ID Nos: 273 + 274)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 13: IC50 (nM) of different bNAbs11-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAbs11-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	0.48	2.65	>500	1.58
X2088.C9	0.15	7.06	95.12	9.20
ZM106.9	0.07	14.74	73.68	15.14
3326_V4_C3	51.71	146.99	>500	>500
3637_V5_C3	6.73	410.00	>500	>500
3468_V1_C12	1.80	25.99	>500	64.15
620345_C1	1.27	10.97	438.41	99.28
0260.v5.c36	0.20	0.42	0.57	119.29
TH976_17	17.37	55.43	>500	39.05
Q461_E2	0.51	12.32	>500	11.76
928_28	0.27	0.46	>500	0.77
YU-2	0.10	0.26	0.76	0.20
6471_V1_C16	0.25	0.71	253.40	5.07
93UG065	0.22	24.72	89.50	142.61
CC1/85	0.09	*	*	1.98
NL4-3	0.16	*	*	0.31
T278.50	0.26	*	*	1.43

CAP45.2.00.G3	5.82	*	*	20.48
HIV-2-HCC-01	8.69	*	*	>300

* not tested

Table 13 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb11 (SEQ ID NOs: 342 + 279)

Combo = bNAb11 (SEQ ID NOs: 278 + 279) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb11 (SEQ ID NOs: 278 + 279)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 14: IC50 (nM) of different bNAb12-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb12-Derived Molecules						CD4 Controls
	Bispecific1	Bispecific2	Bispecific3	Bispecific4	Combo	mAb	CD4
X2088.C9	0.59	13.09	4.43	>500	7.37	>500	9.20
ZM106.9	0.13	0.13	0.27	3.37	1.55	1.85	15.14
3637_V5_C3	9.45	130.00	62.45	>500	474.07	>500	>500
3468_V1_C12	0.82	2.94	4.41	103.85	16.30	343.72	64.15
Q461_E2	0.26	0.3	0.5	4.5	5.16	41.90	11.76
3326_V4_C3	9.63	63.69	81.80	>500	266.93	>500	>500
42368	0.15	6.2	1.3	167.0	1.84	344.45	1.58
620345_C1	0.33	*	*	*	2.13	179.12	99.28
0260.v5.c36	0.44	*	*	*	0.50	5.19	119.29
TH976_17	29.83	*	*	*	36.40	>500	39.05

928_28	0.46	*	*	*	0.48	482.30	0.77
YU-2	0.21	*	*	*	0.29	77.41	0.20
6471_V1_C16	0.26	*	*	*	0.59	>500	5.07
93UG065	0.42	*	*	*	0.86	3.17	142.61
CC1/85	0.12	*	*	*	*	*	1.98
NL4-3	0.14	*	*	*	*	*	0.31
T278.50	0.19	*	*	*	*	*	1.43
CAP45.2.00.G3	1.29	*	*	*	*	*	20.48
HIV-2-HCC-01	4.04	*	*	*	*	*	>300

* not tested

Table 14 Molecule Key:

Bispecific1 = D1m-K8C-G99C_1xG4S_bNAb12 (SEQ ID NOs: 343 + 284)

Bispecific2 = bNAb12_HC_1xG4S_D1m-K8C-G99C (SEQ ID NOs: 344 + 284)

5 Bispecific3 = D1m-K8C-G99C_1xG4S_LC-bNAb12 (SEQ ID NOs: 283 + 345)

Bispecific4 = bNAb12_LC_1xG4S_D1m-K8C-G99C (SEQ ID NOs: 283 + 346)

Combo = bNAb12 (SEQ ID NOs: 283 + 284) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

mAb = bNAb12 (SEQ ID NOs: 283 + 284)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 15: IC50 (nM) of different bNAbs13-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAbs13-Derived Molecules			CD4 Controls
Envelope	Bispecific	Combo	mAb	CD4
42368	0.24	1.52	>500	1.58
X2088.C9	2.05	5.18	>500	9.20
ZM106.9	0.28	3.04	22.43	15.14
3326_V4_C3	52.07	191.00	>500	>500
3637_V5_C3	37.30	266.00	>500	>500
3468_V1_C12	4.25	25.00	>500	64.15
Q461_E2	0.50	4.14	>500	11.76
CC1/85	0.19	*	*	1.98
620345_C1	3.58	*	>500	99.28
0260.v5.c36	0.36	*	18.10	119.29
TH976_17	37.26	*	>500	39.05
928_28	0.79	*	201.39	0.77
YU-2	0.17	*	48.30	0.20
6471_V1_C16	0.16	*	133.35	5.07
93UG065	0.58	*	46.41	142.61
NL4-3	0.21	*	*	0.31
T278.50	0.34	*	*	1.43

CAP45.2.00.G3	2.26	*	*	20.48
HIV-2-HCC-01	11.13	*	*	>300

* not tested

Table 15 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb13 (SEQ ID NOs: 347 + 289)

Combo = bNAb13 (SEQ ID NOs: 288 + 289) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb13 (SEQ ID NOs: 288 + 289)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 16: IC50 (nM) of different bNAb14-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

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Envelope	bNAb14-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	1.26	1.73	2.79	9.20
ZM106.9	0.62	1.08	1.26	15.14
3637_V5_C3	22.85	84.20	>500	>500
3468_V1_C12	17.35	35.05	>500	64.15
Q461_E2	2.77	11.40	>500	11.76
3326_V4_C3	196.50	>500	>500	>500
42368	1.15	1.84	>500	1.58
CC1/85	1.74	*	*	1.98
NL4-3	0.29	*	*	0.31

T278.50	6.81	*	*	1.43
CAP45.2.00.G3	2.85	*	*	20.48
HIV-2-HCC-01	98.75	*	*	>300

* not tested

Table 16 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb14 (SEQ ID NOs: 348 + 294)

Combo = bNAb14 (SEQ ID NOs: 293 + 294) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb14 (SEQ ID NOs: 293 + 294)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 17: IC50 (nM) of different bNAb15-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb15-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	1.19	0.95	2.58	9.20
ZM106.9	0.68	0.40	1.34	15.14
3637_V5_C3	25.45	5.33	5.00	>500
3468_V1_C12	22.00	35.80	>500	64.15
Q461_E2	2.81	5.98	>500	11.76
3326_V4_C3	142.00	>500	>500	>500
42368	1.11	1.55	>500	1.58
CC1/85	1.65	*	*	1.98
NL4-3	0.36	*	*	0.31

T278.50	7.66	*	*	1.43
CAP45.2.00.G3	4.48	*	*	20.48
HIV-2-HCC-01	142.16	*	*	>300

* not tested

Table 17 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb15 (SEQ ID NOs: 349 + 299)

Combo = bNAb15 (SEQ ID NOs: 298 + 299) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb15 (SEQ ID NOs: 298 + 299)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 18: IC50 (nM) of different bNAb16-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb16-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	0.25	2.02	289.00	9.20
ZM106.9	2.42	11.63	>500	15.14
3637_V5_C3	19.15	129.50	>500	>500
3468_V1_C12	11.21	26.75	>500	64.15
Q461_E2	2.03	6.06	>500	11.76
3326_V4_C3	31.75	148.50	>500	>500
42368	0.69	1.92	>500	1.58
CC1/85	0.56	*	*	1.98
NL4-3	0.14	*	*	0.31

T278.50	2.29	*	*	1.43
CAP45.2.00.G3	2.08	*	*	20.48
HIV-2-HCC-01	237.46	*	*	>300

* not tested

Table 18 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb16 (SEQ ID NOs: 350 +304)

Combo = bNAb16 (SEQ ID NOs: 303 + 304) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb16 (SEQ ID NOs: 303 + 304)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 19: IC50 (nM) of different bNAb17-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb17-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	0.84	2.44	>500	9.20
ZM106.9	8.48	9.13	>500	15.14
3637_V5_C3	45.75	97.90	>500	>500
3468_V1_C12	39.60	27.85	>500	64.15
Q461_E2	6.70	6.03	>500	11.76
3326_V4_C3	287.50	171.50	>500	>500
42368	2.14	1.50	>500	1.58
CC1/85	0.91	*	*	1.98
NL4-3	0.43	*	*	0.31

T278.50	4.25	*	*	1.43
CAP45.2.00.G3	1.39	*	*	20.48
HIV-2-HCC-01	300.00	*	*	>300

* not tested

Table 19 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb17 (SEQ ID NOs: 351 + 309)

Combo = bNAb17 (SEQ ID NOs: 308 + 309) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb17 (SEQ ID NOs: 308 + 309)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 20: IC50 (nM) of different bNAb18-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb18-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	0.63	0.26	0.20	9.20
ZM106.9	0.25	0.08	0.11	15.14
3637_V5_C3	102.85	377.00	>500	>500
3468_V1_C12	26.60	38.60	>500	64.15
Q461_E2	3.16	9.98	>500	11.76
3326_V4_C3	157.00	369.50	>500	>500
42368	0.94	2.18	>500	1.58
CC1/85	2.06	*	*	1.98
NL4-3	0.33	*	*	0.31

T278.50	5.83	*	*	1.43
CAP45.2.00.G3	20.89	*	*	20.48
HIV-2-HCC-01	93.74	*	*	>300

* not tested

Table 20 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb18 (SEQ ID NOs: 352 + 314)

Combo = bNAb18 (SEQ ID NOs: 313 + 314) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb18 (SEQ ID NOs: 313 + 314)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 21: IC50 (nM) of different bNAb19-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

Envelope	bNAb19-Derived Molecules			CD4 Controls
	Bispecific	Combo	mAb	CD4
X2088.C9	1.63	4.40	>300	9.20
ZM106.9	3.91	8.27	>300	15.14
3637_V5_C3	16.50	168.00	>300	>500
3468_V1_C12	4.56	24.54	>300	64.15
Q461_E2	3.18	4.49	>300	11.76
3326_V4_C3	130.00	241.67	>300	>500
42368	1.16	1.10	>300	1.58
CC1/85	0.52	*	*	1.98
NL4-3	0.23	*	*	0.31

T278.50	0.79	*	*	1.43
CAP45.2.00.G3	5.54	*	*	20.48
HIV-2-HCC-01	6.54	*	*	>300

* not tested

Table 21 Molecule Key:

Bispecific = D1m-K8C-G99C_1xG4S_bNAb19 (SEQ ID NOs: 353 + 319)

Combo = bNAb19 (SEQ ID NOs: 318 + 319) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

5 mAb = bNAb19 (SEQ ID NOs: 318 + 319)

CD4 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 22: IC50 (nM) of different bNAb20/21/22-derived bispecific formats and control molecules against a panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAb20-Derived Molecules			bNAb21-Derived Molecules			bNAb22-Derived Molecules			CD4 Controls
Envelope	1	2	3	4	5	6	7	8	9	10
X2088.C9	0.03	0.04	0.04	0.02	0.02	0.02	0.04	0.03	0.04	9.20
ZM106.9	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	15.14
3637_V5_C3	6.2	21.9	61.6	4.7	117.0	326.0	6.8	115.0	484.0	>500
3468_V1_C1 2	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.02	0.01	64.15
Q461_E2	0.9	5.9	72.1	0.4	10.0	186.0	2.0	7.1	>500	11.76
3326_V4_C3	1.3	24.1	24.0	0.3	14.5	12.5	0.6	6.1	16.0	>500
42368	0.5	3.7	59.4	0.2	1.9	128.0	0.7	1.2	391.0	1.58

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Table 22 Molecule Key:

1 = D1m-K8C-G99C_1xG4S_bNAb20 (SEQ ID NOs: 354 + 324)

2 = bNAb20 (SEQ ID NOs: 323 + 324) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)

3 = bNAb20 (SEQ ID NOs: 323 + 324)

- 4 = D1m-K8C-G99C_1xG4S_bNAb21 (SEQ ID NOs: 355 + 329)
- 5 = bNAb21 (SEQ ID NOs: 328 + 329) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)
- 6 = bNAb21 (SEQ ID NOs: 328 + 329)
- 7 = D1m-K8C-G99C_1xG4S_bNAb22 (SEQ ID NOs: 356 + 366)
- 5 8 = bNAb22 (SEQ ID NOs: 332 + 366) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)
- 9 = bNAb22 (SEQ ID NOs: 332 + 366)
- 10 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Table 23: IC50 (nM) of different bNAb23-derived bispecific formats and control molecules against a

10 panel of HIV-1 envelopes in PSV assay (ACTOne cells)

	bNAb23-Derived Molecules					CD4 Controls
Envelope	1	2	3	4	5	6
X2088.C9	6.05	0.09	12.05	5.89	>500	9.20
ZM106.9	3.96	0.12	6.06	15.06	17.4	15.14
3637_V5_C3	129.50	2.26	>500	294.00	>500	>500
3468_V1_C12	62.10	6.17	384.00	53.05	>500	64.15
Q461_E2	4.29	0.80	116.00	7.11	>500	11.76
3326_V4_C3	44.90	3.94	108.00	173.00	15.3	>500
42368	0.62	0.30	10.70	1.57	>500	1.58

Table 23 Molecule Key:

- 1 = D1m-K8C-G99C_1xG4S_bNAb23 (SEQ ID NOs: 357 + 337)
- 2 = D1m-K8C-G99C_1xG4S_bNAb23-LC (SEQ ID NOs: 336 + 358)
- 15 3 = bNAb23-HC_1xG4S_D1m-K8C-G99C (SEQ ID NOs: 359 + 337)
- 4 = bNAb23 (SEQ ID NOs: 336 + 337) + D1m-K8C-G99C_Fc (SEQ ID NO:158) (combo)
- 5 = bNAb23 (SEQ ID NOs: 336 + 337)
- 6 = D1m-K8C-G99C_Fc (SEQ ID NO:158)

Example 8 – Broad Spectrum Anti-Viral Activity of a bNAb1-derived Bispecific Molecule (SEQ ID NO:121 and SEQ ID NO:63)

A selected bispecific molecule derived from bNAb1 having two heavy chains (SEQ ID NO:121) and two light chains (SEQ ID NO:63) was independently tested against an external panel of pseudo-typed HIV-1 virus containing 119 HIV-1 envelopes and 1 control envelope in a PSV assay (TMZ.bl – see Example 3 above), to further evaluate its breadth and potency. As shown in Table 24, the bispecific molecule completely and potently inhibited all of the 119 HIV-1 envelopes in this assay.

Table 24: IC50 and IC80 values (µg/ml) of bNAb1-derived bispecific molecule (SEQ ID NO:121 and SEQ ID NO:63) against 119 HIV-1 envelopes in PSV assay

Virus ID	Clade*	IC50	IC80	MPI
6535.3	B	0.007	0.021	100
QH0692.42	B	0.020	0.066	100
SC422661.8	B	0.013	0.032	100
PVO.4	B	0.010	0.037	100
TRO.11	B	0.011	0.026	100
AC10.0.29	B	0.006	0.022	100
RHPA4259.7	B	0.007	0.021	100
THRO4156.18	B	0.027	0.095	100
REJO4541.67	B	0.022	0.054	100
TRJO4551.58	B	0.006	0.022	100
WITO4160.33	B	0.024	0.099	100
CAAN5342.A2	B	0.023	0.085	100
WEAU_d15_410_787	B (T/F)	0.009	0.033	100
1006_11_C3_1601	B (T/F)	0.005	0.014	100
1054_07_TC4_1499	B (T/F)	0.014	0.041	100
1056_10_TA11_1826	B (T/F)	0.009	0.026	100
1012_11_TC21_3257	B (T/F)	0.004	0.015	100
6240_08_TA5_4622	B (T/F)	0.019	0.054	100
6244_13_B5_4576	B (T/F)	0.011	0.039	100
62357_14_D3_4589	B (T/F)	0.021	0.060	100

SC05_8C11_2344	B (T/F)	0.016	0.045	100
Du156.12	C	0.005	0.018	100
Du172.17	C	0.010	0.029	100
Du422.1	C	0.011	0.044	100
ZM197M.PB7	C	1.148	5.807	100
ZM214M.PL15	C	0.020	0.069	100
ZM233M.PB6	C	0.046	0.171	100
ZM249M.PL1	C	0.006	0.021	100
ZM53M.PB12	C	0.275	0.908	100
ZM109F.PB4	C	0.036	0.132	100
ZM135M.PL10a	C	0.030	0.119	100
CAP45.2.00.G3	C	0.260	2.976	100
CAP210.2.00.E8	C	0.023	0.102	100
HIV-001428-2.42	C	0.002	0.004	100
HIV-0013095-2.11	C	0.016	0.042	100
HIV-16055-2.3	C	0.044	0.159	100
HIV-16845-2.22	C	0.042	0.147	100
Ce1086_B2	C (T/F)	0.085	0.297	100
Ce0393_C3	C (T/F)	0.008	0.022	100
Ce1176_A3	C (T/F)	0.010	0.028	100
Ce2010_F5	C (T/F)	0.206	0.693	100
Ce0682_E4	C (T/F)	0.080	1.232	100
Ce1172_H1	C (T/F)	0.005	0.015	100
Ce2060_G9	C (T/F)	0.016	0.059	100
Ce703010054_2A2	C (T/F)	0.342	1.030	100
BF1266.431a	C (T/F)	0.106	1.283	100
246F C1G	C (T/F)	0.009	0.031	100
249M B10	C (T/F)	0.627	5.222	99
ZM247v1(Rev-)	C (T/F)	0.004	0.014	100
7030102001E5(Rev-)	C (T/F)	0.010	0.025	100
1394C9G1(Rev-)	C (T/F)	0.008	0.028	100
Ce704809221_1B3	C (T/F)	0.014	0.060	100

CNE19	BC	0.054	0.270	100
CNE20	BC	0.001	0.004	100
CNE21	BC	0.004	0.013	100
CNE17	BC	0.023	0.073	100
CNE30	BC	0.026	0.074	100
CNE52	BC	0.018	0.043	100
CNE53	BC	0.005	0.013	100
CNE58	BC	0.008	0.022	100
MS208.A1	A	1.457	6.230	100
Q23.17	A	0.010	0.025	100
Q461.e2	A	0.025	0.086	100
Q769.d22	A	0.046	0.122	100
Q259.d2.17	A	0.167	0.459	100
Q842.d12	A	0.006	0.015	100
0260.v5.c36	A	0.031	0.111	100
3415.v1.c1	A	0.010	0.028	100
3365.v2.c20	A	0.011	0.036	100
191955_A11	A (T/F)	0.032	0.115	100
191084 B7-19	A (T/F)	0.009	0.027	100
9004SS_A3_4	A (T/F)	0.008	0.023	100
T257-31	CRF02_AG	0.022	0.064	100
928-28	CRF02_AG	0.029	0.086	100
263-8	CRF02_AG	0.011	0.043	100
T250-4	CRF02_AG	0.005	0.012	100
T251-18	CRF02_AG	0.023	0.064	100
T278-50	CRF02_AG	0.010	0.027	100
T255-34	CRF02_AG	0.025	0.091	100
211-9	CRF02_AG	0.025	0.085	100
235-47	CRF02_AG	0.170	0.800	100
620345.c01	CRF01_AE	0.247	2.737	100
CNE8	CRF01_AE	0.007	0.021	100

C1080.c03	CRF01_AE	0.014	0.027	100
R2184.c04	CRF01_AE	0.006	0.022	100
R1166.c01	CRF01_AE	0.252	1.001	100
R3265.c06	CRF01_AE	0.065	0.254	100
C2101.c01	CRF01_AE	0.005	0.016	100
C3347.c11	CRF01_AE	0.006	0.015	100
C4118.c09	CRF01_AE	0.512	4.356	100
CNE5	CRF01_AE	0.014	0.038	100
BJOX009000.02.4	CRF01_AE	0.006	0.020	100
BJOX015000.11.5	CRF01_AE (T/F)	0.013	0.035	100
BJOX010000.06.2	CRF01_AE (T/F)	0.035	0.114	100
BJOX025000.01.1	CRF01_AE (T/F)	0.035	0.140	100
BJOX028000.10.3	CRF01_AE (T/F)	0.004	0.010	100
X1193_c1	G	0.015	0.034	100
P0402_c2_11	G	0.005	0.019	100
X1254_c3	G	0.014	0.040	100
X2088_c9	G	0.017	0.048	100
X2131_C1_B5	G	0.014	0.039	100
P1981_C5_3	G	0.014	0.038	100
X1632_S2_B10	G	0.027	0.097	100
3016.v5.c45	D	0.041	0.117	100
A07412M1.vrc12	D	0.009	0.034	100
231965.c01	D	0.023	0.068	100
231966.c02	D	0.006	0.018	100
6405.v4.c34	D	0.029	0.082	100
3817.v2.c59	CD	0.025	0.063	100
6480.v4.c25	CD	0.008	0.024	100
6952.v1.c20	CD	0.037	0.109	100
6811.v7.c18	CD	0.004	0.014	100
89-F1_2_25	CD	0.035	0.110	100

3301.v1.c24	AC	0.005	0.018	100
6041.v3.c23	AC	0.109	0.553	100
6540.v4.c1	AC	0.002	0.012	100
6545.v4.c1	AC	0.011	0.031	100
0815.v3.c3	ACD	0.003	0.008	100
3103.v3.c10	ACD	0.012	0.027	100
MuLV	Negative Control	>50	>50	0

Example 9 – Activity of bNAb1-derived Bispecific Molecules against Laboratory and Clinical Isolates of HIV-1 in Replicating Virus Assays

Method

5 Clinical and laboratory isolates

All clinical and laboratory isolates were originally obtained from the NIH AIDS Reagent Program (currently NIH HIV Reagent Program, <https://www.hivreagentprogram.org/>). The proviral clone of NL₄₋₃ (obtained from NIH) was used to make the replicating reporter virus NLRepRluc, in which a section of the nef gene from the proviral clone of NL₄₋₃ was replaced with the Renilla luciferase gene. Virus was produced through transfection of HEK293T cells using Lipofectamine Plus (Invitrogen, Carlsbad, CA), according to the manufacturer's instructions. The replication-competent virus was harvested 3 days after transfection of HEK 293T cells with the modified pNLRepRluc proviral clone and titrated in MT-2 cells using luciferase activity as a biomarker.

15 Clinical isolates were initially propagated in human PBMC cells. T-tropic laboratory virus strains IIIB, NL₄₋₃, HXB2, LAI, MN and RF viruses were propagated in MT-2 cells, while M-tropic laboratory strains BaL and JR-FL were propagated in PM1 cells. Titers of virus stocks were determined in PBMC using a virus infectivity assay with a p24 antigen endpoint (p24 ELISA kit; PerkinElmer Life Sciences). All those viruses were further titrated in MT2 or CCR5-B6 cells before experiments by using luciferase enzyme activity as an endpoint for 50% tissue culture infectious dose (TCID₅₀) determination.

20 Cells

MT-2 cells were obtained from the American Type Culture Collection (ATCC) and were propagated in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 units/ml of penicillin G, 100 µg/ml of streptomycin, 10 mM HEPES buffer pH 7.55 and 2-

mM L-glutamine. HEK293T cells were obtained from the ATCC and propagated in DMEM media supplemented with 10% heat-inactivated FBS. The ACTOne cells were originally derived from HEK293T cells and express CD4, CCR5 and CXCR4. They are grown in DMEM media supplemented with 10% heat-inactivated FBS, 100 U/ml of penicillin G, 100 µg/ml of streptomycin, 5 µg/ml blasticidin, 200 µg/ml G418 and 1.5 µg/ml puromycin. CCR5-B6 cells were generated in-house at ViiV Branford CT USA. To generate CCR5-B6 cells, human CCR5 lentiviral particles were used to infect the MT4-B6 cells (obtained from Bristol-Myers Squibb) that has an integrated copy of the LTR-fire-fly luciferase reporter (backbone: plenti-P2A-Puro, RC223291L3V, Origene) and stable cells were selected by using G418 (0.6 mg/ml) and puromycin (2 µg/ml). The CCR5-B6 cells express firefly luciferase from an HIV-1 LTR promoter after infection with HIV. They are grown in RPMI 1640 supplemented with 10% heat inactivated fetal bovine serum (FBS), 10 mM HEPES buffer pH 7.55, 2 mM L-glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin, 2 µg/ml puromycin, 0.6 mg/ml G418.

15 *Replicating virus assay*

Assay using NLRepRluc virus

The NLRepRluc was used to infect MT-2 cells at a multiplicity of 0.01 for 1 hour before adding the proteins to the 96-well plates. Antibodies were serially diluted four-fold and 11 concentrations were plated in triplicate. After 4 days of incubation, cells were processed and quantitated for virus growth by the amount of expressed luciferase. Luciferase was quantitated using the ENDUREN substrate from Promega (Madison, WI) according to the manufacturer's instructions. Luciferase activity was measured immediately on an ENVISION multilabel plate reader (PerkinElmer, Waltham MA). EC₅₀ values were calculated by comparing the amount of luciferase produced in the presence of antigen binding protein compared to wells where no antigen binding protein (DMSO control) was added. A 5-parameter sigmoidal equation was used to fit the resulting signal vs. concentration curves, and the concentration of each antigen binding protein that produced 50% maximal inhibition (EC₅₀) was determined. The results of three independent experiments were averaged and plotted, with error bars corresponding to 1 standard deviation.

Replicating virus assay using laboratory strains and clinical isolates

30 Replicating laboratory strains and clinical isolates were prepared as described above. MT2 cells or CCR5-B6 cells were resuspended in corresponding media and distributed to 96-well assay plates (26,000 cells/well in 100 µL; Corning, Tewksbury, MA) containing serial dilutions of inhibitors in DMSO (5 or 3-fold dilutions, columns 1-10). The blank controls were wells containing DMSO (column 11,12). Replicating whole viruses of laboratory strains or clinic isolates were diluted in

RPMI-1640 culture medium based on 50% tissue culture infectious dose (TCID₅₀) determination such that undiluted stock virus was added to the first well, and 100 µl of viral culture medium were loaded to the wells already containing compounds and cells (total 200 µl/well), resulting in a final concentration of DMSO of 1%. Plates were incubated at 37 °C and 5% CO₂ for approximately 4 days. After that, *Renilla* luciferase activity was measured (Enduren reagent, Promega Corp., Madison, WI) on an EnVision Multilabel plate reader (Perkin Elmer, Inc., Waltham MA). The 50% effective concentration (EC₅₀) was calculated by using the exponential form of the median effect equation where $(Fa) = 1/[1 + (ED_{50}/\text{drug conc.})]$.

10 Results

Table 25.1 shows that the bNAb1-derived bispecific molecules are consistently about 10-fold more active than the mixture of the component parts (bNAb1 and CD4 domain), again indicating a clear anti-viral synergy result from fusing these component binding domains.

Table 25.1: EC₅₀ (nM) values of bNAb1-derived bispecific and control molecules against NL4-3 in a replicating virus assay

Molecules (SEQ ID NO)	EC ₅₀ (nM)
D1m_1xG4S_bNAb1 (102+63)	0.03
D1m_2xG4S_bNAb1 (103+63)	0.03
D1m_3xG4S_bNAb1 (104+63)	0.02
D1m_4xG4S_bNAb1 (105+63)	0.03
D1m_His (4*) + bNAb1 (62+63)	0.22
D1m_His (4*)	0.23
bNAb1 (62+63)	>500

* plus a 6xHis tag (six C-terminal histidine residues)

A bNAb1-derived bispecific molecule (D1m-K8C-G99C_1xG4S_bNAb1, SEQ ID NOs: 121+63) was tested against a panel of 13 clinical and 8 laboratory HIV-1 isolates in a replicating virus assay using MT-2 and CCR5-B6 cells. As shown in Table 25.2, this molecule neutralized all strains, with

EC50s less than 1 nM (geometric mean EC50 being 0.11 nM against clinical isolates and 0.26 nM against lab strains), demonstrating again its strong potency and breadth of activity.

Table 25.2: EC₅₀ (nM) of a bNAb1-derived bispecific against a panel of HIV-1 clinical isolates and laboratory strains in a replicating virus assay

Isolates	Clade	bNAb1-Derived Bispecific
Clinical isolates		
93US141	B	0.04
93US144	B	0.07
ASM34	B	0.15
BK132	B	0.19
BZ167	B	0.05
CC1/85	B	0.2
CM237	B	0.03
ETH2220	C	0.08
I-2496	A	0.15
SE364	C	0.2
UG268	C	0.06
UG270	D	0.42
US4	B	0.39
Laboratory strains		
HXB2		0.04
BaL		0.83
IIIB/H9		0.56
IIIB/HOS		0.56
JR-FL		0.04
LAI		0.39
MIN		0.15
NL4-3		0.39

RF		0.56
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Table 25.2 Molecule Key:

1 = D1m-K8C-G99C_1xG4S_bNAb1 (SEQ ID NOs:121+63)

Example 10 – *In vitro* Resistance Barrier

To assess the resistance barrier of the bispecific molecules, we examined the relative rates at which HIV NL4-3 virus can escape inhibition by a panel of antibodies versus a DMSO control.

MT2 cells (2.0×10^5 /well in RPMI 1640 + 50 mg/ml penicillin and streptomycin + 10 mM HEPES buffer pH 7.55 + 2 mM L-glutamine + 0.2% DMSO) were pre-infected at an MOI (multiplicity of infection) of 0.005 for 2.5 hours and then pelleted to remove unbound virus particles. One mL of infected cells was added to each well of a 24 well plate. Replicates of antibody dilutions at the concentrations of 20-, 30-, or 40-fold of IC₅₀ values were then added (1mL of a 2X stock) to achieve 2mL assay volume.

Every 3-4 days images of the wells were captured and 1mL of each well is removed and replaced by fresh preparations of each condition. This process was continued until there was viral breakthrough (observed cytopathic effect (CPE) > 80%) or until there was a confirmed elimination of infected cells (via challenged elimination). When either condition was achieved, the sample was collected as pellet and supernatant (via centrifugation) and stored at -80°C until genotypic analysis was performed to confirm the presence of resistance mutations. The days from infection to breakthrough were used to estimate the resistance barrier of a certain molecule. The longer it takes the virus to develop CPE, which indicates resistance, the higher the resistance barrier is.

Table 26 shows that, in this experimental setting, the bNAb1-derived bispecific molecule (SEQ ID NO:105 and SEQ ID NO:63) exhibited a much higher resistance barrier than the soluble CD4 domain or bNAb1 alone at all concentrations. This again indicates synergy between soluble CD4 domains and bNAb1 when fused together.

Table 26

Group	Molecule	Conc. (nM)	Average days before CPE
20x EC ₅₀	D1m_4xG4S_bNAb1	4.2	16
	D1m_His	8.4	4

	bNAb1	18	4
30x EC50	D1m_4xG4S_bNAb1	6.3	54
	D1m_His	12.5	5
	bNAb1	27	4
40x EC50	D1m_4xG4S_bNAb1	8.4	62
	D1m_His	16.7	7
	bNAb1	36	4

Table 26 Molecule Key:

D1m_4xG4S_bNAb1 = SEQ ID NO:105 and 63

D1m_His = SEQ ID NO:4 plus a 6xHis tag (six C-terminal histidine residues)

bNAb1 = SEQ ID NOs:62 and 63

Example 11 – Anti-HIV-2 Activity of a bNAb1-Derived Bispecific Molecule (SEQ ID NO:121 and SEQ ID NO:63) in Pseudotyped and Replicating Virus Assays

HIV-2 differs from HIV-1 in that it originates from the transmission of simian immunodeficiency virus (SIV) from sooty mangabeys (SIVsmm) to human (Gao *et al*, J Virol. 1994;68(11):7433-7447) whilst HIV-1 stems from the transmission from chimpanzees and western gorillas (HIV-1 group M and O, respectively). HIV-2 can also cause AIDS but is far less pathogenic and wide-spread than HIV-1 (de Silva *et al*, Trends Microbiol. 2008;16(12):588-595; Da Silva *et al*, AIDS. 2008;22(10):1195-1202). Though also using CD4 for infection (Sattentau *et al*, AIDS. 1988;2(2):101-105), HIV-2 shares only 40% identity in the gp160 amino acid sequence with HIV-1, and is therefore less sensitive or insensitive to HIV-1 envelope-directed bnAbs (Kong *et al*, JVI 2012;86(2):947-960). The bNAb1-derived bispecific molecule (SEQ ID NO:121 and SEQ ID NO:63) showed strong potency and anti-viral synergy against the 2 HIV-2 Env-pseudotypes tested in PSV assays and the laboratory NIHZ strain examined in a replicating virus assay (Table 27), illustrating its exceptional breadth of anti-HIV activity and excellent synergy.

Table 27: IC50 (nM) of a bNAb1-derived bispecific and control molecules against HIV-2 strains

Strain	Assay	bNAb1-derived molecules			
		1	2	3	4
HIV-2-ATM88	PSV	0.07	3.93	>500	10.53
HIV-2-HCC-01	PSV	0.78	>500	>500	>500
HIV-2 NIHZ	Replicating virus	2.68	*	*	*

* not tested

5 Table 27 Molecule Key:

1 = D1m-K8C-G99C_1xG4S_bNAb1 (SEQ ID NOs:121+63)

2 = D1m_His (SEQ ID NO:4*)

3 = bNAb1 (SEQ ID NOs:62+63)

4 = D1m_His (SEQ ID NO:4*) + bNAb1(SEQ ID NOs:62+63) (combo)

* plus a 6xHis tag (six C-terminal histidine residues)

SEQUENCE LISTING

SEQ ID NO	Name/Identifier	Description
1	D1D2	Human CD4 D1D2 (wild type)
2	D1mD2	Human CD4 mD1.22-D2 (D1 mutations S23N, A55V, and L96V)
3	D1	Human CD4 D1 (wild type)
4	D1m	Human CD4 mD1.22 (NCBI accession code: QHY83614.1; D1 mutations L5Y, S23N, A55V, I76P, L96V and F98V)
5	D1m-K8V	Human CD4 mD1.22 + K8V
6	D1m-E91Q	Human CD4 mD1.22 + E91Q
7	D1m-E91H	Human CD4 mD1.22 + E91H
8	D1m-E87G	Human CD4 mD1.22 + E87G
9	D1m-N52W	Human CD4 mD1.22 + N52W
10	D1m-K8I	Human CD4 mD1.22 + K8I
11	D1m-K8C-G99C	Human CD4 mD1.22 + K8C, G99C
12	D1m-T11C-K72C	Human CD4 mD1.22 + T11C, K72C
13	D1m-E13C-I70C	Human CD4 mD1.22 + E13C, I70C
14	D1m-H27C-G38C	Human CD4 mD1.22 + H27C, G38C
15	D1m-K21C-G65C	Human CD4 mD1.22 + K21C, G65C
16	D1m-Q25E	Human CD4 mD1.22 + Q25E
17	D1m-H27D	Human CD4 mD1.22 + H27D
18	D1m-R58V	Human CD4 mD1.22 + R58V
19	D1m-R58N	Human CD4 mD1.22 + R58N
20	D1m-R58T	Human CD4 mD1.22 + R58T
21	D1m-L61M	Human CD4 mD1.22 + L61M
22	bNAb1 CDRH1	CDRH1 of bNAb1
23	bNAb1 CDRH2	CDRH2 of bNAb1
24	bNAb1 CDRH3	CDRH3 of bNAb1
25	bNAb1 CDRL1	CDRL1 of bNAb1
26	bNAb1 CDRL2	CDRL2 of bNAb1
27	bNAb1 CDRL3	CDRL3 of bNAb1
28	bNAb2 CDRH1	CDRH1 of bNAb2
29	bNAb2 CDRH2	CDRH2 of bNAb2
30	bNAb2 CDRH3	CDRH3 of bNAb2
31	bNAb2 CDRL1	CDRL1 of bNAb2
32	bNAb2 CDRL2	CDRL2 of bNAb2
33	bNAb2 CDRL3	CDRL3 of bNAb2
34	bNAb3 CDRH1	CDRH1 of bNAb3
35	bNAb3 CDRH2	CDRH2 of bNAb3
36	bNAb3 CDRH3	CDRH3 of bNAb3
37	bNAb3 CDRL1	CDRL1 of bNAb3
38	bNAb3 CDRL2	CDRL2 of bNAb3
39	bNAb3 CDRL3	CDRL3 of bNAb3
40	bNAb4 CDRH1	CDRH1 of bNAb4
41	bNAb4 CDRH2	CDRH2 of bNAb4

42	bNAb4 CDRH3	CDRH3 of bNAb4
43	bNAb4 CDRL1	CDRL1 of bNAb4
44	bNAb4 CDRL2	CDRL2 of bNAb4
45	bNAb4 CDRL3	CDRL3 of bNAb4
46	bNAb5 CDRH1	CDRH1 of bNAb5
47	bNAb5 CDRH2	CDRH2 of bNAb5
48	bNAb5 CDRH3	CDRH3 of bNAb5
49	bNAb5 CDRL1	CDRL1 of bNAb5
50	bNAb5 CDRL2	CDRL2 of bNAb5
51	bNAb5 CDRL3	CDRL3 of bNAb5
52	bNAb6 CDRH1	CDRH1 of bNAb6
53	bNAb6 CDRH2	CDRH2 of bNAb6
54	bNAb6 CDRH3	CDRH3 of bNAb6
55	bNAb6 CDRL1	CDRL1 of bNAb6
56	bNAb6 CDRL2	CDRL2 of bNAb6
57	bNAb6 CDRL3	CDRL3 of bNAb6
58	bNAb1 VH	Heavy chain variable region of bNAb1
59	bNAb1 VL	Light chain variable region of bNAb1
60	bNAb1* VL	Light chain variable region of bNAb1 with F32Y mutation
61	bNAb1 HC	Full heavy chain of bNAb1
62	bNAb1 HC+LS	Full heavy chain of bNAb1 with M428L/N434S mutations
63	bNAb1 LC	Full light chain of bNAb1
64	bNAb1* LC	Full light chain of bNAb1 with F32Y mutation
65	bNAb2 VH	Heavy chain variable region of bNAb2
66	bNAb2 VL	Light chain variable region of bNAb2
67	bNAb2 HC	Full heavy chain of bNAb2
68	bNAb2 HC+LS	Full heavy chain of bNAb2 with M428L/N434S mutations
69	bNAb2 LC	Full light chain of bNAb2
70	bNAb3 VH	Heavy chain variable region of bNAb3
71	bNAb3 VL	Light chain variable region of bNAb3
72	bNAb3 HC	Full heavy chain of bNAb3
73	bNAb3 HC+LS	Full heavy chain of bNAb3 with M428L/N434S mutations
74	bNAb3 LC	Full light chain of bNAb3
75	bNAb4 VH	Heavy chain variable region of bNAb4
76	bNAb4 VL	Light chain variable region of bNAb4
77	bNAb4 HC	Full heavy chain of bNAb4
78	bNAb4 HC+LS	Full heavy chain of bNAb4 with M428L/N434S mutations
79	bNAb4 LC	Full light chain of bNAb4
80	bNAb5 VH	Heavy chain variable region of bNAb5
81	bNAb5 VL	Light chain variable region of bNAb5
82	bNAb5 HC	Full heavy chain of bNAb5
83	bNAb5 HC+LS	Full heavy chain of bNAb5 with M428L/N434S mutations
84	bNAb5 LC	Full light chain of bNAb5

85	bNAb6 VH	Heavy chain variable region of bNAb6
86	bNAb6 VL	Light chain variable region of bNAb6
87	bNAb6 HC	Full heavy chain of bNAb6
88	bNAb6 HC+LS	Full heavy chain of bNAb6 with M428L/N434S mutations
89	bNAb6 LC	Full light chain of bNAb6
90	1xG4S	Linker
91	2xG4S	Linker
92	3xG4S	Linker
93	4xG4S	Linker
94	5xG4S	Linker
95	6xG4S	Linker
96	D1mD2_0xG4S_bNAb1-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb1 heavy chain with no linker, Fc includes M428L/N434S
97	D1mD2_1xG4S_bNAb1-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
98	D1mD2_2xG4S_bNAb1-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb1 heavy chain with 2xG4S linker, Fc includes M428L/N434S
99	D1mD2_3xG4S_bNAb1-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb1 heavy chain with 3xG4S linker, Fc includes M428L/N434S
100	D1mD2_4xG4S_bNAb1-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb1 heavy chain with 4xG4S linker, Fc includes M428L/N434S
101	D1m_0xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with no linker, Fc includes M428L/N434S
102	D1m_1xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
103	D1m_2xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 2xG4S linker, Fc includes M428L/N434S
104	D1m_3xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 3xG4S linker, Fc includes M428L/N434S
105	D1m_4xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 4xG4S linker, Fc includes M428L/N434S
106	D1m_5xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 5xG4S linker, Fc includes M428L/N434S
107	D1m_6xG4S_bNAb1-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 heavy chain with 6xG4S linker, Fc includes M428L/N434S

108	D1m_0xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with no linker
109	D1m_1xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 1xG4S linker
110	D1m_2xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 2xG4S linker
111	D1m_3xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 3xG4S linker
112	D1m_4xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 4xG4S linker
113	D1m_5xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 5xG4S linker
114	D1m_6xG4S_bNAb1-LC	Human CD4 mD1.22 fused to the N-terminus of bNAb1 light chain with 6xG4S linker
115	D1m-K8C-G99C_1xG4S_bNAb1-LC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb1 light chain with 1xG4S linker
116	bNAb1-HC-mid_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused in between the CH1 domain and hinge of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
117	bNAb1-HC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
118	bNAb1-LC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb1 light chain with 1xG4S linker
119	D1m-K8I_1xG4S_bNAb1-HC	Human CD4 mD1.22 + K8I fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
120	D1m-K8V_1xG4S_bNAb1-HC	Human CD4 mD1.22 + K8V fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
121	D1m-K8C-G99C_1xG4S_bNAb1-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
122	D1m-T11C-K72C_1xG4S_bNAb1-HC	Human CD4 mD1.22 + T11C + K72C fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
123	D1m-E91Q_1xG4S_bNAb1-HC	Human CD4 mD1.22 + E91Q fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
124	D1m-E91H_1xG4S_bNAb1-HC	Human CD4 mD1.22 + E91H fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
125	D1m-Q25E_1xG4S_bNAb1-HC	Human CD4 mD1.22 + Q25E fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S

126	D1m-H27D_1xG4S_bNAb1-HC	Human CD4 mD1.22 + H27D fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
127	D1m-R58V_1xG4S_bNAb1-HC	Human CD4 mD1.22 + R58V fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
128	D1m-R58N_1xG4S_bNAb1-HC	Human CD4 mD1.22 + R58N fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
129	D1m-R58T_1xG4S_bNAb1-HC	Human CD4 mD1.22 + R58T fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
130	D1m-L61M_1xG4S_bNAb1-HC	Human CD4 mD1.22 + L61M fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
131	D1m-E13C-I70C_1xG4S_bNAb1-HC	Human CD4 mD1.22 + E13C + I70C fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
132	D1m-H27C-G38C_1xG4S_bNAb1-HC	Human CD4 mD1.22 + H27C + G38C fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
133	D1m-K21C-G65C_1xG4S_bNAb1-HC	Human CD4 mD1.22 + K21C + G65C fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
134	D1m-E87G_1xG4S_bNAb1-HC	Human CD4 mD1.22 + E87G fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
135	D1m-N52W_1xG4S_bNAb1-HC	Human CD4 mD1.22 + N52W fused to the N-terminus of bNAb1 heavy chain with 1xG4S linker, Fc includes M428L/N434S
136	D1m-K8C-G99C_1xG4S_bNAb2-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb2 heavy chain with 1xG4S linker, Fc includes M428L/N434S
137	D1m-K8C-G99C_2xG4S_bNAb2-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb2 heavy chain with 2xG4S linker, Fc includes M428L/N434S
138	D1m-K8C-G99C_3xG4S_bNAb2-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb2 heavy chain with 3xG4S linker, Fc includes M428L/N434S
139	D1m-K8C-G99C_4xG4S_bNAb2-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb2 heavy chain with 4xG4S linker, Fc includes M428L/N434S
140	bNAb2-HC-mid_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused in between the CH1 domain and hinge of bNAb2 heavy chain with 1xG4S linkers, Fc includes M428L/N434S
141	bNAb2-HC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb2 heavy chain with 1xG4S linker, Fc includes M428L/N434S

142	D1m-K8C-G99C_1xG4S_bNAb2-LC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb2 light chain with 1xG4S linker
143	bNAb2-LC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb2 light chain with 1xG4S linker
144	D1m-K8C-G99C_1xG4S_bNAb3-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb3 heavy chain with 1xG4S linker, Fc includes M428L/N434S
145	D1m-K8C-G99C_4xG4S_bNAb3-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb3 heavy chain with 4xG4S linker, Fc includes M428L/N434S
146	D1m-K8C-G99C_1xG4S_bNAb4-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb4 heavy chain with 1xG4S linker, Fc includes M428L/N434S
147	D1m-K8C-G99C_4xG4S_bNAb4-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb4 heavy chain with 4xG4S linker, Fc includes M428L/N434S
148	D1m-K8C-G99C_1xG4S_bNAb5-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb5 heavy chain with 1xG4S linker, Fc includes M428L/N434S
149	D1m-K8C-G99C_4xG4S_bNAb5-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb5 heavy chain with 4xG4S linker, Fc includes M428L/N434S
150	D1mD2_4xG4S_bNAb6-HC	Human CD4 mD1.22-D2 fused to the N-terminus of bNAb6 heavy chain with 4xG4S linker, Fc includes M428L/N434S
151	D1m_4xG4S_bNAb6-HC	Human CD4 mD1.22 fused to the N-terminus of bNAb6 heavy chain with 4xG4S linker, Fc includes M428L/N434S
152	D1m_4xG4S_bNAb1-scFv-H4Lss_2xG4S_Fc	Human CD4 mD1.22 fused, via 4xG4S linker, to the N-terminus of bNAb1 scFv (VH-4xG4S-VL, with stabilizing disulfide bond G44C/HC - G100C/LC), which is fused, via 2xG4S linker, to the N-terminus of human Fc fragment including M428L/N434S
153	D1m_3xG4S_bNAb1-scFv-H4Lss_2xG4S_Fc	Human CD4 mD1.22 fused, via 3xG4S linker, to the N-terminus of bNAb1 scFv (VH-4xG4S-VL, with stabilizing disulfide bond G44C/HC - G100C/LC), which is fused, via 2xG4S linker, to the N-terminus of human Fc fragment including M428L/N434S
154	D1m_2xG4S_bNAb1-scFv-H4Lss_2xG4S_Fc	Human CD4 mD1.22 fused, via 2xG4S linker, to the N-terminus of bNAb1 scFv (VH-4xG4S-VL, with stabilizing disulfide bond G44C/HC - G100C/LC), which is fused, via 2xG4S linker, to the N-terminus of human Fc fragment including M428L/N434S
155	D1m_1xG4S_bNAb1-scFv-H4Lss_2xG4S_Fc	Human CD4 mD1.22 fused, via 1xG4S linker, to the N-terminus of bNAb1 scFv (VH-4xG4S-

		VL, with stabilizing disulfide bond G44C/HC - G100C/LC), which is fused, via 2xG4S linker, to the N-terminus of human Fc fragment including M428L/N434S
156	Fc_4xG4S_D1m_3xG4S_bNAb1-scFv-H4Lss	Human CD4 mD1.22 fused, via 3xG4S linker, to the N-terminus of bNAb1 scFv (VH-4xG4S-VL, with stabilizing disulfide bond G44C/HC - G100C/LC), which is fused, via 3xG4S linker, to the C-terminus of human Fc fragment including M428L/N434S
157	bNAb1-scFv-L4Hss_4xG4S_D1m_3xG4S_Fc	bNAb1 scFv (VL-4xG4S-VH, with stabilizing disulfide bond G44C/HC - G100C/LC) fused, via 4xG4S linker, to the N-terminus of human CD4 mD1.22, which is fused, via 3xG4S linker, to the N-terminus of human Fc fragment including M428L/N434S
158	D1m-K8C-G99C_Fc	Human CD4 mD1.22 + K8C, G99C with C-terminal Fc tag including M428L/N434S
159	bNAb7 CDRH1	CDRH1 of bNAb7
160	bNAb7 CDRH2	CDRH2 of bNAb7
161	bNAb7 CDRH3	CDRH3 of bNAb7
162	bNAb7 CDRL1	CDRL1 of bNAb7
163	bNAb7 CDRL2	CDRL2 of bNAb7
164	bNAb7 CDRL3	CDRL3 of bNAb7
165	bNAb8 CDRH1	CDRH1 of bNAb8
166	bNAb8 CDRH2	CDRH2 of bNAb8
167	bNAb8 CDRH3	CDRH3 of bNAb8
168	bNAb8 CDRL1	CDRL1 of bNAb8
169	bNAb8 CDRL2	CDRL2 of bNAb8
170	bNAb8 CDRL3	CDRL3 of bNAb8
171	bNAb9 CDRH1	CDRH1 of bNAb9
172	bNAb9 CDRH2	CDRH2 of bNAb9
173	bNAb9 CDRH3	CDRH3 of bNAb9
174	bNAb9 CDRL1	CDRL1 of bNAb9
175	bNAb9 CDRL2	CDRL2 of bNAb9
176	bNAb9 CDRL3	CDRL3 of bNAb9
177	bNAb10 CDRH1	CDRH1 of bNAb10
178	bNAb10 CDRH2	CDRH2 of bNAb10
179	bNAb10 CDRH3	CDRH3 of bNAb10
180	bNAb10 CDRL1	CDRL1 of bNAb10
181	bNAb10 CDRL2	CDRL2 of bNAb10
182	bNAb10 CDRL3	CDRL3 of bNAb10
183	bNAb11 CDRH1	CDRH1 of bNAb11
184	bNAb11 CDRH2	CDRH2 of bNAb11
185	bNAb11 CDRH3	CDRH3 of bNAb11
186	bNAb11 CDRL1	CDRL1 of bNAb11
187	bNAb11 CDRL2	CDRL2 of bNAb11
188	bNAb11 CDRL3	CDRL3 of bNAb11
189	bNAb12 CDRH1	CDRH1 of bNAb12

190	bNAb12 CDRH2	CDRH2 of bNAb12
191	bNAb12 CDRH3	CDRH3 of bNAb12
192	bNAb12 CDRL1	CDRL1 of bNAb12
193	bNAb12 CDRL2	CDRL2 of bNAb12
194	bNAb12 CDRL3	CDRL3 of bNAb12
195	bNAb13 CDRH1	CDRH1 of bNAb13
196	bNAb13 CDRH2	CDRH2 of bNAb13
197	bNAb13 CDRH3	CDRH3 of bNAb13
198	bNAb13 CDRL1	CDRL1 of bNAb13
199	bNAb13 CDRL2	CDRL2 of bNAb13
200	bNAb13 CDRL3	CDRL3 of bNAb13
201	bNAb14 CDRH1	CDRH1 of bNAb14
202	bNAb14 CDRH2	CDRH2 of bNAb14
203	bNAb14 CDRH3	CDRH3 of bNAb14
204	bNAb14 CDRL1	CDRL1 of bNAb14
205	bNAb14 CDRL2	CDRL2 of bNAb14
206	bNAb14 CDRL3	CDRL3 of bNAb14
207	bNAb15 CDRH1	CDRH1 of bNAb15
208	bNAb15 CDRH2	CDRH2 of bNAb15
209	bNAb15 CDRH3	CDRH3 of bNAb15
210	bNAb15 CDRL1	CDRL1 of bNAb15
211	bNAb15 CDRL2	CDRL2 of bNAb15
212	bNAb15 CDRL3	CDRL3 of bNAb15
213	bNAb16 CDRH1	CDRH1 of bNAb16
214	bNAb16 CDRH2	CDRH2 of bNAb16
215	bNAb16 CDRH3	CDRH3 of bNAb16
216	bNAb16 CDRL1	CDRL1 of bNAb16
217	bNAb16 CDRL2	CDRL2 of bNAb16
218	bNAb16 CDRL3	CDRL3 of bNAb16
219	bNAb17 CDRH1	CDRH1 of bNAb17
220	bNAb17 CDRH2	CDRH2 of bNAb17
212	bNAb17 CDRH3	CDRH3 of bNAb17
222	bNAb17 CDRL1	CDRL1 of bNAb17
223	bNAb17 CDRL2	CDRL2 of bNAb17
224	bNAb17 CDRL3	CDRL3 of bNAb17
225	bNAb18 CDRH1	CDRH1 of bNAb18
226	bNAb18 CDRH2	CDRH2 of bNAb18
227	bNAb18 CDRH3	CDRH3 of bNAb18
228	bNAb18 CDRL1	CDRL1 of bNAb18
229	bNAb18 CDRL2	CDRL2 of bNAb18
230	bNAb18 CDRL3	CDRL3 of bNAb18
231	bNAb19 CDRH1	CDRH1 of bNAb19
232	bNAb19 CDRH2	CDRH2 of bNAb19
233	bNAb19 CDRH3	CDRH3 of bNAb19
234	bNAb19 CDRL1	CDRL1 of bNAb19
235	bNAb19 CDRL2	CDRL2 of bNAb19
236	bNAb19 CDRL3	CDRL3 of bNAb19
237	bNAb20 CDRH1	CDRH1 of bNAb20

238	bNAb20 CDRH2	CDRH2 of bNAb20
239	bNAb20 CDRH3	CDRH3 of bNAb20
240	bNAb20 CDRL1	CDRL1 of bNAb20
241	bNAb20 CDRL2	CDRL2 of bNAb20
242	bNAb20 CDRL3	CDRL3 of bNAb20
243	bNAb21 and bNAb22 CDRH1	CDRH1 of bNAb21 and bNAb22
244	bNAb21 and bNAb22 CDRH2	CDRH2 of bNAb21 and bNAb22
245	bNAb21 and bNAb22 CDRH3	CDRH3 of bNAb21 and bNAb22
246	bNAb21 and bNAb22 CDRL1	CDRL1 of bNAb21 and bNAb22
247	bNAb21 and bNAb22 CDRL2	CDRL2 of bNAb21 and bNAb22
248	bNAb21 and bNAb22 CDRL3	CDRL3 of bNAb21 and bNAb22
249	bNAb23 CDRH1	CDRH1 of bNAb23
250	bNAb23 CDRH2	CDRH2 of bNAb23
251	bNAb23 CDRH3	CDRH3 of bNAb23
252	bNAb23 CDRL1	CDRL1 of bNAb23
253	bNAb23 CDRL2	CDRL2 of bNAb23
254	bNAb23 CDRL3	CDRL3 of bNAb23
255	bNAb7 VH	Heavy chain variable region of bNAb7
256	bNAb7 VL	Light chain variable region of bNAb7
257	bNAb7 HC	Full heavy chain of bNAb7
258	bNAb7 HC+LS	Full heavy chain of bNAb7 with M428L/N434S mutations
259	bNAb7 LC	Full light chain of bNAb7
260	bNAb8 VH	Heavy chain variable region of bNAb8
261	bNAb8 VL	Light chain variable region of bNAb8
262	bNAb8 HC	Full heavy chain of bNAb8
263	bNAb8 HC+LS	Full heavy chain of bNAb8 with M428L/N434S mutations
264	bNAb8 LC	Full light chain of bNAb8
265	bNAb9 VH	Heavy chain variable region of bNAb9
266	bNAb9 VL	Light chain variable region of bNAb9
267	bNAb9 HC	Full heavy chain of bNAb9
268	bNAb9 HC+LS	Full heavy chain of bNAb9 with M428L/N434S mutations
269	bNAb9 LC	Full light chain of bNAb9
270	bNAb10 VH	Heavy chain variable region of bNAb10
271	bNAb10 VL	Light chain variable region of bNAb10
272	bNAb10 HC	Full heavy chain of bNAb10
273	bNAb10 HC+LS	Full heavy chain of bNAb10 with M428L/N434S mutations
274	bNAb10 LC	Full light chain of bNAb10
275	bNAb11 VH	Heavy chain variable region of bNAb11
276	bNAb11 VL	Light chain variable region of bNAb11
277	bNAb11 HC	Full heavy chain of bNAb11
278	bNAb11 HC+LS	Full heavy chain of bNAb11 with M428L/N434S mutations
279	bNAb11 LC	Full light chain of bNAb11
280	bNAb12 VH	Heavy chain variable region of bNAb12
281	bNAb12 VL	Light chain variable region of bNAb12

282	bNAb12 HC	Full heavy chain of bNAb12
283	bNAb12 HC+LS	Full heavy chain of bNAb12 with M428L/N434S mutations
284	bNAb12 LC	Full light chain of bNAb12
285	bNAb13 VH	Heavy chain variable region of bNAb13
286	bNAb13 VL	Light chain variable region of bNAb13
287	bNAb13 HC	Full heavy chain of bNAb13
288	bNAb13 HC+LS	Full heavy chain of bNAb13 with M428L/N434S mutations
289	bNAb13 LC	Full light chain of bNAb13
290	bNAb14 VH	Heavy chain variable region of bNAb13
291	bNAb14 VL	Light chain variable region of bNAb14
292	bNAb14 HC	Full heavy chain of bNAb14
293	bNAb14 HC+LS	Full heavy chain of bNAb14 with M428L/N434S mutations
294	bNAb14 LC	Full light chain of bNAb14
295	bNAb15 VH	Heavy chain variable region of bNAb15
296	bNAb15 VL	Light chain variable region of bNAb15
297	bNAb15 HC	Full heavy chain of bNAb15
298	bNAb15 HC+LS	Full heavy chain of bNAb15 with M428L/N434S mutations
299	bNAb15 LC	Full light chain of bNAb15
300	bNAb16 VH	Heavy chain variable region of bNAb16
301	bNAb16 VL	Light chain variable region of bNAb16
302	bNAb16 HC	Full heavy chain of bNAb16
303	bNAb16 HC+LS	Full heavy chain of bNAb16 with M428L/N434S mutations
304	bNAb16 LC	Full light chain of bNAb16
305	bNAb17 VH	Heavy chain variable region of bNAb17
306	bNAb17 VL	Light chain variable region of bNAb17
307	bNAb17 HC	Full heavy chain of bNAb17
308	bNAb17 HC+LS	Full heavy chain of bNAb17 with M428L/N434S mutations
309	bNAb17 LC	Full light chain of bNAb17
310	bNAb18 VH	Heavy chain variable region of bNAb17
311	bNAb18 VL	Light chain variable region of bNAb17
312	bNAb18 HC	Full heavy chain of bNAb17
313	bNAb18 HC+LS	Full heavy chain of bNAb17 with M428L/N434S mutations
314	bNAb18 LC	Full light chain of bNAb18
315	bNAb19 VH	Heavy chain variable region of bNAb19
316	bNAb19 VL	Light chain variable region of bNAb19
317	bNAb19 HC	Full heavy chain of bNAb19
318	bNAb19 HC+LS	Full heavy chain of bNAb19 with M428L/N434S mutations
319	bNAb19 LC	Full light chain of bNAb19
320	bNAb20 VH	Heavy chain variable region of bNAb20
321	bNAb20 VL	Light chain variable region of bNAb20

322	bNAb20 HC	Full heavy chain of bNAb20
323	bNAb20 HC+LS	Full heavy chain of bNAb20 with M428L/N434S mutations
324	bNAb20 LC	Full light chain of bNAb20
325	bNAb21 VH	Heavy chain variable region of bNAb21
326	bNAb21 VL	Light chain variable region of bNAb21
327	bNAb21 HC	Full heavy chain of bNAb21
328	bNAb21 HC+LS	Full heavy chain of bNAb21 with M428L/N434S mutations
329	bNAb21 LC	Full light chain of bNAb21
330	bNAb22 VH	Full heavy chain of bNAb22
331	bNAb22 HC	Full heavy chain of bNAb22 with M428L/N434S mutations
332	bNAb22 HV+LS	Full light chain of bNAb22
333	bNAb23 VH	Heavy chain variable region of bNAb23
334	bNAb23 VL	Light chain variable region of bNAb23
335	bNAb23 HC	Full heavy chain of bNAb23
336	bNAb23 HC+LS	Full heavy chain of bNAb23 with M428L/N434S mutations
337	bNAb23 LC	Full light chain of bNAb23
338	D1m-K8C-G99C_1xG4S_bNAb7-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb7 heavy chain with 1xG4S linker, Fc includes M428L/N434S
339	D1m-K8C-G99C_1xG4S_bNAb8-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb8 heavy chain with 1xG4S linker, Fc includes M428L/N434S
340	D1m-K8C-G99C_1xG4S_bNAb9-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb9 heavy chain with 1xG4S linker, Fc includes M428L/N434S
341	D1m-K8C-G99C_1xG4S_bNAb10-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb10 heavy chain with 1xG4S linker, Fc includes M428L/N434S
342	D1m-K8C-G99C_1xG4S_bNAb11-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb11 heavy chain with 1xG4S linker, Fc includes M428L/N434S
343	D1m-K8C-G99C_1xG4S_bNAb12-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb12 heavy chain with 1xG4S linker, Fc includes M428L/N434S
344	bNAb12_HC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb12 heavy chain with 1xG4S linker, Fc includes M428L/N434S
345	D1m-K8C-G99C_1xG4S_LC-bNAb12	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb12 light chain with 1xG4S linker
346	bNAb12_LC_1xG4S_D1m-K8C-G99C-HC	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb12 light chain with 1xG4S linker

347	D1m-K8C-G99C_1xG4S_bNAb13-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb13 heavy chain with 1xG4S linker, Fc includes M428L/N434S
348	D1m-K8C-G99C_1xG4S_bNAb14-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb14 heavy chain with 1xG4S linker, Fc includes M428L/N434S
349	D1m-K8C-G99C_1xG4S_bNAb15-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb15 heavy chain with 1xG4S linker, Fc includes M428L/N434S
350	D1m-K8C-G99C_1xG4S_bNAb16-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb16 heavy chain with 1xG4S linker, Fc includes M428L/N434S
351	D1m-K8C-G99C_1xG4S_bNAb17-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb17 heavy chain with 1xG4S linker, Fc includes M428L/N434S
352	D1m-K8C-G99C_1xG4S_bNAb18-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb18 heavy chain with 1xG4S linker, Fc includes M428L/N434S
353	D1m-K8C-G99C_1xG4S_bNAb19-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb19 heavy chain with 1xG4S linker, Fc includes M428L/N434S
354	D1m-K8C-G99C_1xG4S_bNAb20-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb20 heavy chain with 1xG4S linker, Fc includes M428L/N434S
355	D1m-K8C-G99C_1xG4S_bNAb21-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb21 heavy chain with 1xG4S linker, Fc includes M428L/N434S
356	D1m-K8C-G99C_1xG4S_bNAb22-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb22 heavy chain with 1xG4S linker, Fc includes M428L/N434S
357	D1m-K8C-G99C_1xG4S_bNAb23-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb23 heavy chain with 1xG4S linker, Fc includes M428L/N434S
358	D1m-K8C-G99C_1xG4S_bNAb23-LC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb23 light chain with 1xG4S linker
359	bNAb23-HC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb23 heavy chain with 1xG4S linker, Fc includes M428L/N434S
360	bNAb23_LC_1xG4S_D1m-K8C-G99C	Human CD4 mD1.22 + K8C + G99C fused to the C-terminus of bNAb23 light chain with 1xG4S linker
361	V3 loop	V3 loop consensus sequence
362	D1m-K8C-G99C_1xG4S_bNAb6-HC	Human CD4 mD1.22 + K8C + G99C fused to the N-terminus of bNAb6 heavy chain with 1xG4S linker, Fc includes M428L/N434S
363	Exemplary gp160	Exemplary gp160 sequence
364	Exemplary gp120	Exemplary gp120 sequence
365	bNAb22 VL	Light chain variable region of bNAb22

366	bNAb22 LC	Full light chain of bNAb22
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SEQ ID NO:1

KKVVLGKKGDTVELTCTASQKKSQFHWKNSNQIKILGNQGSFLT KGPSKLNDRADSRRLWDQGN
FPLIKNLKI ESDTYICEVEDQKEEVQLLVFGLTANS DTHLLQGQSLTLTLESPPGSSPSVQCRSPRG
KNIQGGKTL SVSQLELQDSGTWTCTVLQNQKKVEFKIDIVVLA

5 SEQ ID NO:2

KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKI ESDTYICEVEDQKEEVQLLVFGLTANS DTHLLQGQSLTLTLESPPGSSPSVQCRSPRG
GKNIQGGKTL SVSQLELQDSGTWTCTVLQNQKKVEFKIDIVVLA

SEQ ID NO:3

- 10 KKVVLGKKGDTVELTCTASQKKSQFHWKNSNQIKILGNQGSFLT KGPSKLNDRADSRRLWDQGN
FPLIKNLKI ESDTYICEVEDQKEEVQLLVFG

SEQ ID NO:4

KKVVYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

15 SEQ ID NO:5

KKVVYGKVGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

SEQ ID NO:6

- 20 KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

SEQ ID NO:7

KKVVYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKHEVQLVVVG

SEQ ID NO:8

- 25 KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVGDQKEEVQLVVVG

SEQ ID NO:9

KKVVYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLWDRVDSRRLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

30 SEQ ID NO:10

KKVVYGKIGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

SEQ ID NO:11

- 35 KKVVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVC

SEQ ID NO:12

KKVVYGKKGDCVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG

SEQ ID NO:13

- 40 KKVVGKKGDTVCLTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRLWDQG
NFPLCIKNLKPEDSDTYICEVEDQKEEVQLVVVG

- SEQ ID NO:14
KKVVGKKGDTVELTCTASQKKNIQFCWKNSNQIKILCNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:15
5 KKVVGKKGDTVELTCTASQCKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQCN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:16
KKVVGKKGDTVELTCTASQKKNIEFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:17
10 KKVVGKKGDTVELTCTASQKKNIQFDWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:18
15 KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSVRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:19
KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSNRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:20
20 KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSTRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:21
KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSMWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVG
- SEQ ID NO:22
25 ACNSFWG
- SEQ ID NO:23
SLSHCASYWNRGWTYHNPSLKS
- SEQ ID NO:24
30 FGGEVLR YTDWPKPAWDL
- SEQ ID NO:25
TGTSNNFVS
- SEQ ID NO:26
DVNKRPS
- SEQ ID NO:27
35 GSLVGNWDVI
- SEQ ID NO:28
DSYWS
- SEQ ID NO:29
40 YVHKSGDTNYSPLKS

SEQ ID NO:30
TLHGRRYIGIVAFNEWFTYFYMDV

SEQ ID NO:31
GEKSLGSRAVQ

5 SEQ ID NO:32
NNQDRPS

SEQ ID NO:33
HIWDSRVPTKWV

10 SEQ ID NO:34
SDHSWT

SEQ ID NO:35
DIHYNGATTYNPSLRS

SEQ ID NO:36
NAIRIYGVALGEWFHYGMDV

15 SEQ ID NO:37
SGAPLTSRFTY

SEQ ID NO:38
RSSQRSS

20 SEQ ID NO:39
QSSDTSDSYKM

SEQ ID NO:40
NYYWT

SEQ ID NO:41
YISDRESATYNPSLNS

25 SEQ ID NO:42
ARRGQRIYGVVSFGEFFYYYSMDV

SEQ ID NO:43
GRQALGSRAVQ

30 SEQ ID NO:44
NNQDRPS

SEQ ID NO:45
HMWDSRSGFSWS

SEQ ID NO:46
GGEWGDYDHWG

35 SEQ ID NO:47
SIHWRGTTHYKESLRR

SEQ ID NO:48
HRHHDVFMVLPIAGWFDV

- SEQ ID NO:49
RASQNINKNLA
- SEQ ID NO:50
ETYSKIA
- 5 SEQ ID NO:51
QQYEEWPRT
- SEQ ID NO:52
DFYIH
- SEQ ID NO:53
10 WMNPQTGRTNTARNFQG
- SEQ ID NO:54
GGWISLYYDSSYYPNFDH
- SEQ ID NO:55
TGTKYDVGSHDLVS
- 15 SEQ ID NO:56
EVNKRPS
- SEQ ID NO:57
CSFGGSATVV
- SEQ ID NO:58
20 QPQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWVRQPPGKGLEWVWGLSHCASYWNRG
WTYHNPSLKSRLTLALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRDTPKPAWVDLWGRG
TLVTVSS
- SEQ ID NO:59
25 QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGKLTVL
- SEQ ID NO:60
QSALTQPPSASGSPGQSITISCTGTSNNYVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGKLTVL
- SEQ ID NO:61
30 QPQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWVRQPPGKGLEWVWGLSHCASYWNRG
WTYHNPSLKSRLTLALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRDTPKPAWVDLWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQS
SGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
35 HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSGSEFLYSLKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK
- SEQ ID NO:62
40 QPQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWVRQPPGKGLEWVWGLSHCASYWNRG
WTYHNPSLKSRLTLALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRDTPKPAWVDLWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQS

5 SGLYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSGSEFLYSKLTVDKSRWQQGNVFCFVLSHLSHYTQKS
LSLSPGK

SEQ ID NO:63

10 QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV
CLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKYAASSYLSLTPEQWKSQRSYSCQVTHE
GSTVEKTVAPTECS

SEQ ID NO:64

15 QSALTQPPSASGSPGQSITISCTGTSNNVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV
CLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKYAASSYLSLTPEQWKSQRSYSCQVTHE
GSTVEKTVAPTECS

SEQ ID NO:65

QMQQLQESGPGLVKPSETLSLTCSVSGASISDSYWSWIRRSPPGKGLEWIGYVHKSGDTNYSPLKSR
VNLSLDTSKNQVLSLSLVAATAADSGKYCARTLHGRRIYGIVAFNEWFTYFYMDVWNGTQVTVSS

SEQ ID NO:66

20 SDISVAPGETARISCGEKSLSRAVQWYQHRAGQAPSLIYNNQDRPSGIPERFSGSPDSPFGTTAT
LTITSVEAGDEADYYCHIWDSPVPTKWVFGGGTTTLTVL

SEQ ID NO:67

25 QMQQLQESGPGLVKPSETLSLTCSVSGASISDSYWSWIRRSPPGKGLEWIGYVHKSGDTNYSPLKSR
VNLSLDTSKNQVLSLSLVAATAADSGKYCARTLHGRRIYGIVAFNEWFTYFYMDVWNGTQVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGSEFLYSKLTVDKSRWQQGNVFCFVLSHLSHYTQKSLSLSPGK

SEQ ID NO:68

30 QMQQLQESGPGLVKPSETLSLTCSVSGASISDSYWSWIRRSPPGKGLEWIGYVHKSGDTNYSPLKSR
VNLSLDTSKNQVLSLSLVAATAADSGKYCARTLHGRRIYGIVAFNEWFTYFYMDVWNGTQVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
35 LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGSEFLYSKLTVDKSRWQQGNVFCFVLSHLSHYTQKSLSLSPGK

SEQ ID NO:69

40 SDISVAPGETARISCGEKSLSRAVQWYQHRAGQAPSLIYNNQDRPSGIPERFSGSPDSPFGTTAT
LTITSVEAGDEADYYCHIWDSPVPTKWVFGGGTTTLTVLGQPKAAPSVTLFPPSSEELQANKATLVCL
ISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKYAASSYLSLTPEQWKSQRSYSCQVTHEGST
VEKTVAPTECS

SEQ ID NO:70

QVQLRESGPGLVKLPSETLSLSCTVSNDSPSDHSWTWVRQSPGKALEWIGDIHYNGATTYNPSLR
SRVRIELDQSIPRFLKMTSMTAADTGMYYCARNAIRIYGVVALGEWFHYGMDVWVGQGTAVTVSS

SEQ ID NO:71

- 5 SSELTPPPSVSVSPGQTARITCSGAPLTSRFTYWYRQKPGQAPVLIISRSSQRSSGWSGRFSASWS
GTTVTLTIRGVQADDEADYYCQSSDTSYSKMFGGGTKLTVL

SEQ ID NO:72

- 10 QVQLRESGPGLVKLPSETLSLSCTVSNDSPSDHSWTWVRQSPGKALEWIGDIHYNGATTYNPSLR
SRVRIELDQSIPRFLKMTSMTAADTGMYYCARNAIRIYGVVALGEWFHYGMDVWVGQGTAVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSS
VWTVPPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

- 15 SEQ ID NO:73

- QVQLRESGPGLVKLPSETLSLSCTVSNDSPSDHSWTWVRQSPGKALEWIGDIHYNGATTYNPSLR
SRVRIELDQSIPRFLKMTSMTAADTGMYYCARNAIRIYGVVALGEWFHYGMDVWVGQGTAVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSS
VWTVPPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
20 MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:74

- 25 SSELTPPPSVSVSPGQTARITCSGAPLTSRFTYWYRQKPGQAPVLIISRSSQRSSGWSGRFSASWS
GTTVTLTIRGVQADDEADYYCQSSDTSYSKMFGGGTKLTVLGQPAAPSVTLFPPSSEELQANKA
TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHKSYSCQVT
HEGSTVEKTVAPTEC

SEQ ID NO:75

- 30 QVQLQESGPGLVKLPSETLSVTCVSGDSMNYYWTWIRQSPGKGLEWIGYISDRESATYNPSLNS
RVVISRDTSKNQSLKLNSTPADTAVYYCATARRGQRIYGVVSFGEFFYYYSMDVWVGKGTTVTVS
S

SEQ ID NO:76

SYVRPLSVALGETARISCGRQALGSRAVQWYQHRPGQAPILLIYNNQDRPSGIPERFSGTPDINFGT
RATLTISGVEAGDEADYYCHMWDSRSGFSWSFGGATRLTVL

- 35 SEQ ID NO:77

- QVQLQESGPGLVKLPSETLSVTCVSGDSMNYYWTWIRQSPGKGLEWIGYISDRESATYNPSLNS
RVVISRDTSKNQSLKLNSTPADTAVYYCATARRGQRIYGVVSFGEFFYYYSMDVWVGKGTTVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSL
SSVWTVPPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
40 TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K

SEQ ID NO:78

QVQLQESGPGLVKPSSETLSVTCVSGDSMNYYWTWIRQSPGKGLEWIGYISDRESATYNPSLNS
RVVISRDTSKNQLSLKLSVTPADTAVYYCATARRGQRIYGVVSFGEFFYYYSMDVWGKTTVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
5 SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG
K

10 SEQ ID NO:79

SYVRPLSVALGETARISCGRQALGSRAVQWYQHRPGQAPILLIYNNQDRPSGIPERFSGTPDINFGT
RATLTISGVEAGDEADYYCHMWDSRSGFSWSFGGATRLTVLGQPKAAPSVTLFPPSSEELQANKA
TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

15 SEQ ID NO:80

QLQMQESGPGLVKPSSETLSLCTVSGDSIRGGEWGD KDYHWGWVRHSAGKGLEWIGSIHWRGTT
HYKESLRRRVMSIDTSRNWFSRLASVTAADTAVYFCARHRHHDVFMVPIAGWFDVWGPGVQV
TVSS

SEQ ID NO:81

20 EIVMTQSPDTLSVPGETVTLSCRASQNINKNLAWYQYKPGQSPRLVIFETYSKIAAFPARFVASGS
GTEFTLTINMQSEDVAVYYCQQYEEWPRTFGQGTKVDIK

SEQ ID NO:82

QLQMQESGPGLVKPSSETLSLCTVSGDSIRGGEWGD KDYHWGWVRHSAGKGLEWIGSIHWRGTT
HYKESLRRRVMSIDTSRNWFSRLASVTAADTAVYFCARHRHHDVFMVPIAGWFDVWGPGVQV
25 TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSL
30 PGK

SEQ ID NO:83

QLQMQESGPGLVKPSSETLSLCTVSGDSIRGGEWGD KDYHWGWVRHSAGKGLEWIGSIHWRGTT
HYKESLRRRVMSIDTSRNWFSRLASVTAADTAVYFCARHRHHDVFMVPIAGWFDVWGPGVQV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
35 YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSL
PGK

40 SEQ ID NO:84

EIVMTQSPDTLSVPGETVTLSCRASQNINKNLAWYQYKPGQSPRLVIFETYSKIAAFPARFVASGS
GTEFTLTINMQSEDVAVYYCQQYEEWPRTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

SEQ ID NO:85

QVQLVQSGAQMKNP GASVKVSCAPSGYTFTDFYIHWLRQAPGQGLQWMGWMNPQTGRTNTARN
FQGRVTMTRDTSIGTAYMELRSLTSDDTAIYYCTTGGWISLYDSSYYPNFDHWGQGTLTVSS

SEQ ID NO:86

- 5 QSALTQPASVSGSPGQSITISCTGTKYDVGSHDLVSWYQQYPGKVPKYMIEVKNRPSGVSNRFSG
SKSGNTASLTISGLRAEDEADYYCCSFSGSATVVCGGGKTQVTVL

SEQ ID NO:87

- 10 QVQLVQSGAQMKNP GASVKVSCAPSGYTFTDFYIHWLRQAPGQGLQWMGWMNPQTGRTNTARN
FQGRVTMTRDTSIGTAYMELRSLTSDDTAIYYCTTGGWISLYDSSYYPNFDHWGQGTLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

- 15 SEQ ID NO:88

- QVQLVQSGAQMKNP GASVKVSCAPSGYTFTDFYIHWLRQAPGQGLQWMGWMNPQTGRTNTARN
FQGRVTMTRDTSIGTAYMELRSLTSDDTAIYYCTTGGWISLYDSSYYPNFDHWGQGTLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
20 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:89

- 25 QSALTQPASVSGSPGQSITISCTGTKYDVGSHDLVSWYQQYPGKVPKYMIEVKNRPSGVSNRFSG
SKSGNTASLTISGLRAEDEADYYCCSFSGSATVVCGGGKTQVTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSQC
VTHEGSTVEKTVAPTECS

SEQ ID NO:90

GGGS

- 30 SEQ ID NO:91

GGGSGGGGS

SEQ ID NO:92

GGGSGGGSGGGGS

SEQ ID NO:93

- 35 GGGSGGGSGGGSGGGGS

SEQ ID NO:94

GGGSGGGSGGGSGGGSGGGGS

SEQ ID NO:95

GGGSGGGSGGGSGGGSGGGSGGGGS

- 40 SEQ ID NO:96

KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGN
FPLIKNLKI ESDTYICEVEDQKEEVQLWVFGLTANS DTHLLQGQSLT LTLESPPGSSPSVQCRSPR

GKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVLAFQPQLQESGPTLVEASETLTLTCAVSGDSTAACNSFWGWWVRQPPGKGLEWWSLHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRYTDWPKPAWVDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:97

10 KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGNFPLIKNLKIETSDTYICEVEDQKEEVQLVWFGLTANSQDTHLLQGQSLTLTLESPPGSSPSVQCRSPRGKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVLAFGGGGSGQPLQESGPTLVEASETLTLTCAVSGDSTAACNSFWGWWVRQPPGKGLEWWSLHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRYTDWPKPAWVDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:98

20 KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGNFPLIKNLKIETSDTYICEVEDQKEEVQLVWFGLTANSQDTHLLQGQSLTLTLESPPGSSPSVQCRSPRGKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVLAFGGGGSGGGGSGQPLQESGPTLVEASETLTLTCAVSGDSTAACNSFWGWWVRQPPGKGLEWWSLHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRYTDWPKPAWVDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:99

35 KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGNFPLIKNLKIETSDTYICEVEDQKEEVQLVWFGLTANSQDTHLLQGQSLTLTLESPPGSSPSVQCRSPRGKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVLAFGGGGSGGGGSGGGGSGQPLQESGPTLVEASETLTLTCAVSGDSTAACNSFWGWWVRQPPGKGLEWWSLHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRYTDWPKPAWVDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:100

45 KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGNFPLIKNLKIETSDTYICEVEDQKEEVQLVWFGLTANSQDTHLLQGQSLTLTLESPPGSSPSVQCRSPRGKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVLAFGGGGSGGGGSGGGGSGGGGSGQPLQESGPTLVEASETLTLTCAVSGDSTAACNSFWGWWVRQPPGKGLEWWSLHCASYWNRG

5 WTYHNP SLKSR LTLALDTPK NLVFLK LNSVTAADTATYYCARFGGEVLRYTDWPKPAWVDLWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDKVEPKSCDKHTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVLHEALHSHYTQKS
LSLSPGK

SEQ ID NO:101

10 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVVGQPQLQESGPTLVEASETSLSTCAVSGDSTAACNSF
WGWWRQPPGKGLEWWSLSHCASYWNRGWTYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTA
TYCARFGGEVLRYPDWPAPAWDLWGRGLTVTVSSASTKGPSVFLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHNKPSNTKVD
15 KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVLHEALHSHYTKQSLSLSPGK

SEQ ID NO:102

20 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVVVGGGGGSQPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWVRQPPGKGLEWVGSLSHCASYWNRGWTYHNPSLKSRLTLALDTPKNLVFLKLNSV
TAADTATYYCARFGGEVLRYTDWPKPAWDLWGRGTLTVTSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVNHKPS
25 NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSSFL
YSKLTVDKSRWQQGNVSCSVLHEALHSHYTKQSLSLSPGK

SEQ ID NO:103

30 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSQPQLQESGPTLVEASETSLTCAV
SGDSTAACNSFWGWVRQPPGKLEWVGSLSHCASYWNRGWYHNPSLSRSLTALDTPKNLVFL
KLNSVTAADTATYYCARFGGEVLRYTDWPKAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSH
35 EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSD
DGSFFLYSKLTVDKSRWQQGNVFCFSLHSEALHSHYTKQSLSLSPGK

SEQ ID NO:104

40 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVWVGSGGGGSGGGGSGGGGSGQPQLQESGPTLVEASETL
SLTCAVSGDSTAACNSFWGWVRQPPGKLEWVGSLSHCASYWNRGWYHNPSLSKRLTLALDTP
KNLVFLKLNSVTAADTATYYCARFGGEVLRYTDWPKPAWDLWGRGLTVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
45 VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGDSFFLYSKLTVDKSRWQQGNVFCSSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:105

KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGPQLQESGPTLV
EASETSLTCAVSGDSTAACNSFWGWRQPPGKGLEWVWGSLSHCASYWNRGWTYHNPSLKSRLT
5 LALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRyTDWPKPAWVDLWGRGTLTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
EVTCAVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
10 NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:106

KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGPQLQESGPTLV
SGPTLVEASETSLTCAVSGDSTAACNSFWGWRQPPGKGLEWVWGSLSHCASYWNRGWTYHN
15 SLKSRLTLALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRyTDWPKPAWVDLWGRGTLTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
20 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:107

KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGGGGSGPQLQESGPTLV
PQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWRQPPGKGLEWVWGSLSHCASYWNRGW
25 TYHNPSLKSRLTLALDTPKNLVFLKLNSTAAADTATYYCARFGGEVLRyTDWPKPAWVDLWGRGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
30 VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSL
SPGK

SEQ ID NO:108

KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGQSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQ
35 HAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGT
KLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS
NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:109

KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
40 FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGQSALTQPPSASGSPGQSITISCTGTSNNFV
SWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLVGNWDVI
FGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:110

45 KKVYYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGQSALTQPPSASGSPGQSITISCTG

TSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLV
GNWDVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:111

5 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSSQSALTQPPSASGSPGQSI
TISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYY
CGSLVGNWDVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD
SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:112

10 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSSQSALTQPPSASG
SPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTD
DEAVYYCGSLVGNWDVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV
15 AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC
S

SEQ ID NO:113

20 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSSQSALTQ
PPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTV
SGLQTDDEAVYYCGSLVGNWDVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY
PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT
VAPTECS

SEQ ID NO:114

25 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGGGGSSQSALTQ
PPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNT
ASLTVSGLQTDDEAVYYCGSLVGNWDVIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY
PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
30 TVEKTVAPTECS

SEQ ID NO:115

35 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSSQSALTQPPSASGSPGQSITISCTGTSNNF
VSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLVGNWD
VIFGGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVET
TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:116

40 QPQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWWRQPPGKGLEWVWGLSHCASYWNRG
WYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRDTPKPAWDLWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPAVLQS
SGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGGGSGKKVYVGKCGDTVELTCT
ASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGNFPPLIKNLKPEDSDTYICE
VEDQKEEVQLVVVCGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPI

EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:117

5 QPQLQESGPTLVEASETSLTCAVSGDSTAACNSFWGWWRQPPGKGLEWVWGLSHCASYWNRG
WYHNPSLKSRLTLALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRDWPAPAWDLWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
10 HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKS
LSLSPGGGGGSKKVVYGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRV
DSRRSLWDQGNFPLIINKLPEDSDTYICEVEDQKEEVQLVWC

SEQ ID NO:118

15 QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCGSLVGNWVIFGGGTGLTVLQPKAAPSVTLFPPSSEELQANKATLV
CLISDFYPGAVTVAWKADSSPVKAGVETTPSKSQSNNKYAASSYLSLTPEQWKSRSYSQCQVTHE
GSTVEKTVAPTECSGGGGSKKVVYGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCK
PSKLNDRVDSRRSLWDQGNFPLIINKLPEDSDTYICEVEDQKEEVQLVWC

SEQ ID NO:119

20 KKVYVGKIGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVWVGSGGGGSSQPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSV
TAADTATYYCARFGGEVLRDWPAPAWDLWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQTYICNVNHKPS
25 NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:120

30 KKVYVGKVGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQGN
FPLIINKLPEDSDTYICEVEDQKEEVQLVWVGSGGGGSSQPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSV
TAADTATYYCARFGGEVLRDWPAPAWDLWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQTYICNVNHKPS
35 NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:121

40 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVGSGGGGSSQPQLQESGPTLVEASETSLTCAVSGDS
TAACNSFWGWWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSV
VTAADTATYYCARFGGEVLRDWPAPAWDLWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQTYICNVNHKPS
45 SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA

KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF
LYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:122

KKVVGKKGDCVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
5 NFPLIICNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDS
TAACNSFWGWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNS
VTAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
10 KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF
LYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:123

KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
15 FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNSV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
20 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFL
YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:124

KKVVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
25 FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNSV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
30 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFL
YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:125

KKVVGKKGDTVELTCTASQKKNIEFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
35 FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNSV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
40 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFL
YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:126

KKVVGKKGDTVELTCTASQKKNIQFDWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
45 FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKGLEWVWGLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNSV

TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
5 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:127

KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSVRSRLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGSGGGSQPQLQESGPTLVEASETSLTCAVSGDST
10 AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSNV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
15 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:128

KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSNRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGSGGGSQPQLQESGPTLVEASETSLTCAVSGDST
20 AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSNV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
25 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:129

KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSTRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGSGGGSQPQLQESGPTLVEASETSLTCAVSGDST
30 AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSNV
TAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
35 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
YSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:130

KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTCKGPSKLNDRVDSRRSMWDQGN
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGSGGGSQPQLQESGPTLVEASETSLTCAVSGDS
40 TAACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLSNV
VTAADTATYYCARFGGEVLRITDWPKEAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
45 KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
LYSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:131

KKVYVGKKGDTVCLTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLCIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGD
STAACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLN
5 VTAADTATYYCARFGGEVLR YTDWPKPAWDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGG
TAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF
10 FLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:132

KKVYVGKKGDTVCLTCTASQKKNIQFCWKNSNQIKILCNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLN
15 TAADTATYYCARFGGEVLR YTDWPKPAWDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
20 YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:133

KKVYVGKKGDTVCLTCTASQCKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQCN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLN
25 TAADTATYYCARFGGEVLR YTDWPKPAWDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
30 YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:134

KKVYVGKKGDTVCLTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVGDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDST
AACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLN
35 TAADTATYYCARFGGEVLR YTDWPKPAWDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
40 YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:135

KKVYVGKKGDTVCLTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLWDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGPQLQESGPTLVEASETSLTCAVSGDS
TAACNSFWGWRQPPGKLEWVGSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLN
45 VTAADTATYYCARFGGEVLR YTDWPKPAWDLWGRGTLTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV

KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF
LYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:136

- 5 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSGMQQLQESGPGLVKPSETLSLTCSVSGAS
ISDSYWSWIRRRSPGKGLEWIGYVHKSGDTNYSPLKSRVNLSDTSKNQVSLSLVAATAADSGKYY
CARTLHGRRYIGIVAFNEWFTYFYMDVWNGTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
10 DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSK
LTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:137

- 15 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSGGGGSGMQQLQESGPGLVKPSETLSLT
SVSGASISDSYWSWIRRRSPGKGLEWIGYVHKSGDTNYSPLKSRVNLSDTSKNQVSLSLVAATAA
DSGKYYCARTLHGRRYIGIVAFNEWFTYFYMDVWNGTQVTVSSASTKGPSVFPLAPSSKSTSGG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
20 PSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSF
FLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:138

- 25 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSGGGGSGGGGSGMQQLQESGPGLVKPSE
TLSLTCSVSGASISDSYWSWIRRRSPGKGLEWIGYVHKSGDTNYSPLKSRVNLSDTSKNQVSLSLV
AATAADSGKYYCARTLHGRRYIGIVAFNEWFTYFYMDVWNGTQVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN
30 VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVL
SDGDSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:139

- 35 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSGGGGSGGGGSGGGGSGMQQLQESGPG
LVKPSETLSLTCSVSGASISDSYWSWIRRRSPGKGLEWIGYVHKSGDTNYSPLKSRVNLSDTSKN
QVSLSLVAATAADSGKYYCARTLHGRRYIGIVAFNEWFTYFYMDVWNGTQVTVSSASTKGPSVF
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL
40 GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:140

- 45 QMQLQESGPGLVKPSETLSLTCSVSGASISDSYWSWIRRRSPGKGLEWIGYVHKSGDTNYSPLKSR
VNLSDTSKNQVSLSLVAATAADSGKYYCARTLHGRRYIGIVAFNEWFTYFYMDVWNGTQVTVSS

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPVAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCGGGSGKKVYVGKCGDTVELTCTASQKKN
QFHWKNSNQIKILGNQGSFLTCKGPSKLNDVRSDRRSLWDQGNFPLIKNLKPEDSDTYICEVEDQKE
EVQLVWVCGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEV
5 KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFF
LYSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

SEQ ID NO:141

QMLQESGPGLVKPSSETLSLTCVSGASISDSYWSWIRSPGKGLEWIGYVHKSGDTNYSPLKSR
10 VNLSLDTSKNQVSLSLVAATAADSGKYYCARTLHGRRIYGIVAFNEWFTYFYMDVWNGTQVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPVAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
15 SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGG
GGGSKKVYVGKCGDTVELTCTASQKKNQFHWKNSNQIKILGNQGSFLTCKGPSKLNDVRSDRRSL
WDQGNFPLIKNLKPEDSDTYICEVEDQKEEVQLVWV

SEQ ID NO:142

KKVYVGKCGDTVELTCTASQKKNQFHWKNSNQIKILGNQGSFLTCKGPSKLNDVRSDRRSLWDQG
20 NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSSDISVAPGETARISCEKSLGSRVQWY
QHRAGQAPSLIYNNQDRPSGIPERFSGSPDPFGTTATLTITSVEAGDEADYYCHIWDSDRVPTKW
FGGGTTTLVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNKYAASSYLSLTPEQWWSHKSYSQVTHEGSTVEKTVAPTECS

SEQ ID NO:143

SDISVAPGETARISCEKSLGSRVQWYQHRAGQAPSLIYNNQDRPSGIPERFSGSPDPFGTTAT
25 LTITSVEAGDEADYYCHIWDSDRVPTKWVFGGGTTTLVLGQPKAAPSVTLFPPSSEELQANKATLVCL
ISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWWSHKSYSQVTHEGST
VEKTVAPTECSGGGGGSKKVYVGKCGDTVELTCTASQKKNQFHWKNSNQIKILGNQGSFLTCKGPSK
LNDVRSDRRSLWDQGNFPLIKNLKPEDSDTYICEVEDQKEEVQLVWV

30 SEQ ID NO:144

KKVYVGKCGDTVELTCTASQKKNQFHWKNSNQIKILGNQGSFLTCKGPSKLNDVRSDRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSGVQLRESGPGLVKPSSETLSLCTVSND
RPSDHSWTWRQSPGKALEWIGDIHYNGATTYNPSLRSRVRIELDQSIPRFLKMTSMTAADTGM
YCARNAIRIYGVALGEWFHYGMDVWGQGTAVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
35 KDYFPEPVTVSWNSGALTSKVHTFPVAVLQSSGLYSLSVTVPSSSLGTQTYICNVNHKPSNTKVD
KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL
VDKSRWQQGNVFCFSLHEALHSHYTQKSLSLSPGK

40 SEQ ID NO:145

KKVYVGKCGDTVELTCTASQKKNQFHWKNSNQIKILGNQGSFLTCKGPSKLNDVRSDRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSGGGGSGGGGSGGGGSGVQLRESGPG
VKPSSETLSLCTVSNDSPSDHSWTWRQSPGKALEWIGDIHYNGATTYNPSLRSRVRIELDQSIPR
FSLKMTSMTAADTGMYYCARNAIRIYGVALGEWFHYGMDVWGQGTAVTVSSASTKGPSVFPLAP
45 SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPVAVLQSSGLYSLSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV

VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PVLDSGDGFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:146

- 5 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSGVQLQESGPGLVKPSSETLSVTCVSGDS
MNNYYWTWIRQSPGKLEWIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLSVTPADTAVYY
CATARRGQRIYGVVSFGEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
10 DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGFFLYSK
LTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:147

- 15 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSGGGGSGGGGSGGGGSGVQLQESGPG
VKPSSETLSVTCVSGDSMNNYYWTWIRQSPGKLEWIGYISDRESATYNPSLNSRVVISRDTSKNQ
LSLKLNSVTPADTAVYYCATARRGQRIYGVVSFGEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLG
20 TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPVLDSGDGFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:148

- 25 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQLQMQUESGPGLVKPSSETLSLCTVSGDS
IRGGEWGDKDYHWGWVRHSAGKLEWIGSIHWRTTHYKESLRRRVMSIDTSRNWFSRLASV
TAADTAVYFCARHRHHDVFMVLPIAGWFDVWGPVQVTSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS
30 NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGFFL
YSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:149

- 35 KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSGGGGSGGGGSGGGGSQLQMQUESGPG
LVKPSSETLSLCTVSGDSIRGGEWGDKDYHWGWVRHSAGKLEWIGSIHWRTTHYKESLRRRV
MSIDTSRNWFSRLASVTAADTAVYFCARHRHHDVFMVLPIAGWFDVWGPVQVTSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
40 SSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSGDGFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:150

- 45 KKVVLGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQGN
FPLIKNLKIEDSDTYICEVEDQKEEVQLVVFGLTANS DTHLLQGQSLTLTLESPPGSSPSVQCRSPR

GKNIQGGKTLVSQLELQDSGTWTCTVLQNKQKVEFKIDIVVLAFGGGGSGGGGSGGGGSGGGG
SQVQLVQSGAQMKNPASVKVSCAPSGYTFTDFYIHWLRQAPGQGLQWMGWMNPQTGRNTAR
NFQGRVTMTRDTSIGTAYMELRSLTSDDTAIYYCTTGGWISLYYDSSYYPNFDHWGQGTLLTVSSA
STKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSS
5 VVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:151

10 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGVQLVQSGAQMK
KNPGASVKVSCAPSGYTFTDFYIHWLRQAPGQGLQWMGWMNPQTGRNTARNFQGRVTMTRDT
SIGTAYMELRSLTSDDTAIYYCTTGGWISLYYDSSYYPNFDHWGQGTLLTVSSASTKGPSVFLAPSS
SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
15 YICNVNHKPSNTKVDKKEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:152

20 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGPQLQESGPTLV
EASETSLTCAVSGDSTAACNSFWGWRQPPGKCLEWVWGSLSHCASYWNRGWTYHNPSLKSRLT
LALDTPKNLVFLKLSVTAADTATYYCARFGGEVLRDTPKPAWVDLWGRGTLTVSSGGGGSG
GGGSGGGGSGGGGSGQSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKR
25 PSGVPDRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLVGNWDVIFGCGTKLTVLGGGGSGGGGS
DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:153

30 KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGGGGSGPQLQESGPTLVEASETL
SLTCAVSGDSTAACNSFWGWRQPPGKCLEWVWGSLSHCASYWNRGWTYHNPSLKSRLTALDTP
KNLVFLKLSVTAADTATYYCARFGGEVLRDTPKPAWVDLWGRGTLTVSSGGGGSGGGGSG
35 GGGSGGGGSGQSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVP
DRFSGSKSGNTASLTVSGLQTDDEAVYYCGSLVGNWDVIFGCGTKLTVLGGGGSGGGGSDKHTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
40 SCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:154

KKVYVGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQGN
FPLIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGGSGGGGSGGGGSGPQLQESGPTLVEASETSLTCAV
SGDSTAACNSFWGWRQPPGKCLEWVWGSLSHCASYWNRGWTYHNPSLKSRLTALDTPKNLVFL
45 KLSVTAADTATYYCARFGGEVLRDTPKPAWVDLWGRGTLTVSSGGGGSGGGGSGGGGSG
GGGQSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSG
SKSGNTASLTVSGLQTDDEAVYYCGSLVGNWDVIFGCGTKLTVLGGGGSGGGGSDKHTHTCPPCPA

PELLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHE
ALHSHYTQKSLSLSPGK

5 SEQ ID NO:155

KKVYGYGKKGDVTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGN
 FPLIINKLPEDSDTYICEVEDQKEEVQLVWVGSGGGSQPQLQESGPTLVEASETSLTCAVSGDST
 AACNSFWGWVRQPPGKCLEWVGSLSHCASYWNRGWTYHNPSLKSRLTLALDTPKNLVFLKLNSV
 TAADTATYYCARFGGEVLRYPDWPKPAWDLWGRGTLVTVSSGGGGSGGGSGGGSGGGSGGGGS
 10 QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVIYDVNKRPSGVPDRFSGSKSGN
 TASLTVSGLQTDDEAVYYCGSLVGNWDVIFGCGTKLTVLGGGSGGGGSDKHTHTCPPCPAPELLG
 GPSVFLFPPKPKDTLMSRTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
 VSVLTVLHQDWLNGKEYCKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
 KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHS
 15 HYTQKSLSI SPGK

SEQ ID NO:156

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQ
20 GNVFSCSVLHEALSHYQTQKSLSLSPGKGGGGSGGGSGGGSGGGSGKKVVGKKGDTVELT
CTASQKKNIQFHWKNSNQIKILGNQGSFLTGPSKLNDRVDSRRSLWDQGNFPLIINKLPEDSDTYI
CEVEDQKEEVQLVWVGSGGGSGGGSGGGSGQPQLQESGPTLVEASETSLSTCAVSGDSTAACN
SFWGWWRQPPGKCLEWWSLSHCASYWNRGWYHNPSLKSRLTLALDTPKNLVFLKLNSVTAAD
TATYYCARFGGEVLRYPDWPKAWDLWGRGTLVTVSSGGGGSGGGSGGGSGGGSGGSQSAL
25 TQPPSASGSPGQSITISCTGTSNNFVSWYQQHAGKAPKLVYDVNKRPSGVPDRFSGSKSGNTASL
TVSGLTQDDEAVYYCGSLVGNWDVIFGCGTKLTVL

SEQ ID NO:157

[illegible]

SEQ ID NO:158

40 KKVVYGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRVDSRRSLWDQG
NFPLIIKNLKPEDSDTYICEVEDQKEEVQLVWCGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPA
PELLGGPSVFLFPKPKD¹TL²MISRTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK³TISKAKGQPREPQVY⁴TLPPSRDELTKNQVS
L⁵TLCLVKGFYPSDIAEVESNGQPENNYKTTPVLSDSGSFFLYSKLTVDKSRWQ⁶QGNVFSCSVLHE
ALHSHY⁷TQKSLSLSPGK

45 SEQ ID NO:159

DNYWS
SEQ ID NO:160
YVHDSGDTNYPNPSLKS
SEQ ID NO:161
5 TKHGRRYGVVAFKEWFTYFYMDV
SEQ ID NO:162
GEESLGSRSVI
SEQ ID NO:163
NNNDRPS
10 SEQ ID NO: 164
HIWDSRRPTNWW
SEQ ID NO: 165
DAYWS
SEQ ID NO: 166
15 YVHHSGDTNYPNPSLKR
SEQ ID NO: 167
ALHGKRIYGIVALGELFTYFYMDV
SEQ ID NO: 168
GKESIGSRAVQ
20 SEQ ID NO:169
NNQDRPA
SEQ ID NO:170
HIYDARGGTNWW
SEQ ID NO:171
25 ACTYFWG
SEQ ID NO:172
SLSHCQSFWGSGWTFHNPSLKS
SEQ ID NO:173
FDGEVLVYNHWPAPAWDL
30 SEQ ID NO:174
NGTATNFVS

SEQ ID NO:175

GVDKRPP

SEQ ID NO:176

GSLVGNWDVI

5 SEQ ID NO:177

ACDYFWG

SEQ ID NO:178

GLSHCAGYYNTGWTYHNPSLKS

SEQ ID NO:179

10 FDGEVLVYHDWPKPAWDL

SEQ ID NO:180

TGTSNRFVS

SEQ ID NO:181

GVNKRPS

15 SEQ ID NO:182

SSLVGNWDVI

SEQ ID NO:183

RCNYFWG

SEQ ID NO:184

20 SLSHCRSYNTDWTYHNPSLKS

SEQ ID NO:185

FGGEVLVYRDWPKPAWDL

SEQ ID NO:186

TGTSNRFVS

25 SEQ ID NO:187

EVNKRPS

SEQ ID NO:188

SSLVGNWDVI

SEQ ID NO:189

30 TGHYYWG

SEQ ID NO:190

HIHYTTAVLHNPSLKS
SEQ ID NO:191
SGGDILYYIEWQKPHWFSP
SEQ ID NO:192
5 NGTSSDIGGWNFVS
SEQ ID NO:193
EVNKRPS
SEQ ID NO:194
SSLFGRWDVV
10 SEQ ID NO: 185
TGHHYWG
SEQ ID NO: 196:
HIHYNTAVLHNPAKLS
SEQ ID NO:197
15 SGGDILYYIEWQKPHWFYP
SEQ ID NO:198
SGTGSDIGSWNFVS
SEQ ID NO:199
EVNRRRS
20 SEQ ID NO:200
SSLSGRWDIV
SEQ ID NO:201
GTDWGENDFHYG
SEQ ID NO:202
25 SIHWRGRTTHYKTSFRS
SEQ ID NO:203
HKYHDIFRVVPVAGWFDP
SEQ ID NO:204
RASQNVKNNLA
30 SEQ ID NO:205
DASSRAG

SEQ ID NO:206
QQYEEWPRT
SEQ ID NO:207
GGEWGDSDYHWG
5 SEQ ID NO:208
SIHWRGTTHYNAPFRG
SEQ ID NO:209
HKYHDIVMVVPIAGWFDP
SEQ ID NO:210
10 RASQSVKNNLA
SEQ ID NO:211
DTSSRAS
SEQ ID NO:212
QQYEEWPRT
15 SEQ ID NO:213
DVWLN
SEQ ID NO:214
RIKSRTDGGTTDYAASVKG
SEQ ID NO:215
20 DGFIMIRGVSEDYYYYYMDV
SEQ ID NO:216
SGSSSNIGNNYVL
SEQ ID NO:217
GNNKRPS
25 SEQ ID NO:218
ATWDSGLSADWW
SEQ ID NO:219
SYVMH
SEQ ID NO:220
30 AISSDGETTYHANSVKG
SEQ ID NO:221

DRYYETSGSNAFDV
SEQ ID NO:222
QASQDISNYLN
SEQ ID NO:223
5 TASNLET
SEQ ID NO:224
QQYDNLGDLS
SEQ ID NO:225
NFAIH
10 SEQ ID NO:226
GRVPVVGIIKYGKKFHD
SEQ ID NO:227
WRGCGMCPYDTSSYYNDASDV
SEQ ID NO:228
15 RASQNISSSWIA
SEQ ID NO:229
AASARAA
SEQ ID NO:230
QYYGGSFFT
20 SEQ ID NO:231
AHTMN
SEQ ID NO:232
SISTSSTYRDYADAVKG
SEQ ID NO:233
25 KGSDRLSDNDPFDA
SEQ ID NO:234
RASQSIETWLA
SEQ ID NO:235
KASTLKT
30 SEQ ID NO:236
QHYAGYSAT

SEQ ID NO:237

SSYWS

SEQ ID NO:238

YTHHSGDTNYAPSLKS

5 SEQ ID NO:239

TLHGRRYIGWVAFNEFFTYFYWEV

SEQ ID NO:240

GGESIGSRAVQ

SEQ ID NO:241

10 NNQDRPP

SEQ ID NO:242

HIWDSRRPTNWW

SEQ ID NO:243

SSYWS

15 SEQ ID NO:244

YTHHSGDTNYAPSLKS

SEQ ID NO:245

TLHGRRYIGWVAFNEYTYFYWPT

SEQ ID NO:246

20 GGESIGSRAVQ

SEQ ID NO:247

NNQDRPP

SEQ ID NO:248

HIWDSRRPTNWE

25 SEQ ID NO:249

SSYWS

SEQ ID NO:250

YTHHSGDTNYAPSLKS

SEQ ID NO:251

30 TLHGRRYIGWVAFNEYTYFYWPT

SEQ ID NO:252

TGTSSDIGASDYVS

SEQ ID NO:253

DVTKRPS

SEQ ID NO:254

5 SSDAGRHTLL

SEQ ID NO:255

QVHLQESGPGLVKPSETLSLTCNVSGTLVRDNYWSWIRQPLGKQPEWIGYVHDSGDTNYNPSLKS
RVHLSLDKSKNLVSLRLTGVTAAADSAIYYCATTKHGRRIYGVAFAKEWFTYFYMDVWVGKGTSVTVS
S

10 SEQ ID NO:256

TFVSVAPGQTARITCGEESLGSRSVIWYQQRPGQAPSLIYNNNDRPSGIPDRFSGSPGSTFGTTAT
LTITSVEAGDEADYYCHIWDSRRPTNWWFGEGTTLIVL

SEQ ID NO:257

15 QVHLQESGPGLVKPSETLSLTCNVSGTLVRDNYWSWIRQPLGKQPEWIGYVHDSGDTNYNPSLKS
RVHLSLDKSKNLVSLRLTGVTAAADSAIYYCATTKHGRRIYGVAFAKEWFTYFYMDVWVGKGTSVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
20 NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFVMSHEALTHYHTQKSLSLSPG
K

SEQ ID NO:258

25 QVHLQESGPGLVKPSETLSLTCNVSGTLVRDNYWSWIRQPLGKQPEWIGYVHDSGDTNYNPSLKS
RVHLSLDKSKNLVSLRLTGVTAAADSAIYYCATTKHGRRIYGVAFAKEWFTYFYMDVWVGKGTSVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFVMSHEALTHYHTQKSLSLSPG
30 K

SEQ ID NO:259

TFVSVAPGQTARITCGEESLGSRSVIWYQQRPGQAPSLIYNNNDRPSGIPDRFSGSPGSTFGTTAT
LTITSVEAGDEADYYCHIWDSRRPTNWWFGEGTTLIVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSRSYSCQVTHEGST
35 VEKTVAPTECS

SEQ ID NO:260

QLHLQESGPGLVKPPETLSLTCVSGASINDAYWSWIRQSPGKRPEWVGYYVHHSGDTNYNPSLKR
RVTFSLDTAKNEVSLKLVDLTAADSATYFCARALHGKRIYGIVALGELFTYFYMDVWVGKGTAVTVSS

SEQ ID NO:261

SSMSVSPGETAKISCGKESIGSRAVQWYQQKPGQPPSLIYNNQDRPAGVPERFSASPDFRPGTTA
TLTITNVDAEDEADYYCHIIDARGGTNWWFDRGTTLTVL

SEQ ID NO:262

5 QLHLQESGPGLVKPPETLSLTCVSGASINDAYWSWIRQSPGKRPEWVGYPVHSGDTNYPNPSLKR
RVTFSLDTAKNEVSLKLVDLTAADSATYFCARALHGKRIYGIVALGELFTYFYMDVWGKGTAFTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHFFPAVLQSSGLYSL
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
10 GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:263

15 QLHLQESGPGLVKPPETLSLTCVSGASINDAYWSWIRQSPGKRPEWVGYPVHSGDTNYPNPSLKR
RVTFSLDTAKNEVSLKLVDLTAADSATYFCARALHGKRIYGIVALGELFTYFYMDVWGKGTAFTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHFFPAVLQSSGLYSL
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:264

20 SSMSVSPGETAKISCGKESIGSRAVQWYQQKPGQPPSLIYNNQDRPAGVPERFSASPDFRPGTTA
TLTITNVDAEDEADYYCHIIDARGGTNWWFDRGTTLTVLGQPKAAPSVTLPSSSEELQANKATLVC
LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS

SEQ ID NO:265

25 QSQLQESGPRLVEASETSLTCNVSGESTGACTYFWGWWRQAPGKGLEWIGSLSHCQSFWSG
WTFHNPSLKSRLTISLDTKPNQVFLKLTSLTAADTATYYCARFDGEVLVYNHWPKPAWDLWGRGI
PVTVTVSS

SEQ ID NO:266

30 QSALTQPPSASGSPGQSITISCNGTATNFVSWYQQFPDKAPKLIIFGVDKRPPGVPDRFSGSRSGTT
ASLTVSRLQTDDEAVYYCGSLVGNWDVIFGGGTTLTVL

SEQ ID NO:267

35 QSQLQESGPRLVEASETSLTCNVSGESTGACTYFWGWWRQAPGKGLEWIGSLSHCQSFWSG
WTFHNPSLKSRLTISLDTKPNQVFLKLTSLTAADTATYYCARFDGEVLVYNHWPKPAWDLWGRGI
PVTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHFFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKS
LSLSPGK

40 SEQ ID NO:268

QSQLQESGPRLVEASETSLTCNVSGESTGACTYFWGWVRQAPGKGLEWIGSLSHCQSFWGS
WTFHNPSLKSRLTISLDTPKNQVFLKLTSLTAADTATYYCARFDGEVLVYNHWPKPAWDLWGRGI
PVTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL
5 FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKS
LSLSPGK

SEQ ID NO:269

10 QSALTQPPSASGSPGQSITISCNGTATNFVSWYQQFPDKAPKLIIFGVDKRPPGVPDRFSGSRSGTT
ASLTVSRLQTDDEAVYYCGSLVGNWDVIFGGGTTTLVLGQPKAAPSVTLFPPSSEELQANKATLVCL
ISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS

SEQ ID NO:270

15 QPQLQESGPGLVEASETSLTCTVSGDSTAACDYFWGWVRQPPGKGLEWIGGLSHCAGYYNTGW
TYHNPSLKSRLTISLDTPKNQVFLKLNSTAAATAIYYCARFDGEVLVYHDWPKPAWDLWGRGTL
VTVTVSS

SEQ ID NO:271

20 QSALTQPPSASGSPGQSSISICTGTSNRFVSWYQQHPGKAPKLVYGVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCSSLVGNWDVIFGGGTKLTVL

SEQ ID NO:272

QPQLQESGPGLVEASETSLTCTVSGDSTAACDYFWGWVRQPPGKGLEWIGGLSHCAGYYNTGW
TYHNPSLKSRLTISLDTPKNQVFLKLNSTAAATAIYYCARFDGEVLVYHDWPKPAWDLWGRGTL
VTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
25 SGLYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKS
LSLSPGK

30 SEQ ID NO:273

QPQLQESGPGLVEASETSLTCTVSGDSTAACDYFWGWVRQPPGKGLEWIGGLSHCAGYYNTGW
TYHNPSLKSRLTISLDTPKNQVFLKLNSTAAATAIYYCARFDGEVLVYHDWPKPAWDLWGRGTL
VTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF
35 PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSCSVLHEALHSHYTQKS
LSLSPGK

SEQ ID NO:274

40 QSALTQPPSASGSPGQSSISICTGTSNRFVSWYQQHPGKAPKLVYGVNKRPSGVPDRFSGSKSGN
TASLTVSGLQTDDEAVYYCSSLVGNWDVIFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCL

LISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS

SEQ ID NO:275

5 QPQLQESGPGLVEASETSLTCTVSGDSTGRCNYFWGWWRQPPGKGLEWIGSLSHCRSYNTDW
TYHNPSLKSRLTISLDTPKNQVFLRLTSVTAADTATYYCARFGGEVLVYRDWPKPAWVDLWGRGTL
VTVSS

SEQ ID NO:276

QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQYPGKAPKLVIEVKNRPSGVPDRFSGSKSGS
TASLTVSGLQADDEGVYYCSSLVGNWDVIFGGGTKLTVL

10 SEQ ID NO:277

QPQLQESGPGLVEASETSLTCTVSGDSTGRCNYFWGWWRQPPGKGLEWIGSLSHCRSYNTDW
TYHNPSLKSRLTISLDTPKNQVFLRLTSVTAADTATYYCARFGGEVLVYRDWPKPAWVDLWGRGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
15 KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSL
SPGK

SEQ ID NO:278

20 QPQLQESGPGLVEASETSLTCTVSGDSTGRCNYFWGWWRQPPGKGLEWIGSLSHCRSYNTDW
TYHNPSLKSRLTISLDTPKNQVFLRLTSVTAADTATYYCARFGGEVLVYRDWPKPAWVDLWGRGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVWTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
25 DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSL
SPGK

SEQ ID NO:279

30 QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQYPGKAPKLVIEVKNRPSGVPDRFSGSKSGS
TASLTVSGLQADDEGVYYCSSLVGNWDVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV
CLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE
GSTVEKTVAPTECS

SEQ ID NO:280

35 QVQLQESGPGLVKPAETLSLTCSVSGESINTGHYYWGWWRQVPKGKLEWIGHIHYTTAVLHNPSLK
SRLTIKIYTLRNQITLRLSNVTAADTAVYHCVRSGGDILYIYEWQKPHWFSPWGPGLHVTVSS

SEQ ID NO:281

QSALTQPPSASGSLGQSVTISCNGTSSDIGGWNFVSWYQQFPGRAPRLIIEVKNRPSGVPGRFSG
SKSGNSASLTVSGLQSDDEGQYFCSSLFGRWDVVFGGGTKLTVL

SEQ ID NO:282

QVQLQESGPGLVKPAETLSLTCSVSGESINTGHYYWGWRQVPGKGLEWIGHIHYTTAVLHNPSLK
SRLTIKIYTLRNQITLRLSNVTAADTAVYHCVRSGGDILYYYEWQKPHWFSWPWGPIHVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
5 RTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:283

QVQLQESGPGLVKPAETLSLTCSVSGESINTGHYYWGWRQVPGKGLEWIGHIHYTTAVLHNPSLK
10 SRLTIKIYTLRNQITLRLSNVTAADTAVYHCVRSGGDILYYYEWQKPHWFSWPWGPIHVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
15 PENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:284

QSALTQPPSASGSLGQSVTISCNGTSSDIGGWNFVSWYQQFPGRAPRLIIFEVNRKPSGVPGRFSG
SKSGNSASLTVSGLQSDDEGQYFCSSLFGRWDVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA
NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSC
20 QVTHEGSTVEKTVAPTECS

SEQ ID NO:285

QVQLQESGPGLVKPSSETLSLTCTVSGDSINTGHYYWGWRQVPGKGPEWIAHIIHYNTAVLHNPAK
SRVTISIFTLKNLITLSLSNVTAADTAVYFCVRSGGDILYYIEWQKPHWFYWPWGPGILVTVSS

SEQ ID NO:286

25 QSALTQPPSASGSLGQSLTISCSGTGSDIGSWNFVSWYQQFPGRAPNLIIFEVNRRRSGVPDRFSG
SKSGNTASLTVSGLRSEDEAEYFCSSLSGRWDIVFGGGTKVTVL

SEQ ID NO:287

QVQLQESGPGLVKPSSETLSLTCTVSGDSINTGHYYWGWRQVPGKGPEWIAHIIHYNTAVLHNPAK
SRVTISIFTLKNLITLSLSNVTAADTAVYFCVRSGGDILYYIEWQKPHWFYWPWGPGILVTVSSASTKGP
30 SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

35 SEQ ID NO:288

QVQLQESGPGLVKPSSETLSLTCTVSGDSINTGHYYWGWRQVPGKGPEWIAHIIHYNTAVLHNPAK
SRVTISIFTLKNLITLSLSNVTAADTAVYFCVRSGGDILYYIEWQKPHWFYWPWGPGILVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
40 PEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:289

QSALTQPPSASGSLGQSLTISCSGTGSDIGSWNFVSWYQQFPGRAPNLIIFEVNRRRSGVPDRFSG
SKSGNTASLTVSGLRSEDEAEYFCSSLSGRWDIVFGGGTKVTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
5 VTHEGSTVEKTVAPTECS

SEQ ID NO:290

QLQLQESGPGLVKPSETLSLTCTVSGGSMRGTDWGENDFHYGWIRQSSAKGLEWIGSIHWRGRTT
HYKTSFRSRATLSIDTSNNRFSLTFSFVTAADTAVYYCARHKYHDIFRVVPVAGWFDWPWGQGLLTV
SS

10 SEQ ID NO:291

EIVMTQSPPTLSVSPGETATLSCRASQNVKNNLAWYQLKPGQAPRLLIFDASSRAGGIPDRFSGSG
YGTDFTLTVNSVQSEDFGDYFCQYEEWPRTFGQGTKVDIK

SEQ ID NO:292

QLQLQESGPGLVKPSETLSLTCTVSGGSMRGTDWGENDFHYGWIRQSSAKGLEWIGSIHWRGRTT
15 HYKTSFRSRATLSIDTSNNRFSLTFSFVTAADTAVYYCARHKYHDIFRVVPVAGWFDWPWGQGLLTV
SSASTKGPSVFPLAPSSKSTSGGTAAAGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
20 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSP
GK

SEQ ID NO:293

QLQLQESGPGLVKPSETLSLTCTVSGGSMRGTDWGENDFHYGWIRQSSAKGLEWIGSIHWRGRTT
HYKTSFRSRATLSIDTSNNRFSLTFSFVTAADTAVYYCARHKYHDIFRVVPVAGWFDWPWGQGLLTV
25 SSASTKGPSVFPLAPSSKSTSGGTAAAGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVLHEALHSHYTQKSLSLSP
30 GK

SEQ ID NO:294

EIVMTQSPPTLSVSPGETATLSCRASQNVKNNLAWYQLKPGQAPRLLIFDASSRAGGIPDRFSGSG
YGTDFTLTVNSVQSEDFGDYFCQYEEWPRTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTH
35 QGLSSPVTKSFNRGEC

SEQ ID NO:295

EVHLEESGPGLVRPSETLSLTCTASGGSIIRGGEGWGDSDYHWGWWRHSPEKGLEWIGSIHWRGTT
HYNAPFRGRGRLSIDLSRNQFSLRLTSVTAEDTAVYYCVKHKYHDIVMWVPIAGWFDWPWGQGLQVT
VSS

40 SEQ ID NO:296

EIMMTQSPAILSVSPGDRATLSCRASQSVKNNLAWYQKRPQGAPRLLIFDTSSRASGIPARFSGGG
SGTEFTLTVNSMQSEDFATYYCQYEEWPRTFGQGTKVEIK

SEQ ID NO:297

5 EVHLEESGPGGLVRPSETLSLTCTASGGGIRGGEWGDSDYHWGWVRHSPEKGLEWIGSIHWRGTT
HYNAPFRGRGRLSIDLSRNQFSLRLTSVTAEDTAVYYCVKHKYHDIVMWVPIAGWFDPPWQGLQVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSWVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
10 WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLS
PGK

SEQ ID NO:298

15 EVHLEESGPGGLVRPSETLSLTCTASGGGIRGGEWGDSDYHWGWVRHSPEKGLEWIGSIHWRGTT
HYNAPFRGRGRLSIDLSRNQFSLRLTSVTAEDTAVYYCVKHKYHDIVMWVPIAGWFDPPWQGLQVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSWVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
20 EWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLS
PGK

SEQ ID NO:299

EIMMTQSPAILSVSPGDRATLSCRASQSVKNNLAWYQKRPQGAPRLLIFDTSSRASGIPARFSGGG
SGTEFTLTVNSMQSEDFATYYCQYEEWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
25 VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKIDSTYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

SEQ ID NO:300

EVQLVESGGGLVKPGGSLRLTCVASGFTFSDVWLNWVRQAPGKGLEWVGRIKSRTDGGTTDYAA
SVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYSCITDGFIMIRGVSEDIYMDVWVGKGTITVTS
S

30 SEQ ID NO:301

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVLWYQQFPGTAPKLLIYGNNKRPSPGIPDRFSGSK
SGTSATLGITGLQTGDEADYFCATWDSGLSADWWFGGGTKLTVL

SEQ ID NO:302

35 EVQLVESGGGLVKPGGSLRLTCVASGFTFSDVWLNWVRQAPGKGLEWVGRIKSRTDGGTTDYAA
SVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYSCITDGFIMIRGVSEDIYMDVWVGKGTITVTS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSWVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
40 NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K

SEQ ID NO:303

EVQLVESGGGLVPGGSLRLTCVASGFTFSDVWLNWVRQAPGKGLEWVGRIKSRTDGGTTDYAA
SVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYSCTTDGFMIRGVSEDDYMDVWGKTTVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
5 SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFVLSHSHYTKKSLSPG
K

10 SEQ ID NO:304

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVLWYQQFPGTAPKLLIYGNNKRPSGIPDRFSGSK
SGTSATLGITGLQTGDEADYFCATWDSGLSADWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSRSYSCQ
VTHEGSTVEKTVAPTECS

15 SEQ ID NO:305

QVQLVQSGGGLVQPGGSLRLSAAFGFNFSSYVMHWVRQAPGQGLEYLSAISSDGETTYHANSVK
GRFTSSRDNSKNTLFLQMGLSLRTEDVAVYYCARDRIYETSGSNAFDVWGQGTMTVTVSS

SEQ ID NO:306

20 NSVLTQSPSSLSASVGDRVTITCQASQDISNYLNWYQHKGPKAPKLLIYTASNLETGVPSRFSGGGS
GTHFSFTITSLQPEDAATYFCQYDNLGDSFGGGTKVEIK

SEQ ID NO:307

QVQLVQSGGGLVQPGGSLRLSAAFGFNFSSYVMHWVRQAPGQGLEYLSAISSDGETTYHANSVK
GRFTSSRDNSKNTLFLQMGLSLRTEDVAVYYCARDRIYETSGSNAFDVWGQGTMTVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVP
25 SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFVLSHSHYTKKSLSPGK

SEQ ID NO:308

30 QVQLVQSGGGLVQPGGSLRLSAAFGFNFSSYVMHWVRQAPGQGLEYLSAISSDGETTYHANSVK
GRFTSSRDNSKNTLFLQMGLSLRTEDVAVYYCARDRIYETSGSNAFDVWGQGTMTVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
35 KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFVLSHSHYTKKSLSPGK

SEQ ID NO:309

NSVLTQSPSSLSASVGDRVTITCQASQDISNYLNWYQHKGPKAPKLLIYTASNLETGVPSRFSGGGS
GTHFSFTITSLQPEDAATYFCQYDNLGDSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
40 CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

SEQ ID NO:310

QVQLVQSGAEVRKPGSSVTISCKPVGGTFTNFAIHWWRQAPGQGLEWVGGRVPVVGIIKYGKKFH
DRLRLYEDDPMKTVFLELRSLTSDDTGVIYCTRWRGCGMCPYDTSSYYNDASDVWGPGTKVIVSA

SEQ ID NO:311

- 5 EIVLTQSPVTLSSLSSGETGTLSCRASQNISSSWIAWYQRRGQVPRLLISAASARAAGIPDRFTGRG
SGTDFTLTITRLEPEDFGVYSCQYYGGSFFTFGPGTQVDVK

SEQ ID NO:312

- QVQLVQSGAEVRKPGSSVTISCKPVGGTFTNFAIHWWRQAPGQGLEWVGGRVPVVGIIKYGKKFH
DRLRLYEDDPMKTVFLELRSLTSDDTGVIYCTRWRGCGMCPYDTSSYYNDASDVWGPGTKVIVSA
10 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

- 15 SEQ ID NO:313

- QVQLVQSGAEVRKPGSSVTISCKPVGGTFTNFAIHWWRQAPGQGLEWVGGRVPVVGIIKYGKKFH
DRLRLYEDDPMKTVFLELRSLTSDDTGVIYCTRWRGCGMCPYDTSSYYNDASDVWGPGTKVIVSA
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDT
20 LMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:314

- EIVLTQSPVTLSSLSSGETGTLSCRASQNISSSWIAWYQRRGQVPRLLISAASARAAGIPDRFTGRG
25 SGTDFTLTITRLEPEDFGVYSCQYYGGSFFTFGPGTQVDVKRTVAAPSVFIFPPSDEQLKSGTASV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

SEQ ID NO:315

- EVQLVESGGGLVKAGGSLILSCGVSNFRISAHTMNWRRVPGGGLEWVASISTSSTYRDYADAVKG
30 RFTVSRDDLEDFVYLQMHKMRVEDTAIYYCARKGSDRLSDNDPFDWGPVTVTVSP

SEQ ID NO:316

DVVMTQSPSTLSASVGDITITCRASQSIETWLAWYQQKPGKAPKLLIYKASTLKTGVPSRFSGSGS
GTEFTLTISGLQFDDFATYHCQHYAGYSATFGQGTRVEIK

SEQ ID NO:317

- 35 EVQLVESGGGLVKAGGSLILSCGVSNFRISAHTMNWRRVPGGGLEWVASISTSSTYRDYADAVKG
RFTVSRDDLEDFVYLQMHKMRVEDTAIYYCARKGSDRLSDNDPFDWGPVTVTVSPASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVSVTVPSS
SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKV

SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:318

5 EVQLVESGGGLVKAGGSLILSCGVSNFRISAHTMNWVRRVPGGGLEWVASISTSSTYRDYADAVKG
RFTVSRDDLEDFVYLQMHKMRVEDTAIYYCARKGSDRLSDNDPFDWGPVTVVSPASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
10 SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:319

DVMTQSPSTLSASVGDITITCRASQSIETWLAWYQQKPGKAPKLLIYKASTLKTGVPSRFSGSGS
GTEFTLTISGLQFDDFATYHCQHYAGYSATFGQGTRVEIKRTVAAPSVFIFPPSDEQLKSGTASVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQG
15 LSSPVTKSFNRGEC

SEQ ID NO:320

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEFFTYFYWEVWGKGTQVTVS
S

20 SEQ ID NO:321

SDISVAPGETVRISCGGESIGSRAVQWYQHRAGQAPKLIYNNQDRPPGIPERFSGSPDIDFGTTATL
TITNVEAGDEATYYCHIWDSRRPTNWWFGGGTTLTVL

SEQ ID NO:322

25 QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEFFTYFYWEVWGKGTQVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
30 ESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K

SEQ ID NO:323

35 QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEFFTYFYWEVWGKGTQVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
40 ESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLSPG
K

SEQ ID NO:324

SDISVAPGETVRISCGGESIGSRAVQWYQHRAGQAPKLIYNNQDRPPGIPERFSGSPDIDFGTTATL
TITNVEAGDEATYYCHIWDSRRPTNWWFGGGTTLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTTSPKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST
VEKTVAPTECS

5 SEQ ID NO:325

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEYTYFYWPTWGKGTQVTVS
S

SEQ ID NO:326

10 SDISVAPGETVRITCGGESIGSRAVQWYQHRPGQAPRLIYNNQDRPPGIPERFSGSPDIDFGTTATL
TISNVEAGDEATYYCHIWDSRRPTNWELGPGTTLTVL

SEQ ID NO:327

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEYTYFYWPTWGKGTQVTVS
15 SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
20 K

SEQ ID NO:328

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVHLGLHPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEYTYFYWPTWGKGTQVTVS
25 SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPG
K

30 SEQ ID NO:329

SDISVAPGETVRITCGGESIGSRAVQWYQHRPGQAPRLIYNNQDRPPGIPERFSGSPDIDFGTTATL
TISNVEAGDEATYYCHIWDSRRPTNWELGPGTTLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTTSPKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST
VEKTVAPTECS

35 SEQ ID NO:330

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVTIGLDPSKNQVSLSLTSVTAADTAVYYCARTLHGRRYGVVAFNEYTYFYWPTWGKGTQVTVS
S

SEQ ID NO:331

QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVTIGLDPSKNQVSLSLTAVTAADTAVYYCARTLHGRRIYGVVAFNEYTYFYWPTWGKGTQVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
5 TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K

SEQ ID NO:332

10 QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVTIGLDPSKNQVSLSLTAVTAADTAVYYCARTLHGRRIYGVVAFNEYTYFYWPTWGKGTQVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
15 TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLSPG
K

SEQ ID NO:333

20 QMQLQESGPGLVKPGETLSLTCSVSGASISSSYWSWLRETPGKGLEWIGYTHHSGDTNYAPSLKS
RVTIGLDPSKNQVSLSLTAVTAADTAVYYCARTLHGRRIYGVVAFNEYTYFYWPTWGKGTQVTVS
S

SEQ ID NO:334

QSVLTQPPSASGSPGQSVTISCTGTSSDIGASDYVSWYQQYPGEAPKVIIDVTKRPSGVPDRFSG
SKSGTTASLTVSGLQAEDADYYC SSDAGRHTLLFGGGTKVTVL

25 SEQ ID NO:335

QVQLLESGLVLRPSETLTLTCSVFNSRVSGYYYSWIRQPPGRGLEWIASTHFSRLRPSRNPSLLSR
VTTSIDTERYQVFLNMRSVTAADTAVYFCARGDASGWRADYFPHWGQGTLLVWSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
30 CVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:336

35 QVQLLESGLVLRPSETLTLTCSVFNSRVSGYYYSWIRQPPGRGLEWIASTHFSRLRPSRNPSLLSR
VTTSIDTERYQVFLNMRSVTAADTAVYFCARGDASGWRADYFPHWGQGTLLVWSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
40 KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:337

QSVLTQPPSASGSPGQSVTISCTGTSSDIGASDYVSWYQQYPGEAPKVIIDVTKRPSGVPDRFSG
SKSGTTASLTVSGLQAEDEADYYCSSDAGRHTLLFGGGTKVTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS

5 SEQ ID NO:338

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVHLQESGPGLVKPPSETLSLTCNVSGTL
VRDNYWSWIRQPLGKQPEWIGYVHDSGDTNYPNPSLKSRLVHSLDKSKNLVSLRLTGVTAAADSAIYY
CATTKHGRRIYGVAFKEWFTYFYMDVWVGKGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
10 VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSK
LTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

15 SEQ ID NO:339

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVHLQESGPGLVKPPETLSLTCVSGASI
NDAYWSWIRQSPGKRPEWVGYYVHSGDTNYPNPSLKRRTVTFSLDTAKNEVSLKLVDLTAADSATYF
CARALHKGRIYGIVALGELFTYFYMDVWVGKGTAVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
20 KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLT
VDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

25 SEQ ID NO:340

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVHLQESGPRLVEASETSLTCNVSGES
TGACTYFWGWWRQAPGKGLEWIGLSHCQSFWSGWT FHNPSLKSRLTISLDTPKNQVFLKLTSL
TAADTATYYCARFDGEVLVYNHWPKPAWDLWGRGIPVTVTVSSASTKGPSVFPLAPSSKSTSGG
30 TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSF
FLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

35 SEQ ID NO:341

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVHLQESGPRLVEASETSLTCTVSGDS
TAACDYFWGWWRQPPGKGLEWIGLSHCAGYYNTGWTYHNP SLKSRLTISLDTPKNQVFLKLNVS
TAADTAIYYCARFDGEVLVYHDWPKPAWDLWGRGTLVTVTVSSASTKGPSVFPLAPSSKSTSGGT
40 AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFF
LYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:342

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQPQLQESGPGLEASETLSLTCTVSGDS
TGRCNFYWGWRQPPGKGLEWIGLSHCRSYNTDWTYHNPSLKSRLTISLDTPKNQVFLRLTSV
5 TAADTATYYCARFGGEVLVYRDWPKPAWDLWGRGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHNKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFL
10 YSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:343

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVQLQESGPGLVKPAETLSLTCSVSGESI
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15 CVRSGGDILYYEYQKPHWFSPWGPDIHVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHNKPSNTKVDKKV
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK
20 SRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:344

QVQLQESGPGLVKPAETLSLTCSVSGESINTGHYYWGWRQVPKGKLEWIGHIHYTTAVLHNPSLK
SRLTIKIYTLRNQITLRLSNVTAADTAVYHCVRSGGDILYYEYQKPHWFSPWGPDIHVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
25 VPSSSLGTQTYICNVNHNKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGKGGGG
SKKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
30 NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVC

SEQ ID NO:345

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQSALTQPPSASGSLGQSVTISCNGTSSDI
GGWNFVSWYQQFPGRAPRLIIFEVNKRPSGVPGRFSGSKSGNSASLTVSGLQSDDEGQYFCSSLF
35 GRWDVVFGGGKTLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK
AGVETTPPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:346

QSALTQPPSASGSLGQSVTISCNGTSSDIGGWNFVSWYQQFPGRAPRLIIFEVNKRPSGVPGRFSG
SKSGNSASLTVSGLQSDDEGQYFCSSLFGRWDVVFGGGKTLTVLGQPKAAPSVTLFPPSSEELQA
40 NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPPSKQSNNKYAASSYLSLTPEQWKSHRSYSC
QVTHEGSTVEKTVAPTECSGGGGSKKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGS
FLT KGPSKLNDRVDSRRSLWDQGNFPLIINKLPEDSDTYICEVEDQKEEVQLVVVC

SEQ ID NO:347

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVCGGGGSQVQLQESGPGLVKPSSETLSLTCTVSGDSI
NTGHHYWGWWRVPGKGPEWIAHIHYNTAVLHNPALKSRVTISIFTLKNLITLSLSNVTAAADVYFC
5 VRSGGDILYYIEWQKPHWFPWGPGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
10 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:348

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVCGGGGSQVQLQESGPGLVKPSSETLSLTCTVSGGS
MRGTDWGENDFHYGWIRQSSAKGLEWIGSIHWRGRTTHYKTSFRSRATLSIDTSNNRFSLTFSFVT
15 AADTAVYYCARHKYHDIFRVVPVAGWFDPWGQGLLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKF
NWWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLY
20 SKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:349

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVCGGGGSEVHLEESGPGLVKPSSETLSLTCTASGGSI
RGGEWGDSDYHWGWVRHSPEKGLEWIGSIHWRGTTTHYNAPFRGRGRLSIDLSRNQFSLRLTSVT
25 AEDTAVYYCVKHKYHDIVMVPIAGWFDPWGQGLQVTVSSASTKGPSVFPLAPSSKSTSGGTAALG
CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS
30 KLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:350

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVCGGGGSEVQLVESGGGLVKPGGSLRLTCVASGFT
FSDVWLNWVRQAPGKGLEWVGRIKSRDGGTTDYAASVKGRFTISRDDSKNTLYLQMNSLKTEDT
35 AVYSCTTDGFIMIRGVSEDDYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSK
40 LTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:351

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVWVCGGGGSQVQLVQSGGGLVQPGGSLRLSAAFGF
NFSSYVMHWVRQAPGQGLEYLSAISSDGETTYHANSVKGRFTSSRDNSKNTFLQMGLSLRTEDVA

VYYCARDRYETSGSNAFDVWGQGTMMVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
5 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:352

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVQLVQSGAEVRKPGSSVTISCKPVGGT
10 FTNFAIHWWRQAPGQGLEWVGGRVPVVGIIYKYGKFKHDLRLYEDDPMKTVFLELRSLTSDDTGVY
YCTRWRGCGMCPYDTSSYYNDASDVWGPSTKIVVSAASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
15 EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:353

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVQLVESGGGLVKAGGSLILSCGVSNFRI
20 SAHTMNWRRVPGGLEWVASISTSSYRDYADAVKGRFTVSRDDLEDFVYLQMHKMRVEDTAIY
YCARKGSDRLSDNDPFDWGPSTVTVSPASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
CDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
25 PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:354

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
NFPLIINKLPEDSDTYICEVEDQKEEVQLVVVCGGGGSQMLQESGPGLVKPGETLSLTCSVSGAS
30 ISSSYWSWLRETPGKLEWIGYTHHSGDTNYAPSLKSRVHLGLHPSKNQVLSLTSVTAADTAVYY
CARTLHGRRIGVWAFNEFFTYFYWEVWGKTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGP
35 REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:355

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGKPSKLNDRVDSRRSLWDQG
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40 ISSSYWSWLRETPGKLEWIGYTHHSGDTNYAPSLKSRVHLGLHPSKNQVLSLTSVTAADTAVYY
CARTLHGRRIGVWAFNEYTYFYWPTWGKTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGP

REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL
LTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:356

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
5 NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSGMQLQESGPGLVKPGETLSLTCSVSGAS
ISSSYWSWLRETPGKLEWIGYTHHSGDTNYAPSLKSRVTIGLDPSKNQVSLSLTSVTAADTAVYYC
ARTLHGRRYIGVVAFNEYTYFYWPTWGKGTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
10 VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:357

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
15 NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSGVQLLESGLVLPSETLTLTCSVFNSR
VSGYYYSWIRQPPGRGLEWIASTHFSRLRPSRNPSSLRVTTSIDTERYQVFLNMRSVTAADTAVYFC
ARGDASGWRADYFPHWGQGTLVWVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
20 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVLHEALHSHYTQKSLSLSPGK

SEQ ID NO:358

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQG
25 NFPLIKNLKPEDSDTYICEVEDQKEEVQLVWVCGGGGSGSVLTQPPSASGSPGQSVTISCTGTSSDI
GASDYVSWYQQYPGEAPKVIIDVTKRPSGVPDRFSGSKSGTTASLTVSGLQAEDEADYYCSDA
GRHTLLFGGGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:359

QVQLLESGLVLRPSETLTLTCSVFNSRVSGYYYSWIRQPPGRGLEWIASTHFSRLRPSRNPSSLR
30 VTTSIDTERYQVFLNMRSVTAADTAVYFCARGDASGWRADYFPHWGQGTLVWVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL
GTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
35 NALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGKGGGSGSKV
YGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLT KGPSKLNDRVDSRRSLWDQGNFPLI
KNLKPEDSDTYICEVEDQKEEVQLWVC

SEQ ID NO:360

QSVLTQPPSASGSPGQSVTISCTGTSSDIGASDYVSWYQQYPGEAPKVIIDVTKRPSGVPDRFSG
40 SKSGTTASLTVSGLQAEDEADYYCSDAGRHTLLFGGGTKVTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQ

VTHEGSTVEKTVAPTECSGGGGSKKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSF
LTGGPSKLNDRVDSRRSLWDQGNFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVC

SEQ ID NO:361

CTRPNNNTRKSIHIGPGRAFYTTEIIGDIRQAHC

5 SEQ ID NO:362

KKVYVGKCGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTGGPSKLNDRVDSRRSLWDQG
NFPLIKNLKPEDSDTYICEVEDQKEEVQLVVVCGGGGSQVQLVQSGAQMKNPGASVKVSCAPSGY
TFTDFYIHWLRQAPGQGLQWMGWMNPQTGRTNTARNFQGRVTMTRDTSIGTAYMELRSLTSDDT
AIYYCTTGGWISLYYDSSYPNFDHWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
10 DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

15 SEQ ID NO: 363

MKVMGTCKNYQHLWRWGMILLGMLMMSSAAEQLWVTVYYGVPVWREANTTLFCASDAKAYDTEV
HNWVWATHACVPTDPNPQEVVMGNVTEDFNMWKNNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLH
CTNVTISSTNGSTANVTMREEMKNCSFNNTTVIRDKIKEYALFYKLDIVPIEGKNTNTSYRLINCNTS
VITQACPKVSFEPIPIHYCAPAGFAILKCNKTFNGKGPCRVSTVQCTHGIKPVVSTQLLLNGSLAE
20 EDIIRSENFTNNGKNIIVQLKEPVKINCTRPGNNTRRSINIGPGRAFYATGAIIGDIRKAHCNISTEQWN
NTLTQIVDKLREQFGNKTIIFNQSSGGDPEVVMHTFNCGGEFFYCNSTQLFNSTWFNNGTSTWNST
ADNITLPCRIKQVINMWQEVGKAMYAPPIRGQIDCSSNITGLILTRDGGSNSSQNETFRPGGGMKMD
NWRSELYKYKVKIEPLGIAPTRAKRRVVQREKRAVTLGAVFLGFLGAAGSTMGAASLTTLTVQARLL
LSGIVQQQSNLLRAIEAQHMLQLTVWGKQLQARVLAIERYLKQQLLGIWGCSGKLICTTTVPWN
25 TSWSNKSQYDIWNNMTWMQWEREIDNYTGFIYTLIEESQNQQEKNELLELDKWASLWNWFNITN
WLWYIKLFIMIIGGLVGLRIVCAVLSIVNRVRQGYSPLSFQTRLPNPRGPDRPEETEGEGGERDRDR
SARLVNGFLAIWDDLRLSLCLFSYHRLRDLILLIVARVVEILGRRGWELKYWWNLLKYWSQELKNSAV
SLLNVTIAVAEGTDRVIEIVQRAVRAILHIPTRIRQGERALL

SEQ ID NO: 364

30 AEQLWVIVYYGVPVWREANTTLFCASDAKAYDTEVHNWVWATHACVPTDPNPQEVVMGNVTEDFN
MWKNNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLHCTNVTISSTNGSTANVTMREEMKNCSFNNT
TVIRDKIKEYALFYKLDIVPIEGKNTNTSYRLINCNTSVITQACPKVSFEPIPIHYCAPAGFAILKCNK
TFNGKGPCRVSTVQCTHGIKPVVSTQLLLNGSLAEEDIIRSENFTNNGKNIIVQLKEPVKINCTRP
NNTRRSINIGPGRAFYATGAIIGDIRKAHCNISTEQWNNNTLTQIVDKLREQFGNKTIIFNQSSGGDPEV
35 VMHTFNCGGEFFYCNSTQLFNSTWFNNGTSTWNSTADNITLPCRIKQVINMWQEVGKAMYAPPIR
GQIDCSSNITGLILTRDGGSNSSQNETFRPGGGMKMDNWRSELYKYKVKIEPLGIAPTRAKRRVVQ
REKR

SEQ ID NO: 365

40 SDISVAPGETVRITCGGESIGSRAVQWYQHRPGQAPRLIYNNQDRPPGIPERFSGSPDIDFGTTATLTISNVEAG
DEATYYCHIWDSSRRPTNWELGPGTTLTVL

SEQ ID NO: 366

SDISVAPGETVRITCGGESIGSRAVQWYQHRPGQAPRLIYNNQDRPPGIPERFSGSPDIDFGTTATLTISNVEAG
DEATYYCHIWDSRRPTNWLGP GTTLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD
SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

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CLAIMS

1. A bispecific anti-HIV gp120-binding protein comprising (i) an anti-V3 bNAb comprising two heavy chains and two light chains; and (ii) at least one CD4 domain, wherein the CD4 domain is attached directly or by a linker to the N-terminus or C-terminus of one of the anti-V3 bNAb heavy chains or light chains.
2. The bispecific protein as claimed in claim 1, wherein the CD4 domain is attached via a linker to the N-terminus or C-terminus of one or both anti-V3 bNAb heavy chains.
3. The bispecific protein as claimed in claim 1, wherein the CD4 domain is attached via a linker to the N-terminus or C-terminus of one or both anti-V3 bNAb light chains.
4. The bispecific protein as claimed in claim 1, further comprising at least four CD4 domains.
5. The bispecific protein as claimed in claim 4, wherein the C-terminus of the first and second CD4 domains are attached by a linker to the N-terminus of each of the anti-V3 heavy chains, and wherein the C-terminus of the third and fourth CD4 domains are attached by a linker to the N-terminus of each of the anti-V3 light chains.
6. The bispecific protein as claimed in any one of claims 1 to 5, wherein the linker is selected from the group consisting of SEQ ID NOs: 90 to 95.
7. The bispecific protein as claimed in claim 6, wherein the linker is SEQ ID NO:90.
8. The bispecific protein as claimed in any one of claims 1 to 5, wherein the CD4 domain is selected from the group consisting of SEQ ID NO:1-21.
9. The bispecific protein as claimed in claim 8, wherein the CD4 domain is SEQ ID NO:11.
10. The bispecific protein as claimed in any one of claims 1 to 9, wherein the anti-V3 bNAb is selected from the group consisting of bNAb1, bNAb1*, bNAb2, bNAb3, bNAb4, bNAb5 and bNAb6 as set forth in Table 2.
11. The bispecific protein as claimed in claim 10, wherein the anti-V3 bNAb is bNAb1.
12. The bispecific protein as claimed in any one of claims 1 to 11, wherein the anti-V3 bNAb Fc comprises LS.
13. An anti-HIV gp120-binding protein having two identical heavy chains and two identical light chains, comprising or consisting of:
 - a heavy chain that is at least 95% identical to SEQ ID NO:121 and
 - a light chain that is at least 95% identical to SEQ ID NO:63.
14. An anti-HIV gp120-binding protein consisting of two heavy chains of SEQ ID NO:121 and two light chains of SEQ ID NO:63.

15. A pharmaceutical composition comprising the anti-HIV gp120-binding protein as defined in any one of the preceding claims and a pharmaceutically acceptable excipient.
16. A method of treating or preventing an HIV infection in a human comprising administering to the human an anti-HIV gp120-binding protein according to any one of
5 claims 1 to 14, or a pharmaceutical composition according to claim 15, whereby viral load in the human is decreased.
17. An anti-HIV gp120-binding protein according to any one of claims 1 to 14, or a pharmaceutical composition according to claim 15, for use in treating or preventing an HIV infection in a human.
- 10 18. Use of an anti-HIV gp120-binding protein according to any one of claims 1 to 14, or a pharmaceutical composition according to claim 15, in the manufacture of a medicament for treating or preventing an HIV infection in a human.
19. A kit comprising in separate containers: an anti-HIV gp120-binding protein according to any one of claims 1 to 14 and an anti-viral drug that inhibits cellular entry, replication, or
15 transcription of HIV in a human.
20. The kit as claimed in claim 19, wherein the antiviral drug is selected from the group consisting of: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Entry Inhibitors, Integrase Strand Transfer Inhibitors (INSTI), Maturation Inhibitors (MIs), Capsid
20 Inhibitors (CIs) and Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTIs).
21. The kit as claimed in claim 20, wherein the antiviral drug is an INSTI.
22. The kit as claimed in claim 21, wherein the INSTI is dolutegravir or cabotegravir.
23. A nucleic acid sequence that encodes an anti-HIV gp120-binding protein according to any one of claims 1 to 14.
- 25 24. An expression vector that comprises the nucleic acid sequence of claim 23.
25. A host cell that comprises the nucleic acid sequence of claim 23 or the expression vector of claim 24.
26. A host cell that comprises two expression vectors:
a first expression vector comprising a nucleic acid sequence encoding a heavy chain
30 of SEQ ID NO:121; and
a second expression vector comprising a nucleic acid sequence encoding a light chain of SEQ ID NO:63.

27. A method of producing an anti-HIV gp120-binding protein, comprising culturing the host cell as defined in claim 25 or 26 under conditions suitable for expression of said nucleic acid sequence or vector, whereby an anti-HIV gp120-binding protein is produced.
28. A soluble CD4 domain having a T_m above 70 °C.
- 5 29. A soluble CD4 domain comprising one or more stabilizing mutations selected from the group consisting of K8C, K8I, K8V, T11C, E13C, K21C, Q25E, H27C, H27D, G38C, N52W, R58N, R58T, R58V, L61M, G65C, I70C, K72C, E87G, E91H, E91Q, and G99C.
30. The soluble CD4 domain of claim 28 or claim 29 having a T_m of between 70 °C and 95 °C.
- 10 31. The soluble CD4 domain of claim 28 having a T_m of about 90 °C.
32. The soluble CD4 domain of any one of claims 28 to 31, comprising K8C and G99C.
33. The soluble CD4 domain of any one of claims 28 to 31, comprising K8I.
34. The soluble CD4 domain of any one of claims 28 to 31, comprising K8V.
35. The soluble CD4 domain of any one of claims 28 to 34, comprising T11C and K72C
- 15 36. The soluble CD4 domain of any one of claims 28 to 35, comprising any one of SEQ ID NOs:5-21.
37. The soluble CD4 domain of claim 36, comprising SEQ ID NO:11.
38. The soluble CD4 domain of any one of claims 28 to 37, wherein the CD4 domain is fused directly or via a linker to a human Fc domain.
- 20 39. The soluble CD4 domain of claim 38, wherein the Fc domain comprises LS.
40. The soluble CD4 domain of claim 38 or claim 39, wherein the linker is selected from the group consisting of SEQ ID NOs:90-95.
41. A bispecific anti-HIV gp120-binding protein comprising (i) an anti-V3 bNAb or an antigen-binding Fab' or F(ab')₂ fragment thereof; and (ii) at least one CD4 domain,
- 25 wherein the C-terminus of the CD4 domain is attached directly or by a linker to the N-terminus of the anti-V3 heavy chain variable region or light chain variable region.
42. The bispecific protein as claimed in claim 41, wherein the anti-V3 bNAB is an antigen-binding Fab' fragment, and wherein the CD4 domain is attached via a linker to the heavy chain variable region of the anti-V3 bNAB Fab' fragment.
- 30 43. The bispecific protein as claimed in claim 41, wherein the anti-V3 bNAB is an antigen-binding Fab' fragment, and wherein the CD4 domain is attached via a linker to the light chain variable region of the anti-V3 bNAB Fab' fragment.
44. The bispecific protein as claimed in claim 41, further comprising at least two CD4 domains, wherein the anti-V3 bNAB is an antigen-binding Fab' fragment, wherein the

first CD4 domain is attached via a linker to the heavy chain variable region of the anti-V3 bNAb Fab' fragment and the second CD4 domain is attached via a linker to the light chain variable region of anti-V3 bNAb Fab' fragment.

- 5 45. The bispecific protein as claimed in claim 41, further comprising at least two CD4 domains, wherein the anti-V3 bNAB is an antigen-binding F(ab')₂ fragment, and wherein each of the CD4 domains is attached via a linker to each of the heavy chain variable regions of the anti-V3 bNAB F(ab')₂ fragment.
- 10 46. The bispecific protein as claimed in claim 41, further comprising at least two CD4 domains, wherein the anti-V3 bNAB is an antigen-binding F(ab')₂ fragment, and wherein each of the CD4 domains is attached via a linker to each of the light chain variable regions of the anti-V3 bNAB F(ab')₂ fragment.
- 15 47. The bispecific protein as claimed in claim 41, further comprising at least four CD4 domains, wherein the anti-V3 bNAB is an antigen-binding F(ab')₂ fragment, and wherein each of the CD4 domains is attached via a linker to each of the heavy chain variable regions and each of the light chain variable regions of the anti-V3 bNAB F(ab')₂ fragment.
- 20 48. The bispecific protein as claimed in any one of claims 41 to 48, wherein the C-terminus of the CD4 domains are each attached via a linker to the N-terminus of the heavy chain variable region or light chain variable region of the anti-V3 bNAB Fab or F(ab')₂ fragment.
- 25 49. The bispecific protein as claimed in any one of claims 41 to 28, wherein the linker is selected from the group consisting of SEQ ID NOs: 90 to 95.
50. The bispecific protein as claimed in claim 49, wherein the linker is SEQ ID NO:90.
51. The bispecific protein as claimed in any one of claims 41 to 50, wherein the CD4 domain is selected from the group consisting of SEQ ID NO:1-21.
52. The bispecific protein as claimed in claim 51, wherein the CD4 domain is SEQ ID NO:11.
53. The bispecific protein as claimed in any one of claims 41 to 48, wherein the anti-V3 bNAB or antigen-binding fragment thereof is selected from the group consisting of bNAb1, bNAb1*, bNAb2, bNAb3, bNAb4, bNAb5 and bNAb6 as set forth in Table 2.
- 30 54. The bispecific protein as claimed in claim 53, wherein the anti-V3 bNAB is bNAb1.