IMMUNOBINDERS DIRECTED AGAINST TNF

Cross-reference to Related Applications

This application claims priority to United States Provisional Application Serial No. 61/550,587, filed October 24, 2011, which is incorporated herein by reference in its entirety.

Background of the Invention

Field of the Invention

TNF-α binding proteins and their uses in the prevention and/or treatment of acute and chronic immunological diseases are provided.

Background of the Invention

There is a need in the art for improved binding proteins capable of binding TNF-α (also referred to as tumor necrosis factor, tumor necrosis factor-alpha, tumor necrosis factor-α, TNF, and cachectin). Provided are a novel family of binding proteins, CDR grafted binding proteins, humanized binding proteins, and fragments thereof, capable of binding TNF-α with high affinity and neutralizing TNF-α.

Brief Summary of the Invention

TNF-α binding proteins, or antigen-binding portions thereof, that bind TNF-α are provided. In an embodiment, the antigen binding domain comprises the VH region chosen from any one of SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077, or one, two, or three CDRs therefrom. In another embodiment, the antigen binding domain comprises the VL region chosen from any one of SEQ ID NOs: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078, or one, two, or three CDRs therefrom. In a particular embodiment, the antigen binding domain comprises a VH region and a VL region, for example, wherein the VH region comprises SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077, or one, two, or three CDRs therefrom, and the VL region comprises SEQ ID NOs: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078, or one, two, or three CDRs therefrom.

In an embodiment, the binding protein binds TNF-α. In another embodiment, the binding protein modulates a biological function of TNF-α. In another embodiment, the binding protein neutralizes TNF-α. In yet another embodiment, the binding protein diminishes the ability of TNF-α to bind to its receptor, for example, the binding protein diminishes the ability of pro-

human TNF-α, mature-human TNF-α, or truncated-human TNF-α to bind to its receptor. In yet another embodiment, the binding protein reduces one or more TNF-α biological activities selected from: TNF-dependent cytokine production; TNF-dependent cell killing; TNF-dependent inflammation; TNF-dependent bone erosion; and TNF-dependent cartilage damage.

In an embodiment , the binding protein has an on rate constant (K_{on}) selected from: at least about $10^2M^{-1}s^{-1}$; at least about $10^3M^{-1}s^{-1}$; at least about $10^4M^{-1}s^{-1}$; at least about $10^5M^{-1}s^{-1}$; and at least about $10^6M^{-1}s^{-1}$; as measured by surface plasmon resonance. In another embodiment, the binding protein has an off rate constant (K_{off}) selected from: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance. In yet another embodiment, the binding protein has a dissociation constant (K_D) selected from: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

In another aspect, a method for treating a mammal is provided comprising administering to the mammal an effective amount of the pharmaceutical composition disclosed herein. In another embodiment, a method for reducing human TNF-α activity is provided, the method comprising: contacting human TNF-α with the binding protein disclosed herein such that human TNF-α activity is reduced. In another embodiment, provided is a method for reducing human TNF-α activity in a human subject suffering from a disorder in which TNF-α activity is detrimental, the method comprising administering to the human subject the binding protein disclosed herein such that human TNF-α activity in the human subject is reduced. In another embodiment, provided is a method for treating a subject for a disease or a disorder in which TNF-α activity is detrimental, the method comprising administering to the subject the binding protein disclosed herein such that treatment is achieved.

In one embodiment, the method treats diseases involving immune and inflammatory elements, such as autoimmune diseases, particularly those assocated with inflammation, including Crohn's disease, psoriasis (including plaque psoriasis), arthritis (including rheumatoid arthritis, psoratic arthritis, osteoarthritis, or juvenile idiopathic arthritis), multiple sclerosis, and ankylosing spondylitis. Therefore, the binding proteins herein may be used to treat these disorders.

Detailed Description of the Invention

Provided are TNF-α binding proteins, or antigen-binding portions thereof, that bind TNF-α, pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such binding proteins and fragments. Also provided are methods of using the binding proteins disclosed herein to detect human TNF-α, to inhibit human TNF-α either in vitro or in vivo, and to regulate gene expression or TNF-α related functions.

Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. In this application, the use of "or" means "and/or", unless stated otherwise. Furthermore, the use of the term "including", as well as other forms of the term, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, pathology, oncology, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook et al. Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The term "human TNF-α" (abbreviated herein as hTNF-α) includes a trimeric cytokine protein. The term includes a homotrimeric protein comprising three 17.5 kD TNF-α proteins. The homotrimeric protein is referred to as a "TNF-α protein". The term human "TNF-α" is intended to include recombinant human TNF-α (rhTNF-α), which can be prepared by standard recombinant expression methods. The sequence of human TNF-α is shown in Table 1.

Table 1: Sequence of Human TNF-α

Protein	Sequence Identifier	Sequence
		12345678901234567890123456789012
Human TNF-α	SEQ ID NO.:1	VRSSSRTPSDKPVAHVVANPQAEGQLQWLNDR ANALLANGVELRDNQLVVPSEGLYLIYSQVLF KGQGCPSTHVLLTHTISRIAVSYQTKVNLLSA IKSPCQRETPEGAEAKPWYEPIYLGGVFQLEK GDRLSAEINRPDYLDFAESGQVYFGIIAL

The term "antibody", broadly refers to any immunoglobulin (Ig) molecule, or antigen binding portion thereof, comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivation thereof, which retains the essential epitope binding features of an Ig molecule. Such mutant, variant, or derivative antibody formats are known in the art.

In a full-length antibody, each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG 1, IgG2, IgG 3, IgG4, IgA1 and IgA2) or subclass.

The term "antigen-binding portion" or "antigen-binding region" of a binding protein (or simply "binding protein portion"), refers to one or more fragments of a binding protein that retain the ability to specifically bind to an antigen (e.g., hTNF-α). The antigen-binding function of a binding protein can be performed by fragments of a full-length binding protein. Such binding protein embodiments may also have bispecific, dual specific, or multi-specific formats; specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "antigen-binding portion" of a binding protein include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al. (1989) Nature 341:544-546, Winter et al., PCT publication WO 90/05144 A1), which comprises a single variable domain; and (vi) an isolated complementarity determining region

(CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see, e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain binding proteins are also intended to be encompassed within the term "antigen-binding portion" of a binding protein. Other forms of single chain binding proteins, such as diabodies are also encompassed. Diabodies are bivalent, bispecific binding proteins in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see, e.g., Holliger, et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, et al. (1994) Structure 2:1121-1123).

The term "binding protein" refers to a polypeptide comprising one or more antigen-binding portions disclosed herein optionally linked to a linker polypeptide or a constant domain. Linker polypeptides comprise two or more amino acid residues joined by peptide bonds and are used to link one or more antigen binding portions. Such linker polypeptides are well known in the art (see e.g., Holliger, et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, et al. (1994) Structure 2:1121-1123). A constant domain refers to a heavy or light chain constant domain. Human IgG heavy chain and light chain constant domain amino acid sequences are known in the art and represented in Table 2.

Table 2: Sequence of Human IgG Heavy Chain Constant Domain and Light Chain Constant Domain

Protein	Sequence Identifier	Sequence
		123456789012345678901234567890 12
Ig gamma-1 constant region	SEQ ID NO.:2	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK

Protein	Sequence Identifier	Sequence
		123456789012345678901234567890 12
Ig gamma-1 constant region mutant	SEQ ID NO.:3	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Ig Kappa constant region	SEQ ID NO.:4	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
Ig Lambda constant region	SEQ ID NO.:5	QPKAAPSVTLFPPSSEELQANKATLVCLISDF YPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

A binding protein, or antigen-binding portion thereof, may be part of a larger immunoadhesion molecule, formed by covalent or noncovalent association of the binding protein or binding protein portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, et al. (1995) *Hum. Antibod. Hybridomas* 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, et al. (1994) *Mol. Immunol.* 31:1047-1058). Antibody portions, such as Fab and $F(ab')_2$ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, binding proteins, binding protein portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques, as described herein.

An "isolated binding protein" refers to a binding protein, or antigen-binding portion thereof, that is substantially free of other binding proteins having different antigenic specificities (e.g., an isolated binding protein that specifically binds hTNF-α is substantially free of binding proteins that specifically bind antigens other than hTNF-α). An isolated binding protein that specifically binds hTNF-α may, however, have cross-reactivity to other antigens, such as TNF-α molecules from other species. Moreover, an isolated binding protein may be substantially free of other cellular material and/or chemicals.

The term "human binding protein" includes binding proteins, or antigen-binding portion thereof, that having variable and constant regions derived from human germline immunoglobulin sequences. The human binding proteins disclosed herein may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for

example in the CDRs and in particular CDR3. However, the term "human binding protein", is not intended to include binding proteins in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The terms "Kabat numbering", "Kabat definitions" and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (i.e., hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) *Ann. NY Acad. Sci.* 190:382-391 and Kabat, et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). See also, Martin, "Protein Sequence and Structure Analysis of Antibody Variable Domains," *In* Kontermann and Dübel, eds., Antibody Engineering (Springer-Verlag, Berlin, 2001), Chapter 31, especially pages 432-433. For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 106 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

The term "CDR" refers to the complementarity determining region within antibody variable sequences. There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Chothia and coworkers (Chothia and Lesk (1987) *J. Mol. Biol.* 196:901-917) and Chothia et al. (1989) *Nature* 342:877-883) found that certain sub-portions within Kabat CDRs adopt nearly identical peptide backbone conformations, despite having great diversity at the level of amino acid sequence. These sub-portions were designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (1995) *FASEB J.* 9:133-139 and MacCallum (1996) *J. Mol. Biol.* 262(5):732-745. Still other

CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems, although particular embodiments use Kabat or Chothia defined CDRs.

Human heavy chain and light chain acceptor sequences are known in the art. In one embodiment of the disclosure the human heavy chain and light chain acceptor sequences are selected from the sequences listed from V-base (hvbase.mrc-cpe.cam.ac.uk/) or from IMGT®, the international ImMunoGeneTics information system® (himgt.cines.fr/textes/IMGTrepertoire/LocusGenes/). In another embodiment of the disclosure the human heavy chain and light chain acceptor sequences are selected from the sequences described in Table 3 and Table 4, respectively.

Table 3: Heavy Chain Acceptor Sequences

SEQ ID No.	Protein region	Sequence
		123456789012345678901234567890 12
SEQ ID NO:6	VH4-59 FR1	QVQLQESGPGLVKPSETLSLTCTVSGGSISS
SEQ ID NO:7	VH4-59 FR2	WIRQPPGKGLEWIG
SEQ ID NO:8	VH4-59 FR3	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
SEQ ID NO:9	VH3-53 FR1	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS
SEQ ID NO:10	VH3-53 FR2	WVRQAPGKGLEWVS
SEQ ID NO:11	VH3-53 FR3	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:12	JH1/JH4/JH5 FR4	WGQGTLVTVSS
SEQ ID NO:13	JH2 FR4	WGRGTLVTVSS
SEQ ID NO:14	JH6 FR4	WGQGTTVTVSS

Table 4: Light Chain Acceptor Sequences

SEQ ID No.	Protein region	Sequence
		123456789012345678901234567890 12
SEQ ID NO:15	1-39/O12 FR1	DIQMTQSPSSLSASVGDRVTITC
SEQ ID NO:16	1-39/O12 FR2	WYQQKPGKAPKLLIY
SEQ ID NO:17	1-39/O12 FR3	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
SEQ ID NO:18	3-15/L2 FR1	EIVMTQSPATLSVSPGERATLSC
SEQ ID NO:19	3-15/L2 FR2	WYQQKPGQAPRLLIY
SEQ ID NO:20	3-15/L2 FR3	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC
SEQ ID NO:21	JK2 FR4	FGQGTKLEIKR

The term "multivalent binding protein" is used in this specification to denote a binding protein comprising two or more antigen binding sites. The multivalent binding protein may be engineered to have the three or more antigen binding sites, and is generally not a naturally occurring antibody. The term "multispecific binding protein" refers to a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins or immunoglobulins (DVD-Ig) as used herein, are binding proteins that comprise two or more antigen binding sites and are tetravalent or multivalent binding proteins. Such DVD-

binding proteins may be monospecific, i.e., capable of binding one antigen or multispecific, i.e., capable of binding two or more antigens. DVD-binding proteins comprising two heavy chain DVD-Ig polypeptides and two light chain DVD-Ig polypeptides are referred to a DVD-Ig. Each half of a DVD-Ig comprises a heavy chain DVD-Ig polypeptide, and a light chain DVD-Ig polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. DVD binding proteins and methods of making DVD binding proteins are disclosed in U.S. Patent No. 7,612,181.

One aspect of the disclosure pertains to a DVD binding protein comprising binding proteins capable of binding TNF-α. In a particular embodiment, the DVD binding protein is capable of binding TNF-α and a second target.

The term "neutralizing" refers to neutralization of a biological activity of a cytokine when a binding protein specifically binds the cytokine. In a particular embodiment, binding of a neutralizing binding protein to hTNF-α results in inhibition of a biological activity of hTNF-α, e.g., the neutralizing binding protein binds hTNF-α and reduces a biologically activity of hTNF-α by at least about 20%, 40%, 60%, 80%, 85% or more. Inhibition of a biological activity of hTNF-α by a neutralizing binding protein can be assessed by measuring one or more indicators of hTNF-α biological activity well known in the art. For example neutralization of the cytoxicity of TNF-α on L929 cells.

In another embodiment, the terms "agonist" or "agonizing" refer to an increase of a biological activity of TNF-α when a binding protein specifically binds TNF-α, e.g., hTNF-α. In a particular embodiment, binding of an agonizing binding protein to TNF-α results in the increase of a biological activity of TNF-α. In a particular embodiment, the agonistic binding protein binds TNF-α and increases a biologically activity of TNF-α by at least about 20%, 40%, 60%, 80%, 85%, 90%, 95, 96%, 97%, 98%, 99%, and 100%. An inhibition of a biological activity of TNF-α by an agonistic binding protein can be assessed by measuring one or more indicators of TNF-α biological activity well known in the art.

The term "activity" includes activities such as the binding specificity/affinity of a binding protein for an antigen, for example, a hTNF-α binding protein that binds to a TNF-α antigen and/or the neutralizing potency (or agonizing potency) of a binding protein, for example, a hTNF-α binding protein whose binding to hTNF-α inhibits the biological activity of hTNF-α, e.g., neutralization of the cytoxicity of TNF-α on L929 cells.

The term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ).

The term "K_{on}" refers to the on rate constant for association of a binding protein (e.g., an antibody) to the antigen to form, e.g., the antibody/antigen complex as is known in the art. The "K_{on}" also is known by the terms "association rate constant", or "ka", as used interchangeably herein. This value indicating the binding rate of an antibody to its target antigen or the rate of complex formation between an antibody and antigen also is shown by the equation below:

Antibody ("Ab") + Antigen ("Ag")→Ab-Ag

The term "K_{off}" refers to the off rate constant for dissociation, or "dissociation rate constant", of a binding protein (e.g., an antibody), from the, e.g., antibody/antigen complex as is known in the art. This value indicates the dissociation rate of an antibody from its target antigen or separation of Ab-Ag complex over time into free antibody and antigen as shown by the equation below:

Ab + Ag ←Ab-Ag

The term "K_D" refers to the "equilibrium dissociation constant" and refers to the value obtained in a titration measurement at equilibrium, or by dividing the dissociation rate constant (K_{off}) by the association rate constant (K_{on}). The association rate constant, the dissociation rate constant and the equilibrium dissociation constant are used to represent the binding affinity of an antibody to an antigen. Methods for determining association and dissociation rate constants are well known in the art. Using fluorescence–based techniques offers high sensitivity and the ability to examine samples in physiological buffers at equilibrium. Other experimental approaches and instruments such as a BIAcore® (biomolecular interaction analysis) assay can be used (e.g., instrument available from BIAcore International AB, a GE Healthcare company, Uppsala, Sweden). Additionally, a KinExA® (Kinetic Exclusion Assay) assay, available from Sapidyne Instruments (Boise, Idaho) can also be used.

I. Binding proteins That Bind Human TNF-α

One aspect of the present disclosure provides isolated fully-human anti-human TNF binding proteins, such as monoclonal antibodies, or antigen-binding portions thereof, that bind to TNF-α with high affinity, a slow off rate and high neutralizing capacity. A second aspect of the disclosure provides affinity-matured fully-human anti-TNF binding proteins, such as monoclonal antibodies, or antigen-binding portions thereof, that bind to TNF-α with high affinity, a slow off rate and high neutralizing capacity.

A. Method of Making TNF-α Binding Proteins

The binding proteins disclosed herein may be made by any of a number of techniques known in the art.

1. Anti-TNF-α Monoclonal Antibodies Using Transgenic Animals

In another embodiment of the disclosure, binding proteins are produced by immunizing a non-human animal comprising some, or all, of the human immunoglobulin locus with a TNF-α antigen. In a particular embodiment, the non-human animal is a XENOMOUSE transgenic mouse, an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. See, e.g., Green et al. (1994) *Nature Genet.* 7:13-21 and United States Patents 5,916,771; 5,939,598; 5,985,615; 5,998,209; 6,075,181; 6,091,001; 6,114,598 and 6,130,364. See also PCT Publications WO 91/10741, published July 25,1991; WO 94/02602, published February 3, 1994; WO 96/34096 and WO 96/33735, both published October 31, 1996; WO 98/16654, published April 23, 1998; WO 98/24893, published June 11, 1998; WO 98/50433, published November 12, 1998; WO 99/45031, published September 10, 1999; WO 99/53049, published October 21, 1999; WO 00/09560, published February 24, 2000; and WO 00/37504, published June 29, 2000. The XENOMOUSE transgenic mouse produces an adult-like human repertoire of fully human antibodies, and generates antigen-specific human Mabs. The XENOMOUSE transgenic mouse contains approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and x light chain loci. See, Mendez et al. (1997) *Nature Genet.* 15:146-156; Green and Jakobovits (1998) *J. Exp. Med.* 188:483-495.

2. Anti-TNF-α Monoclonal Antibodies Using Recombinant Antibody Libraries

In vitro methods also can be used to make the binding protein disclosed herein, wherein an antibody library is screened to identify an antibody having the desired binding specificity. Methods for such screening of recombinant antibody libraries are well known in the art and include methods described in, for example, U.S. Patent No. 5,223,409; PCT Publications WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; and WO 97/29131; Fuchs et al. (1991) *Bio/Technology* 9:1369-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; McCafferty et al. (1990) *Nature* 348:552-554; Griffiths et al. (1993) *EMBO J.* 12:725-734; Hawkins et al. (1992) *J. Mol. Biol.* 226:889-896; Clackson et al. (1991) *Nature* 352:624-628; Gram et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrard et al. (1991) *Bio/Technology* 9:1373-1377; Hoogenboom et al. (1991) *Nucl. Acid Res.* 19:4133-4137; and Barbas et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and U.S. Patent Publication No. 2003.0186374.

The recombinant antibody library may be from a subject immunized with TNF-α, or a portion of TNF-α. Alternatively, the recombinant antibody library may be from a naïve subject,

i.e., one who has not been immunized with TNF-α, such as a human antibody library from a human subject who has not been immunized with human TNF-α. Antibodies disclosed herein are selected by screening the recombinant antibody library with the peptide comprising human TNF-α to thereby select those antibodies that recognize TNF-α. Methods for conducting such screening and selection are well known in the art, such as described in the references in the preceding paragraph. To select antibodies disclosed herein having particular binding affinities for hTNF-α, such as those that dissociate from human TNF-α with a particular k_{off} rate constant, the art-known method of surface plasmon resonance can be used to select antibodies having the desired k_{off} rate constant. To select antibodies disclosed herein having a particular neutralizing activity for hTNF-α, such as those with a particular an IC_{50}, standard methods known in the art for assessing the inhibition of hTNF-α activity may be used.

In one aspect, provided is an isolated binding protein, or an antigen-binding portion thereof, that binds TNF-α, e.g., human TNF-α. In a particular embodiment, the binding protein is a neutralizing binding protein. In various embodiments, the binding protein is a recombinant binding protein or a monoclonal antibody.

For example, the binding proteins disclosed herein can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular, such phage can be utilized to display antigen-binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the binding proteins disclosed herein can be found in the art.

As described in the above references, after phage selection, the binding protein coding regions from the phage can be isolated and used to generate whole binding proteins including human binding protein or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in PCT Publication WO 92/22324; Mullinax et al. (1992) *BioTechniques* 12(6):864-869; and Sawai et al. (1995) *Am. J. Reprod. Immunol.* 34:26-34; and Better et al. (1998) *Science* 240:1041-1043. Examples of techniques which can be used to produce single-chain Fvs and

antibodies include those described in U.S. Patent Nos. 4,946,778 and 5,258,498; Huston et al. (1991) *Methods Enzymol.* 203:46-88; Shu et al. (1993) *Proc. Natl. Acad Sci. USA* 90:7995-7999; and Skerra et al. (1998) *Science* 240:1038-1041.

Alternative to screening of recombinant antibody libraries by phage display, other methodologies known in the art for screening large combinatorial libraries can be applied to the identification of dual specificity binding protein disclosed herein. One type of alternative expression system is one in which the recombinant antibody library is expressed as RNA-protein fusions, as described in PCT Publication No. WO 98/31700 and in Roberts and Szostak (1997) *Proc. Natl. Acad. Sci. USA* 94:12297-12302. In this system, a covalent fusion is created between an mRNA and the peptide or protein that it encodes by *in vitro* translation of synthetic mRNAs that carry puromycin, a peptidyl acceptor antibiotic, at their 3' end. Thus, a specific mRNA can be enriched from a complex mixture of mRNAs (e.g., a combinatorial library) based on the properties of the encoded peptide or protein, e.g., antibody, or portion thereof, such as binding of the antibody, or portion thereof, to the dual specificity antigen. Nucleic acid sequences encoding antibodies, or portions thereof, recovered from screening of such libraries can be expressed by recombinant means as described above (e.g., in mammalian host cells) and, moreover, can be subjected to further affinity maturation by either additional rounds of screening of mRNA-peptide fusions in which mutations have been introduced into the originally selected sequence(s), or by other methods for affinity maturation in vitro of recombinant antibodies, as described above.

In another approach the binding proteins disclosed herein can also be generated using yeast display methods known in the art. In yeast display methods, genetic methods are used to tether antibody domains to the yeast cell wall and display them on the surface of yeast. In particular, such yeast can be utilized to display antigen-binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Examples of yeast display methods that can be used to make the binding proteins disclosed herein include those disclosed Wittrup et al. U.S. Patent No. 6,699,658 and Frenken et al., U.S. Patent No. 6,114,147.

B. Production of Recombinant TNF-α Binding Proteins

Binding proteins disclosed herein may be produced by any of a number of techniques known in the art. For example, expression from host cells, wherein expression vector(s) encoding the heavy and light chains is (are) transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, e.g., electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is possible to express the binding proteins disclosed herein

in either prokaryotic or eukaryotic host cells, expression of binding protein in eukaryotic cells is contemplated, for example, in mammalian host cells, because such eukaryotic cells (and in particular mammalian cells) are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active binding protein.

Mammalian host cells for expressing the recombinant binding proteins disclosed herein include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, e.g., as described in Kaufman and Sharp (1982) *J. Mol. Biol.* 159:601-621), NS0 myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding binding protein genes are introduced into mammalian host cells, the binding proteins are produced by culturing the host cells for a period of time sufficient to allow for expression of the binding protein in the host cells or, in particular, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Host cells can also be used to produce functional binding protein fragments, such as Fab fragments or scFv molecules. It will be understood that variations on the above procedure are within the scope of the present disclosure. For example, it may be desirable to transfect a host cell with DNA encoding functional fragments of either the light chain and/or the heavy chain of a binding protein disclosed herein. Recombinant DNA technology may also be used to remove some, or all, of the DNA encoding either or both of the light and heavy chains that is not necessary for binding to the antigens of interest. The molecules expressed from such truncated DNA molecules are also encompassed by the binding proteins disclosed herein. In addition, bifunctional binding proteins may be produced in which one heavy and one light chain are a binding protein disclosed herein and the other heavy and light chain are specific for an antigen other than the antigens of interest by crosslinking a binding protein disclosed herein to a second binding protein by standard chemical crosslinking methods.

In an exemplary system for recombinant expression of a binding protein, or antigen-binding portion thereof, disclosed herein, a recombinant expression vector encoding both the heavy chain and the light chain is introduced into dhfr$^-$ CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the heavy and light chain genes are each operatively linked to CMV enhancer/AdMLP promoter regulatory elements to drive high levels of transcription of the genes. The recombinant expression vector also carries a DHFR gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are cultured to allow for expression of the heavy and light chains and intact binding protein is recovered from the culture medium. Standard molecular biology techniques are used to prepare the recombinant

expression vector, transfect the host cells, select for transformants, culture the host cells and recover the binding protein from the culture medium. Still further a method of synthesizing a recombinant binding protein disclosed herein is provided by culturing a host cell disclosed herein in a suitable culture medium until a recombinant binding protein disclosed herein is synthesized. The method can further comprise isolating the recombinant binding protein from the culture medium.

II. hTNF-α Binding Proteins

A. Individual Clone Sequences

Table 5 provides the VH and VL sequences of fully human anti-human TNF binding proteins, including CDRs from each VH and VL sequence.

Table 5. Individual Fully Human Anti-TNF-α VH Sequences

Protein region			Sequence
			123456789**0**123456789**0**1234567890
AE11-1 VH		SEQ ID NO.:22	EVQLVQSGAEVKKPGASVKVSCKASGYTFT **SYDVN**WVRQATGQGLEWMG**WMNPNSGNTGY AQKFQG**RVTITADESTSTAYMELSSLRSED TAVYYCAI**FDSDYMDV**WGKGTLVTVSS
AE11-1 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:22	**SYDVN**
AE11-1 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:22	**WMNPNSGNTGYAQKFQG**
AE11-1 VH	**CDR-H3**	Residues 99-106 of SEQ ID NO.:22	**FDSDYMDV**
AE11-1 VL		SEQ ID NO.:23	SYELTQPPSVSLSPGQTARITC**SGDALPKQ YAY**WYQQKPGQAPVLVIY**KDTERPS**GIPER FSGSSSGTTVTLTISGAQAEDEADYYCQ**SA DSSGTSWV**FGGGTKLTVL
AE11-1 VL	**CDR-L1**	Residues 23-33 of SEQ ID NO.:23	**SGDALPKQYAY**
AE11-1 VL	**CDR-L2**	Residues 49-55 of SEQ ID NO.:23	**KDTERPS**
AE11-1 VL	**CDR-L3**	Residues 89 - 98 of SEQ ID NO.:23	**SADSSGTSWV**
AE11-5 VH		SEQ ID NO.:24	EVQLVQSGAEVKKPGSSAKVSCKASGGTFS **SYAIS**WVRQAPGQGLEWMG**GIIPILGTANY AQKFLG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GLYYDPTRADY**WGQGTLVTVSS
AE11-5 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:24	**SYAIS**
AE11-5 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:24	**GIIPILGTANYAQKFLG**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
AE11-5 VH	**CDR-H3**	Residues 99-109 of SEQ ID NO.:24	**GLYYDPTRADY**
AE11-5 VL		SEQ ID NO.:25	DIVMTQSPDFHSVTPKEKVTITC**RASQSIG SSLH**WYQQKPDQSPKLLIR**HASQSIS**GVPS RFSGSGSGTDFTLTIHSLEAEDAATYYC**HQ SSSSPPPT**FGQGTQVEIK
AE11-5 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:25	**RASQSIGSSLH**
AE11-5 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:25	**HASQSIS**
AE11-5 VL	**CDR-L3**	Residues 89 - 98 of SEQ ID NO.:25	**HQSSSSPPPT**
TNF-JK1 VH		SEQ ID NO.:26	EVQLVESGGGLVQPGGSLRLSCATSGFTFN **NYWMS**WVRQAPGKGLEWVA**NINHDESEKYY VDSAKG**RFTISRDNAEKSLFLQMNSLRAED TAVYYCAR**IIRGRVGFDYYNYAMDV**WGQGT LVTVSS
TNF-JK1 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:26	**NYWMS**
TNF-JK1 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:26	**NINHDESEKYYVDSAKG**
TNF-JK1 VH	**CDR-H3**	Residues 99-115 of SEQ ID NO.:26	**IIRGRVGFDYYNYAMDV**
TNF-JK1 VL		SEQ ID NO.:27	DIRLTQSPSPLSASVGDRVTITC**RASQSIG NYLN**WYQHKPGKAPKLLIY**AASSLQS**GVPS RFSGTGSGTDFTLTISSLQPEDFATYYC**QE SYSLI**FAGGTKVEIK
TNF-JK1 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:27	**RASQSIGNYLN**
TNF-JK1 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:27	**AASSLQS**
TNF-JK1 VL	**CDR-L3**	Residues 89 - 95 of SEQ ID NO.:27	**QESYSLI**
TNF-Y7C VH		SEQ ID NO.:28	EVQLVQSGAEVKKPGASVKVSCKTSGYTFS **NYDIN**WVRQPTGQGLEWMG**WMDPNNGNTGY AQKFVG**RVTMTRDTSKTTAYLELSGLKSED TAVYYCAR**SSGSGGTWYKEYFQS**WGQGTMV TVSS
TNF-Y7C VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:28	**NYDIN**
TNF-Y7C VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:28	**WMDPNNGNTGYAQKFVG**
TNF-Y7C VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.:28	**KSSGSGGTWYKEYFQS**
TNF-Y7C VL		SEQ ID NO.:29	DIVMTQSPLSLPVTPGEPASISC**RSSQSLL HSNGYNYLD**WYLQKPGQFPQLLIY**LGSYRA S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**MQRIEFPPGT**FGQGTKLGIK

Protein region			Sequence
			123456789**0**123456789**0**1234567890
TNF-Y7C VL	**CDR-L1**	Residues 24-39 of SEQ ID NO.:29	**RSSQSLLHSNGYNYLD**
TNF-Y7C VL	**CDR-L2**	Residues 55-61 of SEQ ID NO.:29	**LGSYRAS**
TNF-Y7C VL	**CDR-L3**	Residues 94 - 103 of SEQ ID NO.:29	**MQRIEFPPGT**
AE11-7 VH		SEQ ID NO.:30	EVQLVQSGAEVKKPGASVKVSCKTSGYSLT **QYPIH**WVRQAPGQRPEWMG**WISPGNGNTKL SPKFQG**RVTLSRDASAGTVFMDLSGLTSDD TAVYFCTS**VDLGDH**WGQGTLVTVSS
AE11-7 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:30	**QYPIH**
AE11-7 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:30	**WISPGNGNTKLSPKFQG**
AE11-7 VH	**CDR-H3**	Residues 99-104 of SEQ ID NO.:30	**VDLGDH**
AE11-7 VL		SEQ ID NO.:31	DIVMTQSPEFQSVTPKEKVTITC**RASQSIG SSLH**WYQQKPDQSPKLLIN**YASQSFS**GVPS RFSGGGSGTDFTLTINSLEAEDAATYYC**HQ SSNLPIT**FGQGTRLEIK
AE11-7 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:31	**RASQSIGSSLH**
AE11-7 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:31	**YASQSFS**
AE11-7 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:31	**HQSSNLPIT**
AE11-13 VH		SEQ ID NO.:32	EVQLVESGGGLVQPGRSLRLSCAASGFTFD **DYPMH**WVRQAPGEGLEWVS**GISSNSASIGY ADSVKG**RFTISRDNAQNTLYLQMNSLGDED TAVYYCVS**LTLG**IGQGTLVTVSS
AE11-13 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:32	**DYPMH**
AE11-13 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:332	**GISSNSASIGYADSVKG**
AE11-13 VH	**CDR-H3**	Residues 99-102 of SEQ ID NO.:32	**LTLG**
AE11-13 VL		SEQ ID NO.:33	DIRLTQSPSSLSASVGDRVTITC**RASQSIG NYLH**WYQQKPGKAPKLLIY**AASSLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ SYSTLYS**FGQGTKLEIK
AE11-13 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:33	**RASQSIGNYLH**
AE11-13 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:33	**AASSLQS**
AE11-13 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:33	**QQSYSTLYS**

B. IgG Converted Clones

Table 6 provides the VH sequence of humanized anti-TNF MAK-195 antibodies that were converted into IgG clones as discussed in detail in Example 2.

Table 6. Humanized anti-TNF MAK-195 Ab VH sequences of IgG converted clones

Protein region			Sequence
			123456789**0**123456789**0**1234567890
A8 VH		SEQ ID NO.:34	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVN**WVRQAPGKGLEWVS**MIAADGFTDYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWHHGPVAY**WGQGTLVTVSS
A8 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:34	**NYGVN**
A8 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:34	**MIAADGFTDYASSVKG**
A8 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:34	**EWHHGPVAY**
B5 VH		SEQ ID NO.:35	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**LIRGDGSTDYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWHHGPVAY**WGQGTLVTVSS
B5 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:35	**NYGVS**
B5 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:35	**LIRGDGSTDYASSLKG**
B5 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:35	**EWHHGPVAY**
rHC44 VH		SEQ ID NO.:36	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA DTLKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC44 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:36	**NYGVS**
rHC44 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:36	**MIWADGSTHYADTLKS**
rHC44 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:36	**EWQHGPVAY**
rHC22 VH		SEQ ID NO.:37	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTDYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC22 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:37	**NYGVT**
rHC22 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:37	**MIWADGSTDYADTVKG**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
rHC22 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.:37	**EWQHGPVAY**
rHC81 VH		SEQ ID NO.:38	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA DSVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC81 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.:38	**NYGVT**
rHC81 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.:38	**MIWADGSTHYADSVKS**
rHC81 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.:38	**EWQHGPLAY**
rHC18 VH		SEQ ID NO.:39	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWSDGSTDYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC18 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.:39	**NYGVT**
rHC18 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.:39	**MIWSDGSTDYASSVKG**
rHC18 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.:39	**EWQHGPVAY**
rHC14 VH		SEQ ID NO.:40	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC14 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.:40	**NYGVT**
rHC14 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.:40	**MIWADGSTHYASSLKG**
rHC14 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.:40	**EWQHGPAAY**
rHC3 VH		SEQ ID NO.:41	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC3 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.:41	**NYGVS**
rHC3 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.:41	**MIWADGSTHYASSLKG**
rHC3 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.:41	**EWQHGPVAY**
rHC19 VH		SEQ ID NO.:42	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC19 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.:42	**NYGVT**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
rHC19 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:42	**MIWADGSTHYASSVKG**
rHC19 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:42	**EWQHGPAAY**
rHC34 VH		SEQ ID NO.:43	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPSAY**WGQGTLVTVSS
rHC34 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:43	**NYGVT**
rHC34 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:43	**MIWADGSTHYASSVKG**
rHC34 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:43	**EWQHGPSAY**
rHC83 VH		SEQ ID NO.:44	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC83 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:44	**NYGVT**
rHC83 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:44	**MIWADGSTHYASSVKG**
rHC83 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:44	**EWQHGPVAY**
S4-19 VH		SEQ ID NO.:45	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-19 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:45	**NYGVE**
S4-19 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:45	**GIWADGSTHYADTVKS**
S4-19 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:45	**EWQHGPVAY**
S4-50 VH		SEQ ID NO.:46	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS
S4-50 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:46	**NYGVE**
S4-50 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:46	**GIWADGSTHYADTVKS**
S4-50 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:46	**EWQHGPVGY**
S4-63 VH		SEQ ID NO.:47	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-63 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:47	**NYGVE**
S4-63 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:47	**GIWADGSTHYADTVKS**
S4-63 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:47	**EWQHGPVGY**
S4-55 VH		SEQ ID NO.:48	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTDYA** **STVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS
S4-55 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:48	**NYGVT**
S4-55 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:48	**MIWADGSTDYASTVKG**
S4-55 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:48	**EWQHGPVGY**
S4-6 VH		SEQ ID NO.:49	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA** **SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-6 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:49	**NYGVT**
S4-6 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:49	**MIWADGSTHYASSVKG**
S4-6 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:49	**EWQHGPVAY**
S4-18 VH		SEQ ID NO.:50	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA** **DSVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-18 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:50	**NYGVT**
S4-18 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:50	**MIWADGSTHYADSVKS**
S4-18 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:50	**EWQHGPLAY**
S4-31 VH		SEQ ID NO.:51	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVQ**WVRQAPGKGLEWVS**GIGADGSTAYA** **SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHSGLAY**WGQGTLVTVSS
S4-31 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:51	**NYGVQ**
S4-31 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:51	**GIGADGSTAYASSLKG**
S4-31 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:51	**EWQHSGLAY**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-34 VH		SEQ ID NO.:52	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-34 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:52	**NYGVS**
S4-34 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:52	**MIWADGSTHYADTVKG**
S4-34 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:52	**EWQHGPLAY**
S4-74 VH		SEQ ID NO.:53	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-74 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:53	**NYGVT**
S4-74 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:53	**MIWADGSTHYADTVKG**
S4-74 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:53	**EWQHGPLAY**
S4-12 VH		SEQ ID NO.:54	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-12 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:54	**NYGVT**
S4-12 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:54	**MIWADGSTHYASSVKG**
S4-12 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:54	**EWQHGPVAY**
S4-54 VH		SEQ ID NO.:55	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-54 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:55	**NYGVT**
S4-54 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:55	**MIWADGSTHYASSVKG**
S4-54 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:55	**EWQHGPVAY**
S4-17 VH		SEQ ID NO.:56	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-17 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:56	**NYGVT**
S4-17 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:56	**MIWADGSTHYASSVKG**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-17 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:56	**EWQHGPVAY**
S4-40 VH		SEQ ID NO.:57	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA** **SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-40 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:57	**NYGVT**
S4-40 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:57	**MIWADGSTHYASSVKG**
S4-40 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:57	**EWQHGPVAY**
S4-24 VH		SEQ ID NO.:58	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA** **SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-24 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:58	**NYGVT**
S4-24 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.:58	**MIWADGSTHYASSVKG**
S4-24 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.:58	**EWQHGPVAY**

Table 7 provides VL sequences of IgG converted clones for Humanized anti-TNF MAK-195 antibodies as discussed in detail in Example 2.

Table 7. Humanized anti-TNF MAK-195 Ab VL sequences of IgG converted clones

Protein region			Sequence
			123456789**0**123456789**0**1234567890
hMAK195 VL.1 VL		SEQ ID NO.:59	DIQMTQSPSSLSASVGDRVTITC**KASQAVS** **SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ** **HYSTPFT**FGQGTKLEIKR
hMAK195 VL.1 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:59	**KASQAVSSAVA**
hMAK195 VL.1 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:59	**WASTRHT**
hMAK195 VL.1 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:59	**QQHYSTPFT**
S4-24 VL		SEQ ID NO.:60	DIQMTQSPSSLSASVGDRVTITC**RASQLVS** **SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ** **HYRTPFT**FGQGTKLEIKR
S4-24 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:60	**RASQLVSSAVA**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-24 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:60	**WASTLHT**
S4-24 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:60	**QQHYRTPFT**
S4-40 VL		SEQ ID NO.:61	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFS**FGQGTKLEIKR
S4-40 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:61	**RASQLVSSAVA**
S4-40 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:61	**WASTRHS**
S4-40 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:61	**QQHYRTPFS**
S4-17 VL		SEQ ID NO.:62	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-17 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:62	**RASQLVSSAVA**
S4-17 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:62	**WASTRHS**
S4-17 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:62	**QQHYRTPFT**
S4-54 VL		SEQ ID NO.:63	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYKTPFS**FGQGTKLEIKR
S4-54 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:63	**RASQLVSSAVA**
S4-54 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:63	**WASARHT**
S4-54 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:63	**QQHYKTPFS**
S4-12 VL		SEQ ID NO.:64	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYKTPFT**FGQGTKLEIKR
S4-12 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:64	**RASQLVSSAVA**
S4-12 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:64	**WASARHT**
S4-12 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:64	**QQHYKTPFT**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-74 VL		SEQ ID NO.:65	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-74 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:65	**RASQLVSSAVA**
S4-74 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:65	**WASARHT**
S4-74 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:65	**QQHYRTPFT**
S4-34 VL		SEQ ID NO.:66	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-34 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:66	**RASQLVSSAVA**
S4-34 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:66	**WASTRHT**
S4-34 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:66	**QQHYRTPFT**
S4-31 VL		SEQ ID NO.:67	DIQMTQSPSSLSASVGDRVTITC**RASQGVS SALA**WYQQKPGKAPKLLIY**WASALHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSAPFT**FGQGTKLEIKR
S4-31 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:67	**RASQGVSSALA**
S4-31 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:67	**WASALHS**
S4-31 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:67	**QQHYSAPFT**
S4-18 VL		SEQ ID NO.:68	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPFT**FGQGTKLEIKR
S4-18 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:68	**RASQLVSSAVA**
S4-18 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:68	**WASTLHS**
S4-18 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:68	**QQHYSTPFT**
S4-6 VL		SEQ ID NO.:69	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPFT**FGQGTKLEIKR
S4-6 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:69	**KASQLVSSAVA**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
S4-6 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:69	**WASTRHT**
S4-6 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:69	**QQHYSTPFT**
S4-55 VL		SEQ ID NO.:70	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-55 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:70	**KASQLVSSAVA**
S4-55 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:70	**WASTLHT**
S4-55 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:70	**QQHYRTPFT**
S4-63 VL		SEQ ID NO.:71	DIQMTQSPSSLSASVGDRVTITC**KASQKVS SALA**WYQQKPGKAPKLLIY**WASALHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRPPFT**FGQGTKLEIKR
S4-63 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:71	**KASQKVSSALA**
S4-63 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:71	**WASALHS**
S4-63 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:71	**QQHYRPPFT**
S4-50 VL		SEQ ID NO.:72	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASALHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSSPYT**FGQGTKLEIKR
S4-50 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:72	**KASQLVSSAVA**
S4-50 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:72	**WASALHT**
S4-50 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:72	**QQHYSSPYT**
S4-19 VL		SEQ ID NO.:73	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-19 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:73	**KASQLVSSAVA**
S4-19 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:73	**WASTLHT**
S4-19 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.:73	**QQHYRTPFT**

C. Individual hMAK-199 Sequences from Converted Clones

Table 8 provides VH sequences of humanized anti-TNF MAK-199 converted clones as discussed in detail in Example 3.

Table 8. Humanized Anti-TNF MAK-199 Ab VH sequences of IgG converted clones

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3 #10 **VH**		SEQ ID NO.:74	EVQLVQSGAEVKKPGASVKVSCKASGYTFA **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 10 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:74	**NYGII**
J662M2S3# 10 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:74	**WINTYTGKPTYAQKFQG**
J662M2S3# 10 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:74	**RASQDISQYLN**
J662M2S3# 13 **VH**		SEQ ID NO.:75	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKLQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFNTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 13 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:75	**NYGII**
J662M2S3# 13 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:75	**WINTYTGKPTYAQKLQG**
J662M2S3# 13 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:75	**KLFNTVDVTDNAMD**
J662M2S3# 15 **VH**		SEQ ID NO.:76	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGVPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFNTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 15 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:76	**NYGII**
J662M2S3# 15 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:76	**WINTYTGVPTYAQKFQG**
J662M2S3# 15 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:76	**KLFNTVDVTDNAMD**
J662M2S3# 16 **VH**		SEQ ID NO.:77	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFNTVAVTDNAMD**YWGQGTTV TVSS
J662M2S3# 16 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:77	**NYGII**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3# 16 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:77	**WINTYTGKPTYAQKFQG**
J662M2S3# 16 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:77	**KLFNTVAVTDNAMD**
J662M2S3# 21 **VH**		SEQ ID NO.:78	EVQLVQSGAEVKKPGASVKVSCKASGYTFR **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 21 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:78	**NYGII**
J662M2S3# 21 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:78	**WINTYTGKPTYAQKFQG**
J662M2S3# 21 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:78	**KLFTTVDVTDNAMD**
J662M2S3# 34 **VH**		SEQ ID NO.:79	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGIN**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KFRNTVAVTDYAMD**YWGQGTTV TVSS
J662M2S3# 34 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:79	**NYGIN**
J662M2S3# 34 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:79	**WINTYTGKPTYAQKFQG**
J662M2S3# 34 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:79	**KFRNTVAVTDYAMD**
J662M2S3# 36 **VH**		SEQ ID NO.:80	EVQLVQSGAEVKKPGASVKVSCKASGYTFR **NYGIT**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 36 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:80	**NYGIT**
J662M2S3# 36 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:80	**WINTYTGKPTYAQKFQG**
J662M2S3# 36 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:80	**KLFTTMDVTDNAMD**
J662M2S3# 45 **VH**		SEQ ID NO.:81	EVQLVQSGAEVKKPGASVKVSCKASGYTFA **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 45 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.:81	**NYGII**
J662M2S3# 45 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.:81	**WINTYTGKPTYAQKFQG**
J662M2S3# 45 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.:81	**KLFTTMDVTDNAMD**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#58 VH		SEQ ID NO.:82	EVQLVQSGAEVKKPGASVKVSCKASGYTFS **NYGIN**WVRQAPGQGLEWMG**WINTYTGQPSY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFKTEAVTDYAMD**YWGQGTTV TVSS
J662M2S3#58 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:82	**NYGIN**
J662M2S3#58 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:82	**WINTYTGQPSYAQKFQG**
J662M2S3#58 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.:82	**KLFKTEAVTDYAMD**
J662M2S3#72 VH		SEQ ID NO.:83	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYSGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3#72 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.:83	**NYGII**
J662M2S3#72 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.:83	**WINTYSGKPTYAQKFQG**
J662M2S3#72 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.:83	**KLFTTMDVTDNAMD**

Table 9 provides VL sequences of humanized anti-TNF MAK-199 converted clones as discussed in detail in Example 3.

Table 9. Humanized Anti-TNF MAK-199 Ab VL sequences of IgG converted clones

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#10 VL		SEQ ID NO.:84	DIQMTQSPSSLSASVGDRVTITC**RASQDIS QYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYFC**QQ GNTWPPT**FGQGTKLEIK
J662M2S3#10 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:84	**RASQDISQYLN**
J662M2S3#10 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:84	**YTSRLQS**
J662M2S3#10 VL	**CDR-L3**	Residues 89-97 of SEQ ID NO.:84	**QQGNTWPPT**
J662M2S3#13 VL		SEQ ID NO.:85	DIQMTQSPSSLSASVGDRVTITC**RASQDIS NYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ GNSWPPT**FGQGTKLEIK
J662M2S3#13 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.:85	**RASQDISNYLN**
J662M2S3#13 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.:85	**YTSRLQS**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#13 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:85	**QQGNSWPPT**
J662M2S3#15 **VL**		SEQ ID NO.:86	DIQMTQSPSSLSASVGDRVTITC**RASQDIY** **NYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ** **GNTQPPT**FGQGTKLEIK
J662M2S3#15 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:86	**RASQDIYNYLN**
J662M2S3#15 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:86	**YTSRLQS**
J662M2S3#15 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:86	**QQGNTQPPT**
J662M2S3#16 **VL**		SEQ ID NO.:87	DIQMTQSPSSLSASVGDRVTITC**RASQDIE** **NYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYFC**QQ** **GNTQPPT**FGQGTKLEIK
J662M2S3#16 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:87	**RASQDIENYLN**
J662M2S3#16 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:87	**YTSRLQS**
J662M2S3#16 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:87	**QQGNTQPPT**
J662M2S3#21 **VL**		SEQ ID NO.:88	DIQMTQSPSSLSASVGDRVTITC**RASQDIS** **NYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ** **GNTWPPT**FGQGTKLEIK
J662M2S3#21 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:88	**RASQDISNYLN**
J662M2S3#21 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:88	**YTSRLQS**
J662M2S3#21 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:88	**QQGNTWPPT**
J662M2S3#34 **VL**		SEQ ID NO.:89	DIQMTQSPSSLSASVGDRVTITC**RASQDIY** **DVLN**WYQQKPGKAPKLLIY**YASRLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ** **GITLPPT**FGQGTKLEIK
J662M2S3#34 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:89	**RASQDIYDVLN**
J662M2S3#34 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:89	**YASRLQS**
J662M2S3#34 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:89	**QQGITLPPT**
J662M2S3#36 **VL**		SEQ ID NO.:90	DIQMTQSPSSLSASVGDRVTITC**RASQDIS** **NYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ** **GNTWPPT**FGQGTKLEIK

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#36 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:90	**RASQDISNYLN**
J662M2S3#36 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:90	**YTSRLQS**
J662M2S3#36 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:90	**QQGNTWPPT**
J662M2S3#45 **VL**		SEQ ID NO.:91	DIQMTQSPSSLSASVGDRVTITC**RASQDIS QYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYFC**QQ GNTWPPT**FGQGTKLEIK
J662M2S3#45 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:91	**RASQDISQYLN**
J662M2S3#45 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:91	**YTSRLQS**
J662M2S3#45 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:91	**QQGNTWPPT**
J662M2S3#58 **VL**		SEQ ID NO.:92	DIQMTQSPSSLSASVGDRVTITC**RASQNIY NVLN**WYQQKPGKAPKLLIY**YASRLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYFC**QQ GNTMPPT**FGQGTKLEIK
J662M2S3#58 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:92	**RASQNIYNVLN**
J662M2S3#58 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:92	**YASRLQS**
J662M2S3#58 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:92	**QQGNTMPPT**
J662M2S3#72 **VL**		SEQ ID NO.:93	DIQMTQSPSSLSASVGDRVTITC**RASQDIS NFLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ GNTQPPT**FGQGTKLEIK
J662M2S3#72 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.:93	**RASQDISNFLN**
J662M2S3#72 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.:93	**YTSRLQS**
J662M2S3#72 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.:93	**QQGNTQPPT**

In an embodiment, the antigen binding domain comprises the VH region chosen from any one of SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077, or one, two, or three CDRs therefrom. In another embodiment, the antigen binding domain comprises the VL region chosen from any one of SEQ ID NOs: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078, or one, two, or three CDRs therefrom. In a particular embodiment, the antigen binding domain comprises a VH region and a VL region, for example,

wherein the VH region comprises SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077, or one, two, or three CDRs therefrom, and the VL region comprises SEQ ID NOs: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078, or one, two, or three CDRs therefrom.

In an embodiment where the VH and/or the VL CDR sequences are provided above, the human acceptor framework comprises at least one amino acid sequence selected from: SEQ ID NOs: 6-21. In a particular embodiment, the human acceptor framework comprises an amino acid sequence selected from: SEQ IN NOs: 9, 10, 11, 12, 15, 16, 17, and 21. In another embodiment, the human acceptor framework comprises at least one framework region amino acid substitution, wherein the amino acid sequence of the framework is at least 65% identical to the sequence of the human acceptor framework and comprises at least 70 amino acid residues identical to the human acceptor framework. In another embodiment, the human acceptor framework comprises at least one framework region amino acid substitution at a key residue. The key residue selected from: a residue adjacent to a CDR; a glycosylation site residue; a rare residue; a residue capable of interacting with human TNF-α; a residue capable of interacting with a CDR; a canonical residue; a contact residue between heavy chain variable region and light chain variable region; a residue within a Vernier zone; and a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework. In an embodiment, the key residue is selected from: H1, H12, H24, H27, H29, H37, H48, H49, H67, H71, H73, H76, H78, L13, L43, L58, L70, and L80. In an embodiment, the VH mutation is selected from: Q1E, I12V, A24V, G27F, I29L, V29F F29L I37V, I48L, V48L, S49G, V67L, F67L, V71K, R71K, T73N, N76S, L78I, and F78I. In another embodiment, the VL mutation is selected from: V13L, A43S, I58V, E70D, and S80P. In an embodiment, the binding protein comprises two variable domains, wherein the two variable domains have amino acid sequences selected from: SEQ ID NOS: 22 and 23; 23 and 24; 24 and 25; 26 and 27; 28 and 29; 30 and 31; or 32 and 33.

III. Production of Binding Proteins and Binding Protein-Producing Cell Lines

In an embodiment, TNF-α binding proteins disclosed herein exhibit a high capacity to reduce or to neutralize TNF-α activity, e.g., as assessed by any one of several *in vitro* and *in vivo* assays known in the art. Alternatively, TNF-α binding proteins disclosed herein, also exhibit a high capacity to increase or agonize TNF-α activity.

In particular embodiments, the isolated binding protein, or antigen-binding portion thereof, binds human TNF-α, wherein the binding protein, or antigen-binding portion thereof, dissociates from human TNF-α with a k_{off} rate constant of about $0.1s^{-1}$ or less, as determined by

surface plasmon resonance, such as 1×10^{-2} s^{-1}or less, 1×10^{-3} s^{-1}or less, 1×10^{-4} s^{-1}or less, 1×10^{-5} s^{-1}or less and 1×10^{-6} s^{-1}or less; or which inhibits human TNF-α activity with an IC_{50} of about 1×10^{-6} M or less, such as 1×10^{-7} M or less, 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less and 1×10^{-11} M or less. In certain embodiments, the binding protein comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. In an embodiment, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the binding protein can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. In another embodiment, the binding protein comprises a kappa light chain constant region. Alternatively, the binding protein portion can be, for example, a Fab fragment or a single chain Fv fragment.

Replacements of amino acid residues in the Fc portion to alter binding protein effector function are known in the art (See U.S. Patent Nos. 5,648,260 and 5,624,821). The Fc portion of a binding protein mediates several important effector functions, e.g., cytokine induction, ADCC, phagocytosis, complement dependent cytotoxicity (CDC) and half-life/clearance rate of antibody and antigen-antibody complexes. In some cases these effector functions are desirable for therapeutic antibody but in other cases might be unnecessary or even deleterious, depending on the therapeutic objectives. Certain human IgG isotypes, particularly IgG1 and IgG3, mediate ADCC and CDC via binding to FcγRs and complement C1q, respectively. Neonatal Fc receptors (FcRn) are the critical components determining the circulating half-life of antibodies. In still another embodiment at least one amino acid residue is replaced in the constant region of the binding protein, for example the Fc region of the binding protein, such that effector functions of the binding protein are altered.

One embodiment provides a labeled binding protein wherein an antibody or antibody portion disclosed herein is derivatized or linked to another functional molecule (e.g., another peptide or protein). For example, a labeled binding protein disclosed herein can be derived by functionally linking an antibody or antibody portion disclosed herein (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate associate of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

Useful detectable agents with which an antibody or antibody portion disclosed herein may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized

with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

Another embodiment of the disclosure provides a crystallized binding protein. In an embodiment, provided are crystals of whole TNF-α binding proteins and fragments thereof as disclosed herein, and formulations and compositions comprising such crystals. In one embodiment the crystallized binding protein has a greater half-life in vivo than the soluble counterpart of the binding protein. In another embodiment the binding protein retains biological activity after crystallization.

Crystallized binding protein disclosed herein may be produced according methods known in the art and as disclosed in PCT Publication WO 02/72636.

Another embodiment of the disclosure provides a glycosylated binding protein wherein the binding protein or antigen-binding portion thereof comprises one or more carbohydrate residues. Nascent *in vivo* protein production may undergo further processing, known as post-translational modification. In particular, sugar (glycosyl) residues may be added enzymatically, a process known as glycosylation. The resulting proteins bearing covalently linked oligosaccharide side chains are known as glycosylated proteins or glycoproteins. Protein glycosylation depends on the amino acid sequence of the protein of interest, as well as the host cell in which the protein is expressed. Different organisms may produce different glycosylation enzymes (e.g., glycosyltransferases and glycosidases), and have different substrates (nucleotide sugars) available. Due to such factors, protein glycosylation pattern, and composition of glycosyl residues, may differ depending on the host system in which the particular protein is expressed. Glycosyl residues useful in the disclosure may include, but are not limited to, glucose, galactose, mannose, fucose, n-acetylglucosamine and sialic acid. In an embodiment, the glycosylated binding protein comprises glycosyl residues such that the glycosylation pattern is human.

It is known to those skilled in the art that differing protein glycosylation may result in differing protein characteristics. For instance, the efficacy of a therapeutic protein produced in a microorganism host, such as yeast, and glycosylated utilizing the yeast endogenous pathway may be reduced compared to that of the same protein expressed in a mammalian cell, such as a CHO cell line. Such glycoproteins may also be immunogenic in humans and show reduced half-life in vivo after administration. Specific receptors in humans and other animals may recognize

specific glycosyl residues and promote the rapid clearance of the protein from the bloodstream. Other adverse effects may include changes in protein folding, solubility, susceptibility to proteases, trafficking, transport, compartmentalization, secretion, recognition by other proteins or factors, antigenicity, or allergenicity. Accordingly, a practitioner may prefer a therapeutic protein with a specific composition and pattern of glycosylation, for example glycosylation composition and pattern identical, or at least similar, to that produced in human cells or in the species-specific cells of the intended subject animal.

Expressing glycosylated proteins different from that of a host cell may be achieved by genetically modifying the host cell to express heterologous glycosylation enzymes. Using techniques known in the art a practitioner may generate antibodies or antigen-binding portions thereof exhibiting human protein glycosylation. For example, yeast strains have been genetically modified to express non-naturally occurring glycosylation enzymes such that glycosylated proteins (glycoproteins) produced in these yeast strains exhibit protein glycosylation identical to that of animal cells, especially human cells (U.S. Patent Nos. 7,449,308 and 7,029,872).

Further, it will be appreciated by one skilled in the art that a protein of interest may be expressed using a library of host cells genetically engineered to express various glycosylation enzymes, such that member host cells of the library produce the protein of interest with variant glycosylation patterns. A practitioner may then select and isolate the protein of interest with particular novel glycosylation patterns. In an embodiment, the protein having a particularly selected novel glycosylation pattern exhibits improved or altered biological properties.

IV. Uses of TNF-α Binding Proteins

Given their ability to bind to human TNF-α, e.g., the human TNF-α binding proteins, or portions thereof, disclosed herein can be used to detect TNF-α (e.g., in a biological sample, such as serum or plasma), using a conventional immunoassay, such as an enzyme linked immunosorbent assays (ELISA), an radioimmunoassay (RIA) or tissue immunohistochemistry. A method for detecting TNF-α in a biological sample is provided comprising contacting a biological sample with a binding protein, or binding protein portion, disclosed herein and detecting either the binding protein (or binding protein portion) bound to TNF-α or unbound binding protein (or binding protein portion), to thereby detect TNF-α in the biological sample. The binding protein is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include

umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of suitable radioactive material include ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, or ^{153}Sm.

Alternative to labeling the binding protein, human TNF-α can be assayed in biological fluids by a competition immunoassay utilizing rhTNF-α standards labeled with a detectable substance and an unlabeled human TNF-α binding protein. In this assay, the biological sample, the labeled rhTNF-α standards and the human TNF-α binding protein are combined and the amount of labeled rhTNF-α standard bound to the unlabeled binding protein is determined. The amount of human TNF-α in the biological sample is inversely proportional to the amount of labeled rhTNF-α standard bound to the TNF-α binding protein. Similarly, human TNF-α can also be assayed in biological fluids by a competition immunoassay utilizing rhTNF-α standards labeled with a detectable substance and an unlabeled human TNF-α binding protein.

In an embodiment, the binding proteins and binding protein portions disclosed herein are capable of neutralizing TNF-α activity, e.g., human TNF-α activity, both *in vitro* and *in vivo*. In another embodiment, the binding proteins and binding protein portions disclosed herein are capable of increasing or agonizing human TNF-α activity, e.g., human TNF-α activity. Accordingly, such binding proteins and binding protein portions disclosed herein can be used to inhibit or increase hTNF-α activity, e.g., in a cell culture containing hTNF-α, in human subjects or in other mammalian subjects having TNF-α with which a binding protein disclosed herein cross-reacts. In one embodiment, a method for inhibiting or increasing hTNF-α activity is provided comprising contacting hTNF-α with a binding protein or binding protein portion disclosed herein such that hTNF-α activity is inhibited or increased. For example, in a cell culture containing, or suspected of containing hTNF-α, a binding protein or binding protein portion disclosed herein can be added to the culture medium to inhibit or increase hTNF-α activity in the culture.

In another embodiment, a method is provided for reducing or increasing hTNF-α activity in a subject, advantageously from a subject suffering from a disease or disorder in which TNF-α-activity is detrimental or, alternatively, beneficial. Methods for reducing or increasing TNF-α activity in a subject suffering from such a disease or disorder is provided, which method comprises administering to the subject a binding protein or binding protein portion disclosed herein such that TNF-α activity in the subject is reduced or increased. In a particular embodiment, the TNF-α is human TNF-α, and the subject is a human subject. Alternatively, the subject can be a mammal expressing a TNF-α to which a binding protein provided is capable of binding. Still further the subject can be a mammal into which TNF-α has been introduced (e.g., by administration of TNF-α or by expression of a TNF-α transgene). A

binding protein disclosed herein can be administered to a human subject for therapeutic purposes. Moreover, a binding protein disclosed herein can be administered to a non-human mammal expressing a TNF-α with which the binding protein is capable of binding for veterinary purposes or as an animal model of human disease. Regarding the latter, such animal models may be useful for evaluating the therapeutic efficacy of binding proteins disclosed herein (e.g., testing of dosages and time courses of administration).

The term "a disorder in which TNF-α activity is detrimental" includes diseases and other disorders in which the presence of TNF-α activity in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in which TNF-α activity is detrimental is a disorder in which reduction of TNF-α activity is expected to alleviate the symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of TNF-α in a biological fluid of a subject suffering from the disorder (e.g., an increase in the concentration of TNF-α in serum, plasma, synovial fluid, etc. of the subject), which can be detected, for example, using an anti-TNF-α antibody as described above. Non-limiting examples of disorders that can be treated with the binding proteins disclosed herein include those disorders discussed in the section below pertaining to pharmaceutical compositions of the antibodies disclosed herein.

Alternatively, the term "a disorder in which TNF-α activity is beneficial" include diseases and other disorders in which the presence of TNF-α activity in a subject suffering from the disorder has been shown to be or is suspected of being either beneficial for treating the pathophysiology of the disorder or a factor that contributes to a treatment of the disorder. Accordingly, a disorder in which TNF-α activity is beneficial is a disorder in which an increase of TNF-α activity is expected to alleviate the symptoms and/or progression of the disorder. Non-limiting examples of disorders that can be treated with the antibodies disclosed herein include those disorders discussed in the section below pertaining to pharmaceutical compositions of the antibodies disclosed herein.

V. Pharmaceutical Compositions

Pharmaceutical compositions are also provided comprising a binding protein, or antigen-binding portion thereof, disclosed herein and a pharmaceutically acceptable carrier. The pharmaceutical compositions comprising binding protein disclosed herein are for use in, but not limited to, diagnosing, detecting, or monitoring a disorder, in preventing, treating, managing, or ameliorating of a disorder or one or more symptoms thereof, and/or in research. In a specific embodiment, a composition comprises one or more binding proteins disclosed herein. In another embodiment, the pharmaceutical composition comprises one or more binding proteins disclosed

herein and one or more prophylactic or therapeutic agents other than binding proteins disclosed herein for treating a disorder in which TNF-α activity is detrimental. In a particular embodiment, the prophylactic or therapeutic agents known to be useful for or having been or currently being used in the prevention, treatment, management, or amelioration of a disorder or one or more symptoms thereof. In accordance with these embodiments, the composition may further comprise of a carrier, diluent or excipient.

The binding proteins and binding protein-portions disclosed herein can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises a binding protein or binding protein portion disclosed herein and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition, may be included. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the binding protein or binding protein portion.

Various delivery systems are known and can be used to administer one or more binding proteins disclosed herein or the combination of one or more binding proteins disclosed herein and a prophylactic agent or therapeutic agent useful for preventing, managing, treating, or ameliorating a disorder or one or more symptoms thereof, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the binding protein or binding protein fragment, receptor-mediated endocytosis (see, e. g., Wu and Wu (1987) *J. Biol. Chem.* 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering a prophylactic or therapeutic agent disclosed herein include, but are not limited to, parenteral administration (e.g., intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural administration, intratumoral administration, and mucosal administration (e.g., intranasal and oral routes). In addition, pulmonary administration can be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. In one embodiment, a binding protein disclosed herein, combination therapy, or a composition disclosed herein is administered using Alkermes AIR® pulmonary drug delivery technology (Alkermes, Inc., Cambridge, Mass.). In a specific embodiment, prophylactic or therapeutic agents disclosed herein are administered intramuscularly, intravenously, intratumorally, orally, intranasally, pulmonary, or subcutaneously. The prophylactic or

therapeutic agents may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

In a specific embodiment, it may be desirable to administer the prophylactic or therapeutic agents disclosed herein locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous or non-porous material, including membranes and matrices, such as sialastic membranes, polymers, fibrous matrices (e.g., Tissuel®), or collagen matrices. In one embodiment, an effective amount of one or more binding proteins disclosed herein antagonists is administered locally to the affected area to a subject to prevent, treat, manage, and/or ameliorate a disorder or a symptom thereof. In another embodiment, an effective amount of one or more binding proteins disclosed herein is administered locally to the affected area in combination with an effective amount of one or more therapies (e.g., one or more prophylactic or therapeutic agents) other than an antibody disclosed herein of a subject to prevent, treat, manage, and/or ameliorate a disorder or one or more symptoms thereof.

In a specific embodiment, where the composition disclosed herein is a nucleic acid encoding a prophylactic or therapeutic agent, the nucleic acid can be administered in vivo to promote expression of its encoded prophylactic or therapeutic agent, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, DuPont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see, e.g., Joliot et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:1864-1868). Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

The method disclosed herein may comprise administration of a composition formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). Formulations for injection may be presented in unit dosage form (e.g., in ampoules or in multi-dose containers) with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g., sterile pyrogen-free water) before use.

The methods disclosed herein may additionally comprise of administration of compositions formulated as depot preparations. Such long acting formulations may be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (e.g., as a sparingly soluble salt).

The methods disclosed herein encompass administration of compositions formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the mode of administration is infusion, composition can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the mode of administration is by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

In particular, it is also provided that one or more of the prophylactic or therapeutic agents, or pharmaceutical compositions disclosed herein is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of the agent. In one embodiment, one or more of the prophylactic or therapeutic agents, or pharmaceutical compositions disclosed herein is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted (e.g., with water or saline) to the appropriate concentration for administration to a subject. In an embodiment, one or more of the prophylactic or therapeutic agents or pharmaceutical compositions disclosed herein is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 75 mg, or at least 100 mg. The lyophilized prophylactic or therapeutic agents or pharmaceutical compositions disclosed herein should be stored at between 2°C and 8°C in its original container and the prophylactic or therapeutic agents, or pharmaceutical compositions disclosed herein should be administered within 1 week, within 5 days, within 72 hours, within 48 hours, within 24 hours, within 12 hours, within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, one or more of the prophylactic or therapeutic agents or pharmaceutical compositions disclosed herein is supplied in liquid form in a hermetically sealed container

indicating the quantity and concentration of the agent. In an embodiment, the liquid form of the administered composition is supplied in a hermetically sealed container at least 0.25 mg/ml, at least 0.5 mg/ml, at least 1 mg/ml, at least 2.5 mg/ml, at least 5 mg/ml, at least 8 mg/ml, at least 10 mg/ml, at least 15 mg/kg, at least 25 mg/ml, at least 50 mg/ml, at least 75 mg/ml or at least 100 mg/ml. The liquid form should be stored at between 2°C and 8°C in its original container.

The binding proteins and binding protein-portions disclosed herein can be incorporated into a pharmaceutical composition suitable for parenteral administration. In an embodiment, the binding protein or binding protein-portions will be prepared as an injectable solution containing 0.1-250 mg/ml binding protein. The injectable solution can be composed of either a liquid or lyophilized dosage form in a flint or amber vial, ampoule or pre-filled syringe. The buffer can be L-histidine (1-50 mM), optimally 5-10mM, at pH 5.0 to 7.0 (optimally pH 6.0). Other suitable buffers include but are not limited to, sodium succinate, sodium citrate, sodium phosphate or potassium phosphate. Sodium chloride can be used to modify the toxicity of the solution at a concentration of 0-300 mM (optimally 150 mM for a liquid dosage form). Cryoprotectants can be included for a lyophilized dosage form, principally 0-10% sucrose (optimally 0.5-1.0%). Other suitable cryoprotectants include trehalose and lactose. Bulking agents can be included for a lyophilized dosage form, principally 1-10% mannitol (optimally 2-4%). Stabilizers can be used in both liquid and lyophilized dosage forms, principally 1-50 mM L-Methionine (optimally 5-10 mM). Other suitable bulking agents include glycine, arginine, can be included as 0-0.05% polysorbate-80 (optimally 0.005-0.01%). Additional surfactants include but are not limited to polysorbate 20 and BRIJ surfactants.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (i.e., binding protein or binding protein portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile, lyophilized powders for the preparation of sterile injectable solutions, the methods of preparation include vacuum drying and spray-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle

size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including, in the composition, an agent that delays absorption, for example, monostearate salts and gelatin.

As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, a binding protein or binding protein portion disclosed herein is coformulated with and/or coadministered with one or more additional therapeutic agents that are useful for treating disorders in which TNF-α activity is detrimental. For example, an anti-hTNF-α antibody or antibody portion disclosed herein may be coformulated and/or coadministered with one or more additional antibodies that bind other targets (e.g., antibodies that bind other cytokines or that bind cell surface molecules). Furthermore, one or more binding proteins disclosed herein may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

In certain embodiments, a binding protein to TNF-α or fragment thereof is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, the Fc domain, polyethylene glycol, and dextran. Such vehicles are described, e.g., in U.S. Patent No. 6,660,843.

In a specific embodiment, nucleic acid sequences comprising nucleotide sequences encoding a binding protein disclosed herein or another prophylactic or therapeutic agent disclosed herein are administered to treat, prevent, manage, or ameliorate a disorder or one or more symptoms thereof by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the disclosure, the nucleic acids produce their encoded binding protein or prophylactic or therapeutic agent disclosed herein that mediates a prophylactic or therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present disclosure.

TNF-α plays a critical role in the pathology associated with a variety of diseases involving immune and inflammatory elements, such as autoimmune diseases, particularly those assocated with inflammation, including Crohn's disease, psoriasis (including plaque psoriasis), arthritis (including rheumatoid arthritis, psoratic arthritis, osteoarthritis, or juvenile idiopathic arthritis), multiple sclerosis, systemic lupus erythematosus, and ankylosing spondylitis. Therefore, the binding proteins herein may be used to treat these disorders. In another embodiment, the disorder is a respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs; inflammatory bowel diseases (IBD); ulcerative colitis; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma; glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, suppression of expression of a protective type 1 immune response during vaccination, neurodegenerative diseases, neuronal regeneration, and spinal cord injury.

It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods disclosed herein may be made using suitable equivalents without departing from the scope of the invention or the embodiments disclosed herein. Having now described the present disclosure in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting of the invention.

Examples

Example 1: Identification of fully human antibodies to TNF by in vitro display systems

1.1: Antibody selections

Fully human anti-human TNF monoclonal antibodies were isolated by in vitro display technologies from human antibody libraries by their ability to bind recombinant human TNF proteins. The amino acid sequences of the variable heavy (VH) and variable light (VL) chains were determined from DNA sequencing and listed in Table 10.

Table 10. Individual clones sequences

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
AE11-1 VH		**22**	EVQLVQSGAEVKKPGASVKVSCKASGYTFT **SYDVN**WVRQATGQGLEWMG**WMNPNSGNTGY AQKFQG**RVTITADESTSTAYMELSSLRSED TAVYYCAI**FDSDYMDV**WGKGTLVTVSS
AE11-1 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 22	**SYDVN**
AE11-1 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 22	**WMNPNSGNTGYAQKFQG**
AE11-1 VH	**CDR-H3**	Residues 99-106 of SEQ ID NO.: 22	**FDSDYMDV**
AE11-1 VL		**23**	SYELTQPPSVSLSPGQTARITC**SGDALPKQ YAY**WYQQKPGQAPVLVIY**KDTERPS**GIPER FSGSSSGTTVTLTISGAQAEDEADYYCQ**SA DSSGTSWV**FGGGTKLTVL
AE11-1 VL	**CDR-L1**	Residues 23-33 of SEQ ID NO.: 23	**SGDALPKQYAY**
AE11-1 VL	**CDR-L2**	Residues 49-55 of SEQ ID NO.: 23	**KDTERPS**
AE11-1 VL	**CDR-L3**	Residues 89 - 98 of SEQ ID NO.: 23	**SADSSGTSWV**
AE11-5 VH		**24**	EVQLVQSGAEVKKPGSSAKVSCKASGGTFS **SYAIS**WVRQAPGQGLEWMG**GIIPILGTANY AQKFLG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GLYYDPTRADY**WGQGTLVTVSS
AE11-5 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 24	**SYAIS**
AE11-5 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 24	**GIIPILGTANYAQKFLG**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
AE11-5 VH	**CDR-H3**	Residues 99-109 of SEQ ID NO.: 24	**GLYYDPTRADY**
AE11-5 VL		**25**	DIVMTQSPDFHSVTPKEKVTITC**RASQSIGSSLH**WYQQKPDQSPKLLIR**HASQSIS**GVPSRFSGSGSGTDFTLTIHSLEAEDAATYYC**HQSSSSPPPT**FGQGTQVEIK
AE11-5 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 25	**RASQSIGSSLH**
AE11-5 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 25	**HASQSIS**
AE11-5 VL	**CDR-L3**	Residues 89 - 98 of SEQ ID NO.: 25	**HQSSSSPPPT**
TNF-JK1 VH		**26**	EVQLVESGGGLVQPGGSLRLSCATSGFTFN**NYWMS**WVRQAPGKGLEWVA**NINHDESEKYYVDSAKG**RFTISRDNAEKSLFLQMNSLRAEDTAVYYCAR**IIRGRVGFDYYNYAMDV**WGQGTLVTVSS
TNF-JK1 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 26	**NYWMS**
TNF-JK1 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 26	**NINHDESEKYYVDSAKG**
TNF-JK1 VH	**CDR-H3**	Residues 99-115 of SEQ ID NO.: 26	**IIRGRVGFDYYNYAMDV**
TNF-JK1 VL		**27**	DIRLTQSPSPLSASVGDRVTITC**RASQSIGNYLN**WYQHKPGKAPKLLIY**AASSLQS**GVPSRFSGTGSGTDFTLTISSLQPEDFATYYC**QESYSLI**FAGGTKVEIK
TNF-JK1 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 27	**RASQSIGNYLN**
TNF-JK1 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 27	**AASSLQS**
TNF-JK1 VL	**CDR-L3**	Residues 89 - 95 of SEQ ID NO.: 27	**QESYSLI**
TNF-Y7C VH		**28**	EVQLVQSGAEVKKPGASVKVSCKTSGYTFS**NYDIN**WVRQPTGQGLEWMG**WMDPNNGNTGYAQKFVG**RVTMTRDTSKTTAYLELSGLKSEDTAVYYCAR**SSGSGGTWYKEYFQS**WGQGTMVTVSS
TNF-Y7C VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 28	**NYDIN**
TNF-Y7C VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 28	**WMDPNNGNTGYAQKFVG**
TNF-Y7C VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 28	**KSSGSGGTWYKEYFQS**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
TNF-Y7C VL		**29**	DIVMTQSPLSLPVTPGEPASISC**RSSQSLL HSNGYNYLD**WYLQKPGQFPQLLIY**LGSYRA S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**MQRIEFPPGT**FGQGTKLGIK
TNF-Y7C VL	**CDR-L1**	Residues 24-39 of SEQ ID NO.: 29	**RSSQSLLHSNGYNYLD**
TNF-Y7C VL	**CDR-L2**	Residues 55-61 of SEQ ID NO.: 29	**LGSYRAS**
TNF-Y7C VL	**CDR-L3**	Residues 94 - 103 of SEQ ID NO.: 29	**MQRIEFPPGT**
AE11-7 VH		**30**	EVQLVQSGAEVKKPGASVKVSCKTSGYSLT **QYPIH**WVRQAPGQRPEWMG**WISPGNGNTKL SPKFQG**RVTLSRDASAGTVFMDLSGLTSDD TAVYFCTS**VDLGDH**WGQGTLVTVSS
AE11-7 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 30	**QYPIH**
AE11-7 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 30	**WISPGNGNTKLSPKFQG**
AE11-7 VH	**CDR-H3**	Residues 99-104 of SEQ ID NO.: 30	**VDLGDH**
AE11-7 VL		**31**	DIVMTQSPEFQSVTPKEKVTITC**RASQSIG SSLH**WYQQKPDQSPKLLIN**YASQSFS**GVPS RFSGGGSGTDFTLTINSLEAEDAATYYC**HQ SSNLPIT**FGQGTRLEIK
AE11-7 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 31	**RASQSIGSSLH**
AE11-7 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 31	**YASQSFS**
AE11-7 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 31	**HQSSNLPIT**
AE11-13 VH		**32**	EVQLVESGGGLVQPGRSLRLSCAASGFTFD **DYPMH**WVRQAPGEGLEWVS**GISSNSASIGY ADSVKG**RFTISRDNAQNTLYLQMNSLGDED TAVYYCVS**LTLG**IGQGTLVTVSS
AE11-13 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 32	**DYPMH**
AE11-13 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 32	**GISSNSASIGYADSVKG**
AE11-13 VH	**CDR-H3**	Residues 99-102 of SEQ ID NO.: 32	**LTLG**
AE11-13 VL		**33**	DIRLTQSPSSLSASVGDRVTITC**RASQSIG NYLH**WYQQKPGKAPKLLIY**AASSLQS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ SYSTLYS**FGQGTKLEIK

Protein region		SEQ ID NO:	Sequence
			123456789012345678901234567890
AE11-13 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 33	**RASQSIGNYLH**
AE11-13 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 33	**AASSLQS**
AE11-13 VL	CDR-L3	Residues 89 - 97 of SEQ ID NO.: 33	**QQSYSTLYS**

1.2: Affinity maturation of the fully human anti-human TNF antibody AE11-5

The AE11-5 human antibody to human TNF was affinity matured by in vitro display technology. One light chain library was constructed to contain limited mutagenesis at the following residues: 28, 31, 32, 51, 55, 91, 92, 93, 95a and 96 (Kabat numbering). This library also contained framework germline back-mutations D1E, M4L, H11Q, R49K, H76N and Q103K as well as toggled residues at position 50(R/K) and 94(S/L) to allow for framework germlining during library selections. Two heavy chain libraries were made to contain limited mutagenesis in CDRH1 and CDRH2 at residues 30, 31, 33, 50, 52, and 55 to 58 (Kabat numbering) or in CDRH3 at residues 95 to 100b. The library containing CDRH1 and CDRH2 diversities also had framework germline back-mutations A18V and L64Q and toggled residue at 54(L/F) and 78(V/A). The CDRH3 library has an additional toggled residue at 100c(A/F).

All three libraries were selected separately for the ability to bind human or cynomolgus monkey TNF in the presence of decreasing concentrations of biotinylated human or cynomolgus monkey TNF antigens. All mutated CDR sequences recovered from library selections were recombined into additional libraries and the recombined libraries were subjected to more stringent selection conditions before individual antibodies are identified.

Table 11 provides a list of amino acid sequences of VH regions of affinity matured fully human TNF antibodies derived from AE11-5. Amino acid residues of individual CDRs of each VH sequence are indicated in bold.

Table 11. List of amino acid sequences of affinity matured AE11-5 VH variants

Clone	SEQ ID NO:	VH
J685M2S2-10VH	94	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-12VH	95	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYSIS**WV RQAPGQGLEWMG**GIMPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-13VH	96	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIIPILGSPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-14VH	97	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIIPILGSPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-16VH	98	EVQLVQSGAEVKKPGSSVKVSCKASGGTFA**WYSIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-18VH	99	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**FYAIS**WV RQAPGQGLEWMG**GITPILGAATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-1VH	100	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GITPILGAAVYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-21VH	101	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-23VH	102	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGVAVYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-25VH	103	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-27VH	104	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAHYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-28VH	105	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-29VH	106	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-31VH	107	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYTIS**WV RQAPGQGLEWMG**GIIPILRNPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS

Clone	SEQ ID NO:	VH
J685M2S2-32VH	108	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYAIS**WV RQAPGQGLEWMG**GIMPILGTPTYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-35VH	109	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYTIS**WV RQAPGQGLEWMG**GIIPILGAPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-37VH	110	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-38VH	111	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYSIS**WV RQAPGQGLEWMG**GIMPILGSASYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-43VH	112	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTASYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-44VH	113	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYSIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-45VH	114	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGTATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-46VH	115	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**FYTIS**WV RQAPGQGLEWMG**GIMPILGSPHYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-47VH	116	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-48VH	117	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGSATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-4VH	118	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIIPILGTPTYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-50VH	119	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J685M2S2-51VH	120	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**LYTIS**WV RQAPGQGLEWMG**GIMPILGAPRYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-52VH	121	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYAIS**WV RQAPGQGLEWMG**GIMPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-53VH	122	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GILPILGSPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS

Clone	SEQ ID NO:	VH
J685M2S2-55VH	123	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GIIPILGSPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-56VH	124	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIVPILGAPLYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-58VH	125	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GIMPILGAPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-5VH	126	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYTIS**WV RQAPGQGLEWMG**GIMPILGTPAYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-61VH	127	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYSIS**WV RQAPGQGLEWMG**GITPILGAATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-62VH	128	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIIPILGTPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-63VH	129	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIIPILGTPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-64VH	130	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGIGNYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-66VH	131	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GIVPILGAATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-67VH	132	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSSTYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-68VH	133	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-6VH	134	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNSIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-70VH	135	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-71VH	136	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGTPTYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-72VH	137	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYAIS**WV RQAPGQGLEWMG**GITPILGAANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS

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J685M2S2-73VH	138	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAAIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-75VH	139	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTATYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-76VH	140	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYSIS**WV RQAPGQGLEWMG**GITPILGSAHYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-77VH	141	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNAIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-78VH	142	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILRSAVYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-7VH	143	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYSIS**WV RQAPGQGLEWMG**GIMPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-80VH	144	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTASYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-81VH	145	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTAIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-82VH	146	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPAYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-83VH	147	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**RYAIS**WV RQAPGQGLEWMG**GIIPILGPASYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-84VH	148	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILDAAIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-86VH	149	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGIPNYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-87VH	150	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYAIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-88VH	151	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**YYAIS**WV RQAPGQGLEWMG**GIMPILGTATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-89VH	152	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDPKRADY**WG QGTLVTVSS

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J685M2S2-8VH	153	EVQLVQSGAEVKKPGSSVKVSCKASGGTFN**WYTIS**WV RQAPGQGLEWMG**GIMPILGTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-90VH	154	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDFTRADY**WG QGTLVTVSS
J685M2S2-91VH	155	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIIPILRFPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-92VH	156	EVQLVQSGAEVKKPGSSVKVSCKVSGGTFS**WYSIS**WV RQAPGQGLEWMG**GILPILDTANYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-93VH	157	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGTAVYAQKFQG**RVTITADE STSTAYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J685M2S2-94VH	158	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**IYSIS**WV RQAPGQGLEWMG**GILPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J688M2-11VH	159	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPTRADY**WG QGTLVTVSS
J688M2-13VH	160	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPSRADY**WG QGTLVTVSS
J688M2-14VH	161	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFNPTRADY**WG QGTLVTVSS
J688M2-16VH	162	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPARFDY**WG QGTLVTVSS
J688M2-20VH	163	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYNPSRADY**WG QGTLVTVSS
J688M2-21VH	164	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPKRADY**WG QGTLVTVSS
J688M2-22VH	165	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPRRADY**WG QGTLVTVSS
J688M2-28VH	166	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GFYYDPTRADY**WG QGTLVTVSS
J688M2-29VH	167	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDFTRADY**WG QGTLVTVSS

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J688M2-2VH	168	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYFDPKRADY**WG QGTLVTVSS
J688M2-37VH	169	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDPTRADY**WG QGTLVTVSS
J688M2-3VH	170	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPSRADY**WG QGTLVTVSS
J688M2-46VH	171	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**SLYYERTRADY**WG QGTLVTVSS
J688M2-48VH	172	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**WRFYIPIRFDY**WG QGTLVTVSS
J688M2-4VH	173	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDFTRADY**WG QGTLVTVSS
J688M2-50VH	174	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLFYDPSRADY**WG QGTLVTVSS
J688M2-52VH	175	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPVRADY**WG QGTLVTVSS
J688M2-56VH	176	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPIRADY**WG QGTLVTVSS
J688M2-57VH	177	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J688M2-58VH	178	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYNPIRFDY**WG QGTLVTVSS
J688M2-64VH	179	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDPARADY**WG QGTLVTVSS
J688M2-65VH	180	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVFFDPTRADY**WG QGTLVTVSS
J688M2-68VH	181	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVFYNPTRADY**WG QGTLVTVSS
J688M2-69VH	182	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYEGPSADY**WG QGTLVTVSS

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J688M2-6VH	183	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYAPNRADY**WG QGTLVTVSS
J688M2-73VH	184	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLFYDPTRADY**WG QGTLVTVSS
J688M2-74VH	185	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYNPTRADY**WG QGTLVTVSS
J688M2-75VH	186	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPARADY**WG QGTLVTVSS
J688M2-7VH	187	EVQLVQSGAEVKKSGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPGRADY**WG QGTLVTVSS
J688M2-81VH	188	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDPSRADY**WG QGTLVTVSS
J688M2-82VH	189	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYFDPSRFDY**WG QGTLVTVSS
J688M2-83VH	190	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYFDFTRADY**WG QGTLVTVSS
J688M2-84VH	191	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPTRADY**WG QGTLVTVSS
J688M2-88VH	192	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYFDPSRADY**WG QGTLVTVSS
J688M2-89VH	193	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPSRFDY**WG QGTLVTVSS
J688M2-8VH	194	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GQYYDTSRADY**WG QGTLVTVSS
J688M2-90VH	195	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**SLYYDTTRFDY**WG QGTLVTVSS
J688M2-92VH	196	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVFYDPTRADY**WG QGTLVTVSS
J688M2-94VH	197	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPARADY**WG QGTLVTVSS

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J688M2-95VH	198	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLFYDPRRADY**WG QGTLVTVSS
J688M2-96VH	199	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDTTRADY**WG QGTLVTVSS
J693FRM2S2L-32VH	200	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPARADY**WG QGTLVTVSS
J693FRM2S2L-40VH	201	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCSR**GLYYDPTRADY**WG QGTLVTVSS
J693FRM2S2L-70VH	202	EVQLVQSGAEVMKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCTR**GLYYDPTRADY**WG QGTLVTVSS
J693FRM2S2R-29VH	203	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693FRM2S2R-46VH	204	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCTR**GLYYDPTRADY**WG QGTLVTVSS
J693FRM2S2R-65VH	205	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCTR**GIYYDPTRADY**WG QGTLVTVSS
J693M2S2L-17VH	206	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQEFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-32VH	207	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCVR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-67VH	208	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTASYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-75VH	209	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAK**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-78VH	210	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCER**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-79VH	211	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**NYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2L-94VH	212	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAHKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS

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J693M2S2R-22VH	213	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADC**WG QGTLVTVSS
J693M2S2R-24VH	214	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV QQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2R-2VH	215	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2R-31VH	216	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2R-71VH	217	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYATS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2R-84VH	218	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFLG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J693M2S2R-89VH	219	EVQLVQSGAEVKKPGSSVKVSCKASGGTSS**SYAIS**WV RQAPGQGLEWMG**GIIPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WG QGTLVTVSS
J703M1S3-10VH	220	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPKRADY**WG QGTLVTVSS
J703M1S3-11VH	221	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAASYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPTRADY**WG QGTLVTVSS
J703M1S3-12VH	222	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAASYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPARADY**WG QGTLVTVSS
J703M1S3-13VH	223	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-14VH	224	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGSPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPRRADY**WG QGTLVTVSS
J703M1S3-16VH	225	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-17VH	226	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIVPILGTPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-18VH	227	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPARADY**WG QGTLVTVSS

Clone	SEQ ID NO:	VH
J703M1S3-19VH	228	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-1VH	229	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTPVYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDFRRANY**WG QGTLVTVSS
J703M1S3-20VH	230	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-21VH	231	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGDPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-22VH	232	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDYKRADY**WG QGTLVTVSS
J703M1S3-25VH	233	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLFYDFRRADY**WG QGTLVTVSS
J703M1S3-28VH	234	EVQLVQSGAEVKKPGSSVKVSCKASGGTFA**WYAIS**WV RQAPGQGLEWMG**GITPILGNAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-29VH	235	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-2VH	236	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYATS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDHRRADY**WG QGTLVTVSS
J703M1S3-34VH	237	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDYKRADY**WG QGTLVTVSS
J703M1S3-37VH	238	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-38VH	239	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDFKRADY**WG QGTLVTVSS
J703M1S3-3VH	240	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPRRADY**WG QGTLVTVSS
J703M1S3-41VH	241	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-42VH	242	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAPVYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS

Clone	SEQ ID NO:	VH
J703M1S3-45VH	243	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-46VH	244	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-47VH	245	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGSANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-4VH	246	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-50VH	247	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-51VH	248	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDYRRADY**WG QGTLVTVSS
J703M1S3-53VH	249	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGIPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPARADY**WG QGTLVTVSS
J703M1S3-54VH	250	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-57VH	251	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAVYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-5VH	252	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDYKRADY**WG QGTLVTVSS
J703M1S3-62VH	253	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGYPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-6VH	254	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDFRRADY**WG QGTLVTVSS
J703M1S3-72VH	255	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYPIS**WV RQAPGQGLEWMG**GITPILGSAIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDFRRADY**WG QGTLVTVSS
J703M1S3-78VH	256	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGTANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-79VH	257	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGSAVYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS

Clone	SEQ ID NO:	VH
J703M1S3-7VH	258	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGNPIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPARADY**WG QGTLVTVSS
J703M1S3-81VH	259	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGAPNYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDYTRADY**WG QGTLVTVSS
J703M1S3-83VH	260	EVQLVQSGAEVKKPGSSVKVSCKASGGTFA**WYAIS**WV RQAPGQGLEWMG**GITPILGSPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-86VH	261	EVQLVQSGAEVKKPGSSVKVSCKASGGTFG**WYATS**WV RQAPGQGLEWMG**GIIPILGTPNYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-87VH	262	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGTPTYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDPKRADY**WG QGTLVTVSS
J703M1S3-88VH	263	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYTIS**WV RQAPGQGLEWMG**GIMPILGSPNYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GIYYDPKRADY**WG QGTLVTVSS
J703M1S3-91VH	264	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GIMPILGSATYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYFDPKRADY**WG QGTLVTVSS
J703M1S3-93VH	265	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYAIS**WV RQAPGQGLEWMG**GITPILGAANYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GLYYDPKRADY**WG QGTLVTVSS
J703M1S3-9VH	266	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**WYPIS**WV RQAPGQGLEWMG**GITPILGAGIYAQKFQG**RVTITADE STSTVYMELSSLRSEDTAVYYCAR**GVYYDFKRADY**WG QGTLVTVSS

Table 12 provides a list of amino acid sequences of VL regions of affinity matured fully human TNF antibodies derived from AE11-5. Amino acid residues of individual CDRs of each VH sequence are indicated in bold.

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Table 12. List of amino acid sequences of affinity matured AE11-5 VL variants

Clone	SEQ ID NO:	VL
J685M2S2-17Vk	267	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPPT**FGQGTKVEIK
J685M2S2-94Vk	268	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPPTFGQWTKVEIK**
J688M2-37Vk	269	EIVLTQSPDFQSVTPKEKVTITC**RARQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTNFTLT INSLEAEDAATYYC**HQSSSSPPPT**FGQGTKVEIK
J688M2-90Vk	270	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPPT**FGQGTKVEIK
J693FRM2S2L-26Vk	271	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNRSSPPST**FGQGTKVEIK
J693FRM2S2L-27Vk	272	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPVT**FGQGTKVEIK
J693FRM2S2L-29Vk	273	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSNLPAPT**FGQGTKVEIK
J693FRM2S2L-39Vk	274	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGGSLH**WYQ QKPDQSPKLLIK**YASQSFS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQPICSPPRT**FGQGTKVEIK
J693FRM2S2L-3Vk	275	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSNLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSISPPAT**FGQGTKVEIK
J693FRM2S2L-40Vk	276	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGTSLH**WYQ QKPDQSPKLLIK**YDSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPPPT**FGQGTKVEIK
J693FRM2S2L-42Vk	277	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGNSLH**WYQ QKPDQSPKLLIK**YTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTSSLPLPT**FGQGTKVEIK
J693FRM2S2L-43Vk	278	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQISDLPTST**FGQGTKVEIK
J693FRM2S2L-45Vk	279	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSNLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSLPPPT**FGQGTKVEIK
J693FRM2S2L-46Vk	280	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSSLH**WYQ QKPDQSPKLLIK**HTSQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNSSPLST**FGQGTKVEIK
J693FRM2S2L-47Vk	281	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGGSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSLPLPT**FGQGTKVEIK
J693FRM2S2L-48Vk	282	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSKSPPPT**FGQGTKVEIK
J693FRM2S2L-52Vk	283	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSCLH**WYQ QKPDQSPKLLIK**YASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSLPTPT**FGQGTKVEIK
J693FRM2S2L-53Vk	284	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGGRLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQASSSPSTT**FGQGTKVEIK
J693FRM2S2L-54Vk	285	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGPSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSCLPSTT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J693FRM2S2L-58Vk	286	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**YASQSRS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGISPPTT**FGQGTKVEIK
J693FRM2S2L-59Vk	287	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGMSSPAPT**FGQGTKVEIK
J693FRM2S2L-5Vk	288	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRRNSPPPT**FGQGTKVEIK
J693FRM2S2L-88Vk	289	EIVLTQSPDFQSVTPKEKVTITC**RASQKIGSGLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNNSSPHKT**FGQGTKVEIK
J693FRM2S2L-89Vk	290	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSNLH**WYQ QKPDQSPKLLIK**HSSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPLPT**FGQGTKVEIK
J693FRM2S2L-8Vk	291	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGRSLH**WYQ QKPDQSPKLLIK**YASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPPPT**FGQGTKVEIK
J693FRM2S2L-90Vk	292	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGKSLH**WYQ QKPDQSPKLLIK**HPSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSIGLPPTT**FGQGTKVEIK
J693FRM2S2L-91Vk	293	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSISPPAT**FGQGTKVEIK
J693FRM2S2L-92Vk	294	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**YESQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRCCSPTQT**FGQGTKVEIK
J693FRM2S2L-94Vk	295	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRKLH**WYQ QKPDQSPKLLIK**YSSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRSPPTT**FGQGTKVEIK
J693FRM2S2R-10Vk	296	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGTSLH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPSPT**FGQGTKVEIK
J693FRM2S2R-11Vk	297	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRGSSPPRT**FGQGTKVEIK
J693FRM2S2R-12Vk	298	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSTLH**WYQ QKPDQSPKLLIK**HTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSSPPPT**FGQGTKVEIK
J693FRM2S2R-14Vk	299	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSNLH**WYQ QKPDQSPKLLIK**HGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRHSSPRAT**FGQGTKVEIK
J693FRM2S2R-15Vk	300	EIVLTQSPDFQSVTPKEKVTITC**RASQKIGSNLH**WYQ QKPDQSPKLLIK**YASQSFS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPPAT**FGQGTKVEIK
J693FRM2S2R-16Vk	301	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRSPFRT**FGQGTKVEIK
J693FRM2S2R-34Vk	302	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGRRLH**WYQ QKPDQSPKLLIK**HASQSRS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCTSSPPPT**FGQGTKVEIK
J693FRM2S2R-36Vk	303	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSNLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSLRLPPQT**FGQGTKVEIK
J693FRM2S2R-39Vk	304	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNRSLPRLT**FGQGTKVEIK

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J693FRM2S2R-3Vk	305	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSCLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSSSVASGSGTDFTLT INSLEAEDAATYYC**HQRSSLPQPT**FGQGTKVEIK
J693FRM2S2R-42Vk	306	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRRLH**WYQ QKPDQSPKLLIK**HPSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSIDSPPPT**FGQGTKVEIK
J693FRM2S2R-45Vk	307	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGRSLH**WYQ QKPDQSPKLLIK**YKSQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRWGLPMPT**FGQGTKVEIK
J693FRM2S2R-48Vk	308	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSMLH**WYQ QKPDQSPKLLIK**HSSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTNSLPPRT**FGQGTKVEIK
J693FRM2S2R-50Vk	309	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSRSPLDT**FGQGTKVEIK
J693FRM2S2R-51Vk	310	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGCSLH**WYQ QKPDQSPKLLIK**YASQSVS**VVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSTLPPPT**FGQGTKVEIK
J693FRM2S2R-52Vk	311	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGTSLH**WYQ QKPDQSPKLLIK**HDSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTSSLPPPT**FGQGTKVEIK
J693FRM2S2R-56Vk	312	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPLPT**FGQGTKVEIK
J693FRM2S2R-58Vk	313	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YTSQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGNRSPSTT**FGQGTKVEIK
J693FRM2S2R-59Vk	314	EIVLTQSPDFQSVTPKEKVTITC**RASKRIGSSLH**WYQ QKPDQSPKLLIK**HKSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSASPPPT**FGQGTKVEIK
J693FRM2S2R-5Vk	315	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**HPSQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSTSPPAT**FGQGTKVEIK
J693FRM2S2R-60Vk	316	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSLPTPT**FGQGTKVEIK
J693FRM2S2R-61Vk	317	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**HASQSFS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNCSPAHT**FGQGTKVEIK
J693FRM2S2R-62Vk	318	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSRLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSRLPPPT**FGQGTKVEIK
J693FRM2S2R-63Vk	319	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSTLH**WYQ QKPDQSPKLLIK**HASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSCSPQAT**FGQGTKVEIK
J693FRM2S2R-64Vk	320	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**YPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGRSPPHT**FGQGTKVEIK
J693FRM2S2R-65Vk	321	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSILPPPT**FGQGTKVEIK
J693FRM2S2R-92Vk	322	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSYLH**WYQ QKPDQSPKLLIK**HVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPTLT**FGQGTKVEIK
J693FRM2S2R-93Vk	323	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSMS**GVPSGFSGSGSGTDFTLT INSLEAEDAATYYC**HQTNRSPPPT**FGQGTKVEIK

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J693FRM2S2R-9Vk	324	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGTSLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLN INSLEAEDAATYYC**HQSSCLPRPT**FGQGTKVEIK
J693M2S2L-10Vk	325	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSPLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSSPPPT**FGQGTKVEIK
J693M2S2L-11Vk	326	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**HDSQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSDSPAPT**FGQGTKVEIK
J693M2S2L-12Vk	327	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSCLH**WYQ QKPDQSPKLLIK**HASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRISPLPT**FGQGTKVEIK
J693M2S2L-13Vk	328	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRRLH**WYQ QKPDQSPKLLIK**HSSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSLPHPT**FGQGTKVEIK
J693M2S2L-14Vk	329	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSRLH**WYQ QKPDQSPKLLIK**HASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSCSSPLVT**FGQGTKVEIK
J693M2S2L-16Vk	330	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGSSPQAT**FGQGTKVEIK
J693M2S2L-17Vk	331	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNRGSPPQT**FGQGTKVEIK
J693M2S2L-18Vk	332	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSILH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNTSLPPPT**FGQGTKVEIK
J693M2S2L-19Vk	333	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGNSLH**WYQ QKPDQSPKLLIK**YPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSRLPVPT**FGQGTKVEIK
J693M2S2L-1Vk	334	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HTSQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPAPT**FGQGTKVEIK
J693M2S2L-20Vk	335	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGSSLH**WYQ QKPDQSPKLLIK**HVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNSLPAPT**FGQGTKVEIK
J693M2S2L-21Vk	336	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSMSLPSAT**FGQGTKVEIK
J693M2S2L-22Vk	337	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HLSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQPCRLPPST**FGQGTKVEIK
J693M2S2L-23Vk	338	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSLLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSCSSPRHT**FGQGTKVEIK
J693M2S2L-24Vk	339	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HPSQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRSPAPT**FGQGTKVEIK
J693M2S2L-25Vk	340	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGGSLH**WYQ QKPDQSPKLLIK**YSSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSILPSLT**FGQGTKVEIK
J693M2S2L-26Vk	341	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRNLPPRT**FGQGTKVEIK
J693M2S2L-27Vk	342	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSILH**WYQ QKPDQSPKLLIK**YGSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNGSSPPRT**FGQGTKVEIK

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J693M2S2L-28Vk	343	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YFSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSCLPMQT**FGQGTKVEIK
J693M2S2L-29Vk	344	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGSSLH**WYQ QKPDQSPKLLIK**YSSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSISPPAT**FGQGTKVEIK
J693M2S2L-2Vk	345	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSSLH**WYQ QKPDQSPKLLIK**HASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSTCLPPRT**FGQGTKVEIK
J693M2S2L-30Vk	346	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YVSQSMS**GVLSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQPSTSPRPT**FGQGTKVEIK
J693M2S2L-31Vk	347	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSLPPST**FGQGTKVEIK
J693M2S2L-32Vk	348	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGCSLH**WYQ QKPDQSPKLLIK**YASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPSST**FGQGTKVEIK
J693M2S2L-33Vk	349	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGTSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRSPPRT**FGQGTKVEIK
J693M2S2L-34Vk	350	EIVLTQSPDFQSVTPKEKVTITC**RASQKIGTSLH**WYQ QKPDQSPKLLIK**HESQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSGSPPPT**FGQGTKVEIK
J693M2S2L-35Vk	351	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGGSLH**WYQ QKPDQSPKLLIK**HVSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSISPPPT**FGQGTKVEIK
J693M2S2L-36Vk	352	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSDLH**WYQ QKPDQSPKLLIK**HVSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSCMSPSLT**FGQGTKVEIK
J693M2S2L-37Vk	353	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSNLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPNTT**FGQGTKVEIK
J693M2S2L-38Vk	354	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSILH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGRISPSST**FGQGTKVEIK
J693M2S2L-39Vk	355	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGNRLH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGSLPTLT**FGQGTKVEIK
J693M2S2L-3Vk	356	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**HDSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSLPTHT**FGQGTKVEIK
J693M2S2L-40Vk	357	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGRSLH**WYQ QKPDQSPKLLIK**HGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPPST**FGQGTKVEIK
J693M2S2L-41Vk	358	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNCSSPPPT**FGQGTKVEIK
J693M2S2L-44Vk	359	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YESQSDS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRRNSPPST**FGQGTKVEIK
J693M2S2L-45Vk	360	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGSRLH**WYQ QKPDQSPKLLIK**HGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNRGLPAPT**FGQGTKVEIK
J693M2S2L-46Vk	361	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNHTSPPPT**FGQGTKVEIK

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J693M2S2L-47Vk	362	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGRLPPPT**FGQGTKVEIK
J693M2S2L-4Vk	363	EIVLTQSPDFQSVTPKEKVTITC**RASQYIGKRLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNISPPPT**FGQGTKVEIK
J693M2S2L-51Vk	364	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HESQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPPT**FGQGTKVEIK
J693M2S2L-52Vk	365	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSLPPST**FGQGTKVEIK
J693M2S2L-54Vk	366	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**HPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSSPAQT**FGQGTKVEIK
J693M2S2L-55Vk	367	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**HTSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSLPLPT**FGQGTKVEIK
J693M2S2L-56Vk	368	EIVLTQSPDFQSVTPKEKVTITC**RASQWIGSSLH**WYQ QKPDQSPKLLIK**HTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPQT**FGQGTKVEIK
J693M2S2L-58Vk	369	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**YSSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSSPPPT**FGQGTKVEIK
J693M2S2L-59Vk	370	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRLPPST**FGQGTKVEIK
J693M2S2L-5Vk	371	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNWSLPLPT**FGQGTKVEIK
J693M2S2L-62Vk	372	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGTSLH**WYQ QKPDQSPKLLIK**YASQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSCSPTPT**FGQGTKVEIK
J693M2S2L-64Vk	373	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGGSLH**WYQ QKPDQSPKLLIK**YGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRCVSPSPT**FGQGTKVEIK
J693M2S2L-65Vk	374	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGGTLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPART**FGQGTKVEIK
J693M2S2L-66Vk	375	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCGSSPLHT**FGQGTKVEIK
J693M2S2L-67Vk	376	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**HPSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSTSSPPPT**FGQGTKVEIK
J693M2S2L-68Vk	377	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSGLPLPT**FGQGTKVEIK
J693M2S2L-69Vk	378	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRRLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSSPSPT**FGQGTKVEIK
J693M2S2L-6Vk	379	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGGNLH**WYQ QKPDQSPKLLIK**HESQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPSHT**FGQGTKVEIK
J693M2S2L-70Vk	380	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSSPSHT**FGQGTKVEIK

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J693M2S2L-71Vk	381	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRNSPPTT**FGQGTKVEIK
J693M2S2L-72Vk	382	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSRLH**WYQ QKPDQSPKLLIK**HGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPPPT**FGQGTKVEIK
J693M2S2L-74Vk	383	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGSSLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSLLPAPT**FGQGTKVEIK
J693M2S2L-75Vk	384	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGTTLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSNLPPST**FGQGTKVEIK
J693M2S2L-76Vk	385	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGGNLH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSNLPPPT**FGQGTKVEIK
J693M2S2L-77Vk	386	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGGSLH**WYQ QKPDQSPKLLIK**YASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSACLPTRT**FGQGTKVEIK
J693M2S2L-78Vk	387	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**YASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQIGSLPPPT**FGQGTKVEIK
J693M2S2R-13Vk	388	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSRLPPPT**FGQGTKVEIK
J693M2S2R-14Vk	389	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HNSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSSPPLT**FGQGTKVEIK
J693M2S2R-15Vk	390	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRNLH**WYQ QKPDQSPKLLIK**HVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSRSPPST**FGQGTKVEIK
J693M2S2R-16Vk	391	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSLPAPT**FGQGTKVEIK
J693M2S2R-17Vk	392	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRLPPQT**FGQGTKVEIK
J693M2S2R-18Vk	393	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSRLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRGRLPPRT**FGQGTKVEIK
J693M2S2R-19Vk	394	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSTSLPRLT**FGQGTKVEIK
J693M2S2R-20Vk	395	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPQQT**FGQGTKVEIK
J693M2S2R-21Vk	396	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPPT**FGQGTKVEIK
J693M2S2R-22Vk	397	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGNSLH**WYQ QKPDQSPKLLIK**HGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRRSSPRHT**FGQGTKVEIK
J693M2S2R-27Vk	398	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGRRLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSIGSPPLT**FGQGTKVEIK
J693M2S2R-29Vk	399	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRGLH**WYQ QKPDQSPKLLIK**YGSQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPPT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J693M2S2R-2Vk	400	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGCSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCTSLPLPT**FGQGTKVEIK
J693M2S2R-30Vk	401	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGSSLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSLPTPT**FGQGTKVEIK
J693M2S2R-31Vk	402	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**HASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSRLPPLT**FGQGTKVEIK
J693M2S2R-32Vk	403	EIVLTQSPDFQSVTPKEKVTITC**RASQVIGGVLH**WYQ QKPDQSPKLLIK**YTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPRPT**FGQGTKVEIK
J693M2S2R-33Vk	404	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HSSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSNSPHRT**FGQGTKVEIK
J693M2S2R-36Vk	405	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRTLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSISPQPT**FGQGTKVEIK
J693M2S2R-37Vk	406	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGNTLH**WYQ QKPDQSPKLLIK**YPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGSSPPPT**FGQGTKVEIK
J693M2S2R-39Vk	407	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YISQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSCGLPPPT**FGQGTKVEIK
J693M2S2R-3Vk	408	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGTRLH**WYQ QKPDQSPKLLIK**YGSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRISPPPT**FGQGTKVEIK
J693M2S2R-40Vk	409	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSRLPPPT**FGQGTKVEIK
J693M2S2R-44Vk	410	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSNLPSPT**FGQGTKVEIK
J693M2S2R-45Vk	411	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSNLH**WYQ QKPDQSPKLLIK**HASQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPRPT**FGQGTKVEIK
J693M2S2R-46Vk	412	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSISSPSPT**FGQGTKVEIK
J693M2S2R-47Vk	413	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSFS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNCLPPPT**FGQGTKVEIK
J693M2S2R-48Vk	414	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGKSLH**WYQ QKPDQSPKLLIK**HESQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQANSLPPPT**FGQGTKVEIK
J693M2S2R-4Vk	415	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRRLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSSPPST**FGQGTKVEIK
J693M2S2R-52Vk	416	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGHSLH**WYQ QKPDQSPKLLIK**HASQSIL**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSIKSPPAT**FGQGTKVEIK
J693M2S2R-54Vk	417	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTSLH**WYQ QKPDQSPKLLIK**HTSQSKS**GVPSRFSGSGSGTDFALT INSLEAEDAATYYC**HQSSNSPRYT**FGQGTKVEIK
J693M2S2R-55Vk	418	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSHS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGGSPPWT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J693M2S2R-56Vk	419	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGRSLH**WYQ QKPDQSPKLLIK**YASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSNRSPPPT**FGQGTKVEIK
J693M2S2R-5Vk	420	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTTLH**WYQ QKPDQSPKLLIK**HVSQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPHPT**FGQGTKVEIK
J693M2S2R-60Vk	421	EIVLTQSPDFQSVTPKEKVTITC**RASQIIGSSLH**WYQ QKPDQSPKLLIK**YPSQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSWSSPLMT**FGQGTKVEIK
J693M2S2R-61Vk	422	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGNTLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPPT**FGQGTKVEIK
J693M2S2R-62Vk	423	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGICLH**WYQ QKPDQSPKLLIK**YASQSMS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGFSLPPAT**FGQGTKVEIK
J693M2S2R-63Vk	424	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSCLH**WYQ QKPDQSPKLLIK**YPSQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSCSPTTT**FGQGTKVEIK
J693M2S2R-64Vk	425	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGNTLH**WYQ QKPDQSPKLLIK**YPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGSSPPPT**FGQGTKVEIK
J693M2S2R-65Vk	426	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGTSLH**WYQ QKPDQSPKLLIK**YASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRCSLPPPT**FGQGTKVEIK
J693M2S2R-68Vk	427	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGGSLH**WYQ QKPDQSPKLLIK**YASQSHS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCRISPRPT**FGQGTKVEIK
J693M2S2R-69Vk	428	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HPSQSKS**GVPSRFSGSGSGTDFTLS INSLEAEDAATYYC**HQTSRSPLHT**FGQGTKVEIK
J693M2S2R-6Vk	429	EIVLTQSPDFQSVTPKEKVTITC**RASQNIGKNLH**WYQ QKPDQSPKLLIK**YPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPLST**FGQGTKVEIK
J693M2S2R-70Vk	430	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YMSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRVLPPPT**FGQGTKVEIK
J693M2S2R-71Vk	431	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YGSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSISPRRT**FGQGTKVEIK
J693M2S2R-72Vk	432	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGRSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRKSSPTPT**FGQGTKVEIK
J693M2S2R-75Vk	433	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGRQLH**WYQ QKPDQSPKLLIK**HPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPQT**FGQGTKVEIK
J693M2S2R-77Vk	434	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQICRSPSPT**FGQGTKVEIK
J693M2S2R-78Vk	435	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSGSPAPT**FGQGTKVEIK
J693M2S2R-79Vk	436	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YSSQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQISSSPPPT**FGQGTKVEIK
J693M2S2R-7Vk	437	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGNSLH**WYQ QKPDQSPKLLIK**HASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTMTSPPPT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J693M2S2R-80Vk	438	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPSPT**FGQGTKVEIK
J693M2S2R-81Vk	439	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRRWSPPPT**FGQGTKVEIK
J693M2S2R-82Vk	440	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQISCLPLPT**FGQGTKVEIK
J693M2S2R-83Vk	441	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSISLPPPT**FGQGTKVEIK
J693M2S2R-84Vk	442	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRNLH**WYQ QKPDQSPKLLIK**HTSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTSTLPPQT**FGQGTKVEIK
J693M2S2R-85Vk	443	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGRSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRNSPQPT**FGQGTKVEIK
J693M2S2R-86Vk	444	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGTRLH**WYQ QKPDQSPKLLIK**YVSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSHSPPPT**FGQGTKVEIK
J693M2S2R-87Vk	445	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSCLH**WYQ QKPDQSPKLLIK**HRSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQWSSSPPPT**FGQGTKVEIK
J693M2S2R-89Vk	446	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HPSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTSGSPSHT**FGQGTKVEIK
J693M2S2R-8Vk	447	EIVLTQSPDFQSVTPKEKVTITC**RASQGIGSSLH**WYQ QKPDQSPKLLIK**YESQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPPT**FGQGTKVEIK
J693M2S2R-90Vk	448	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HDSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSSSPPTT**FGQGTKVEIK
J693M2S2R-91Vk	449	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSNLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRISSPPST**FGQGTKVEIK
J693M2S2R-92Vk	450	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSCSSPPST**FGQGTKVEIK
J693M2S2R-93Vk	451	EIVLTQSPDFQSVTPKEKVTITC**RASQTIGSSLH**WYQ QKPDQSPKLLIK**YVSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTISSPLPT**FGQGTKVEIK
J693M2S2R-95Vk	452	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSCSPAHT**FGQGTKVEIK
J703M1S3-11Vk	453	EIVLTQSPDFQSVTPKEKVTITC**RDSRCIGSNLH**WYQ QKPDQSPKLLIK**HASQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCSSSPPPT**FGQGTKVEIK
J703M1S3-13Vk	454	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSTLH**WYQ QKPDQSPKLLIK**HASQSNS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPPPT**FGQGTKVEIK
J703M1S3-16Vk	455	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGDSLH**WYQ QKPDQSPKLLIK**HASQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGSTSPPRT**FGQGTKVEIK
J703M1S3-19Vk	456	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HGSQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSWSSPIPT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J703M1S3-22Vk	457	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSNLPSPT**FGQGTKVEIK
J703M1S3-26Vk	458	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**HASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSGSSPPRT**FGQGTKVEIK
J703M1S3-29Vk	459	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRTSSPVRT**FGQGTKVEIK
J703M1S3-2Vk	460	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGNTLH**WYQ QKPDQSPKLLIK**HVSQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQKVSSPSPT**FGQGTKVEIK
J703M1S3-30Vk	461	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HASQSVS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSRSSPPPT**FGQGTKVEIK
J703M1S3-33Vk	462	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPPST**FGQGTKVEIK
J703M1S3-34Vk	463	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPSTT**FGQGTKVEIK
J703M1S3-57Vk	464	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSSLH**WYQ QKPDQSPKLLIK**HESQSSS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRCTSPSPT**FGQGTKVEIK
J703M1S3-5Vk	465	EIVLTQSPDFQSVTPKEKVTITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**HPSQSDS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNCSLPLPT**FGQGTKVEIK
J703M1S3-62Vk	466	EIVLTQSPDFQSVTPKEKVTITC**RASQCIGSSLH**WYQ QKPDQSPKLLIK**HASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQGISSPPQT**FGQGTKVEIK
J703M1S3-69Vk	467	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HVSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQRSSSPSPT**FGQGTKVEIK
J703M1S3-71Vk	468	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HPSQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSIRLPPST**FGQGTKVEIK
J703M1S3-78Vk	469	EIVLTQSPDFQSVTPKEKVTITC**RANQSIGGSLH**WYQ QKPDQSPKLLIK**HASQSKS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQDSRSPTRT**FGQGTKVEIK
J703M1S3-79Vk	470	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSGLH**WYQ QKPDQSPKLLIK**HTSQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSLPHPT**FGQGTKVEIK
J703M1S3-7Vk	471	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSSSPTPT**FGQGTKVEIK
J703M1S3-81Vk	472	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSRLH**WYQ QKPDQSPKLLIK**YPSQSRS**GVPSRFSGSGSGTDLTLT INSLEAEDAATYYC**HQNGSLPPPT**FGQGTKVEIK
J703M1S3-82Vk	473	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSSLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSSPPPT**FGQGTKVEIK
J703M1S3-86Vk	474	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSALH**WYQ QKPDQSPKLLIK**HASQSLS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQSSILPRPT**FGQGTKVEIK
J703M1S3-90Vk	475	EIVLTQSPDFQSVTPKEKVTITC**RASQSIGSNLH**WYQ QKPDQSPKLLIK**HASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQTRTSPPLT**FGQGTKVEIK

Clone	SEQ ID NO:	VL
J703M1S3-93Vk	476	EIVLTQSPDFQSVTPKEKVTITC**RASQKIGSSLH**WYQ QKPDQSPKLLIK**YGSQSTS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQCISLPTPT**FGQGTKVEIK
J703M1S3-94Vk	477	EIVLTQSPDFQSVTPKEKVAITC**RASQRIGSSLH**WYQ QKPDQSPKLLIK**YASQSIS**GVPSRFSGSGSGTDFTLT INSLEAEDAATYYC**HQNSSLPPPT**FGQGTKVEIK

Table 13. Amino acid residues observed in affinity matured AE11-5 antibodies

AE11-5 Heavy chain variable region (SEQ ID NO: 1073)	
AE11-5VH	1234567890123456789012345678901234567890123456789012a345678901 EVQLVQSGAEVKKPGSSAKVSCKASGGTFS**SYAIS**WVRQAPGQGLEWMG**GIIPILGTANYAQ** V NW TTT WT FRSPI TY SV M TDAST GI P L I NGS AN G V P V F N I H R V A L K R F M L
	2345678901234567890123abc345678901234567890abc1234567890123 **KFLG**RVTIITADESTSTVYMELSSLRSEDTAVYYCAR**GLYYDPTRADY**WGQGTLVTVSS Q A SVFFNTSWF WIVVEFASM TFP TRKP ARH IGRA Q ADI Y V P N G
AE11-5 Light chain variable region (SEQ ID NO: 1074)	
AE11-5VL	12345678901234567890123456789012345678901234567890123456789012345678901 DIVMTQSPDFHSVTPKEKVTITC**RASQSIGSSLH**WYQQKPDQSPKLLIR**HASQSIS**GVPSR E L Q R RR KYV L T TT P V N GN T T I NC G S C KG S M G CI E N K HK D K Y VM F W PL R LY P V
	2345678901234567890123456789012345a67890123456a FSGSGSGTDFTLTIHSLEAEDAATYYC**HQSSSSPPPT**FGQGTQVEIK N RRRL LS K NGI AR GIC SL TCG RT CNN TA ITT QQ MK HH V M

Table 14. Individual VH sequences from converted clones

Protein region		SEQ ID NO:	Sequence
			123456789012345678901234567890
J703M1S3 #2 VH		478	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYATS**WVRQAPGQGLEWMG**GITPILGSPIY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDHRRADY**WGQGTLVTVSS
J703M1S3 #2 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 478	**WYATS**
J703M1S3 #2 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 478	**GITPILGSPIYAQKFQG**
J703M1S3 #2 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 478	**GVYYDHRRADY**
J703M1S3 #13 VH		479	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGAANY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDPKRADY**WGQGTLVTVSS
J703M1S3 #13 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 479	**WYAIS**
J703M1S3 #13 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 479	**GITPILGAANYAQKFQG**
J703M1S3 #13 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 479	**GVYYDPKRADY**
J703M1S3 #26 VH		480	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGTANY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDPKRADY**WGQGTLVTVSS
J703M1S3 #26 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 480	**WYAIS**
J703M1S3 #26 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 480	**GITPILGTANYAQKFQG**
J703M1S3 #26 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 480	**GVYYDPKRADY**
J703M1S3 #30 VH		481	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGSPIY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDPKRADY**WGQGTLVTVSS
J703M1S3 #30 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 481	**WYAIS**
J703M1S3 #30 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 481	**GITPILGSPIYAQKFQG**

Protein region		SEQ ID NO:	Sequence
			12345678901234567890123456789 0
J703M1S3 #30 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 481	**GVYYDPKRADY**
J703M1S3 #33 VH		482	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYPIS**WVRQAPGQGLEWMG**GITPILGAGIY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDFKRADY**WGQGTLVTVSS
J703M1S3 #33 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 482	**WYPIS**
J703M1S3 #33 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 482	**GITPILGAGIYAQKFQG**
J703M1S3 #33 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 482	**GVYYDFKRADY**
J703M1S3 #35 VH		483	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGSATY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GIYYDPKRADY**WGQGTLVTVSS
J703M1S3 #35 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 483	**WYAIS**
J703M1S3 #35 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 483	**GITPILGSATYAQKFQG**
J703M1S3 #35 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 483	**GIYYDPKRADY**
J703M1S3 #38 VH		484	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGTPIY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDFKRADY**WGQGTLVTVSS
J703M1S3 #38 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 484	**WYAIS**
J703M1S3 #38 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 484	**GITPILGTPIYAQKFQG**
J703M1S3 #38 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 484	**GVYYDFKRADY**
J703M1S3 #69 VH		485	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGSPIY** **AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GIYYDPKRADY**WGQGTLVTVSS
J703M1S3 #69 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 485	**WYAIS**
J703M1S3 #69 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 485	**GITPILGSPIYAQKFQG**

Protein region		SEQ ID NO:	Sequence
			1234567890123456789012345678 90
J703M1S3 #69 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 485	**GIYYDPKRADY**
J703M1S3 #90 VH		486	EVQLVQSGAEVKKPGSSVKVSCKASGGTFS **WYAIS**WVRQAPGQGLEWMG**GITPILGSPIY AQKFQG**RVTITADESTSTVYMELSSLRSED TAVYYCAR**GVYYDYKRADY**WGQGTLVTVSS
J703M1S3 #90 VH	CDR-H1	Residues 31-35 of SEQ ID NO.: 486	**WYAIS**
J703M1S3 #90 VH	CDR-H2	Residues 50-66 of SEQ ID NO.: 486	**GITPILGSPIYAQKFQG**
J703M1S3 #90 VH	CDR-H3	Residues 99-109 of SEQ ID NO.: 486	**GVYYDYKRADY**

Table 15. Individual clones VL sequences

Protein region			Sequence
			12345678901234567890123456789 0
J703M1S3 #2 VL		487	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG NTLH**WYQQKPDQSPKLLIK**HVSQSVS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ KVSSPSPT**FGQGTKVEIK
J703M1S3 #2 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 487	**RASQSIGNTLH**
J703M1S3 #2 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 487	**HVSQSVS**
J703M1S3 #2 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 487	**HQKVSSPSPT**
J703M1S3 #13 VL		488	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG STLH**WYQQKPDQSPKLLIK**HASQSNS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ SSSLPPPT**FGQGTKVEI
J703M1S3 #13 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 488	**RASQSIGSTLH**
J703M1S3 #13 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 488	**HASQSNS**
J703M1S3 #13 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 488	**HQSSSLPPPT**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J703M1S3 #26 VL		489	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG SRLH**WYQQKPDQSPKLLIK**HASQSTS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ SGSSPPRT**FGQGTKVEIK
J703M1S3 #26 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 489	**RASQSIGSRLH**
J703M1S3 #26 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 489	**HASQSTS**
J703M1S3 #26 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 489	**HQSGSSPPRT**
J703M1S3 #30 VL		490	EIVLTQSPDFQSVTPKEKVTITC**RASQRIG SSLH**WYQQKPDQSPKLLIK**HASQSVS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ SRSSPPPT**FGQGTKVEIK
J703M1S3 #30 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 490	**RASQRIGSSLH**
J703M1S3 #30 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 490	**HASQSVS**
J703M1S3 #30 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 490	HQSRSSPPPT
J703M1S3 #33 VL		491	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG SSLH**WYQQKPDQSPKLLIK**HASQSTS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ SSSSPPST**FGQGTKVEIK
J703M1S3 #33 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 491	**RASQSIGSSLH**
J703M1S3 #33 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 491	**HASQSTS**
J703M1S3 #33 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 491	**HQSSSSPPST**
J703M1S3 #35 VL		492	EIVLTQSPDFQSVTPKEKVTITC**RASQTIG SSLH**WYQQKPDQSPKLLIK**HASQSIS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ TSSLPTPT**FGQGTKVEIK
J703M1S3 #35 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 492	**RASQTIGSSLH**
J703M1S3 #35 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 492	**HASQSIS**
J703M1S3 #35 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 492	**HQTSSLPTPT**

Protein region			Sequence
			123456789**0**123456789**0**1234567890
J703M1S3 #38 VL		493	EIVLTQSPDFQSVTPKEKVTITC**RASQTIG SSLH**WYQQKPDQSPKLLIK**HASQSIS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ SSSSPPPT**FGQGTKVEIK
J703M1S3 #38 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 493	**RASQTIGSSLH**
J703M1S3 #38 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 493	**HASQSIS**
J703M1S3 #38 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 493	**HQSSSSPPPT**
J703M1S3 #69 VL		494	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG SSLH**WYQQKPDQSPKLLIK**HVSQSLS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ RSSSPSPT**FGQGTKVEIK
J703M1S3 #69 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 494	**RASQSIGSSLH**
J703M1S3 #69 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 494	**HVSQSLS**
J703M1S3 #69 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 494	**HQRSSSPSPT**
J703M1S3 #90 VL		495	EIVLTQSPDFQSVTPKEKVTITC**RASQSIG SNLH**WYQQKPDQSPKLLIK**HASQSIS**GVPS RFSGSGSGTDFTLTINSLEAEDAATYYC**HQ TRTSPPLT**FGQGTKVEIK
J703M1S3 #90 VL	CDR-L1	Residues 24-34 of SEQ ID NO.: 495	**RASQSIGSNLH**
J703M1S3 #90 VL	CDR-L2	Residues 50-56 of SEQ ID NO.: 495	**HASQSIS**
J703M1S3 #90 VL	CDR-L3	Residues 89-98 of SEQ ID NO.: 495	**HQTRTSPPLT**

Table 16. AE11-5 affinity matured scFv clones converted to full length IgG

ScFv clone name	HC plasmid	LC plasmid	Full length IgG (protein) name
J703M1S3#2	pJP368 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#2	pJP369 ; pHybE-hCk V3-J703M1S31#2	AE11-5 AM1
J703M1S3#13	pJP370 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#13	pJP371 ; pHybE-hCk V3-J703M1S3#13	AE11-5 AM2
J703M1S3#26	pJP372 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#26	pJP373 ; pHybE-hCk V3-J703M1S3#26	AE11-5 AM3

J703M1S3#30	pJP374 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#30	pJP375 ; pHybE-hCk V3-J703M1S3#30	AE11-5 AM4
J703M1S3#33	pJP376 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#33	pJP377 ; pHybE-hCk V3-J703M1S3#33	AE11-5 AM5
J703M1S3#35	pJP378 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#35	pJP379 ; pHybE-hCk V3-J703M1S3#35	AE11-5 AM6
J703M1S3#38	pJP382 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#38	pJP383 ; pHybE-hCk V3-J703M1S3#38	AE11-5 AM8
J703M1S3#69	pJP384 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#69	pJP385 ; pHybE-hCk V3-J703M1S3#69	AE11-5 AM9
J703M1S3#90	pJP386 ; pHybE-hCg1,z,non-a,mut(234,235)-J703M1S3#90	pJP387 ; pHybE-hCk V3-J703M1S3#90	AE11-5 AM10

1.3 TNF enzyme-linked immunosorbent assay protocol (ELISA) and assay result

The following protocol is used to characterize the binding of TNF antibodies to biotinylated human or cyno TNF by enzyme-linked immunosorbent assay (ELISA). An ELISA plate was coated with 50 µl per well of goat anti human IgG-Fc at 2µg/ml, overnight at 4°C. The plate was washed 3 times with PBS/Tween. 50µl Mab diluted to 1µg/ml in PBS/ 0.1%BSA was added to appropriate wells and incubated for 1 hour at room temperature (RT). The plate was washed 3 times with PBS/Tween. 50 µl of serial diluted biotin-human TNF was added to appropriate wells and incubated for 1 hour at RT. The plate was washed 3 times with PBS/Tween. 50 µl of streptavidin-HRP diluted 1:10,000 in PBS/0.1% BSA was added to appropriate wells and incubated for 1 hour at RT. The plate was washed 3 times with PBS/Tween. 50 µl of TMB was added to appropriate wells and the reaction was allowed to proceed for 1 minute. The reaction was stopped with 50 µl/ well 2N H_2SO_4 and the absorbance read at 450 nm. Results are shown in Table 17.

Table 17

IgG Name	EC50 in hTNF ELISA(nM)	EC50 in cynoTNF ELISA(nM)
AE11-5-AM1	1.06	2.14
AE11-5-AM2	522.5	>845
AE11-5-AM3	1.57	1.55
AE11-5-AM4	18.32	750.3
AE11-5-AM5	17.7	2.2
AE11-5-AM6	1.37	>720
AE11-5-AM7	10.32	1.26
AE11-5-AM8	250.2	58.58
AE11-5-AM9	16.72	5.29
AE11-5-AM10	0.98	0.28

1.4 TNF neutralization potency of TNF antibodies by L929 bioassay

Human TNF was prepared at Abbott Bioresearch Center (Worcester, Massachusetts, US) and received from the Biologics Pharmacy. Mouse TNF was prepared at Abbott Bioresearch Center and received from the Biologics Pharmacy. Rat TNF was prepared at Abbott Bioresearch Center and received from the Biologics Pharmacy. Rabbit TNF was purchased from R&D Systems. Rhesus/Macaque TNF (rhTNF) was purchased from R&D Systems. Actinomycin was purchased from Sigma Aldrich and resuspended at a stock concentration of 10 mg/mL in DMSO.

Assay Media: 10% FBS (Hyclone#SH30070.03), Gibco reagents: RPMI 1640 (#21870), 2 mM L-glutamine (#25030), 50 units/mL penicillin/ 50 µg/mL streptomycin (#15140), 0.1 mM MEM non-essential amino acids (#11140) and 5.5 X 10^{-5} M 2-mercaptoethanol (#21985-023).

L929 cells were grown to a semi-confluent density and harvested using 0.05% tryspin (Gibco#25300). The cells were washed with PBS, counted, and resuspended at 1E6 cells/mL in assay media containing 4 µg/mL actinomycin D. The cells were seeded in a 96-well plate (Costar#3599) at a volume of 50 µL and 5E4 cells/well. Wells received 50 µL of assay media, bringing the volume to 100 µL.

A test sample was prepared as follows. The test and control IgG proteins were diluted to a 4x concentration in assay media and serial 1:3 dilutions were performed. TNF species were diluted to the following concentrations in assay media: 400 pg/mL huTNF, 200 pg/mL muTNF, 600 pg/mL ratTNF, and 100 pg/mL rabTNF. Antibody sample (200 µL) was added to the TNF (200 µL) in a 1:2 dilution scheme and allowed to incubate for 0.5 hour at room temperature.

To measure huTNF neutralization potency in this assay, the antibody/TNF solution was added to the plated cells at 100 µL for a final concentration at 375 nM – 0.019 nM. The final concentration of TNF was as follows: 100 pg/mL huTNF, 50 pg/mL muTNF, 150 pg/mL ratTNF, and 25 pg/mL rabTNF. The plates were incubated for 20 hours at 37°C, 5% CO_2. To quantitate viability, 100 µL was removed from the wells and 10 µL of WST-1 reagent (Roche cat# 11644807001) was added. Plates were incubated under assay conditions for 3.5 hours, centrifuged at 500 x g, and 75 µL of supernatant transferred to an ELISA plate (Costar cat#3369). The plates were read at OD 420-600 nm on a Spectromax 190 ELISA plate reader. The neutralization potency of selected TNF/IL-17 DVD-Ig binding proteins is shown in Table 18.

Table 18

IgG Name	hu TNF neutralization IC50 (nM)	rhesus TNF neutralization IC50 (nM)
AE11-5 AM1	0.439	0.251
AE11-5 AM2	1.241	0.756
AE11-5 AM3	0.291	0.165

AE11-5 AM4	0.259	0.109
AE11-5 AM5	0.968	0.613
AE11-5 AM6	2.029	0.652
AE11-5 AM7	0.049	0.104
AE11-5 AM8	1.356	3.040
AE11-5 AM9	0.391	0.123
AE11-5 AM10	0.678	0.140

Example 2: Affinity maturation of a humanized anti-human TNF antibody hMAK-195

The mouse anti-human TNF antibody MAK-195 was humanized and affinity-matured to generate a panel of humanized MAK195 variants that have cross-reactivity to cyno-TNF and improved affinity and binding kinetics against both human and cyno TNF.

To improve the affinity of hMAK195 to TNF, hypermutated CDR residues were identified from other human antibody sequences in the IgBLAST database that also shared high identity to germlines VH3-53 and IGKV1-39. The corresponding hMAK195 CDR residues were then subjected to limited mutagenesis by PCR with primers having low degeneracy at these positions to create three antibody libraries in the scFv format. The first library contained mutations at residues 31, 32, 33, 35, 50, 52, 53, 54, 56 and 58 in the VH CDR1 and 2 (Kabat numbering); the second library at residues 95 to 100, 100a, 101, and 102 in VH CDR3; and the third library at residues 28, 30, 31, 32, 50, 53, 92, 93, 94, and 95 in the three VL CDRs. To further increase the identity of hMAK195 to the human germline framework sequences, a binary degeneracy at VH positions 60 (D/A), 61 (S/D), 62 (T/S), 63 (L/V), and 65 (S/G) were introduced into the first library. Also, a binary degeneracy at VL positions 24 (K/R), 33 (V/L), 54 (R/L), 55 (H/Q), 56 (T/S), 91 (H/S) and 96 (F/Y) were introduced into the third library.

These hMAK195 variants were selected against a low concentration of biotinylated TNF for improved on-rate, off-rate, or both were carried out and antibody protein sequences of affinity-modulated hMAK195 were recovered for converting back to IgG for further characterization. All three libraries were selected separately for the ability to bind human or cynomolgus monkey TNF in the presence of decreasing concentrations of biotinylated human or cynomolgus monkey TNF antigens. All mutated CDR sequences recovered from library selections were recombined into additional libraries and the recombined libraries were subjected to more stringent selection conditions before individual antibodies are identified.

Table 19 provides a list of amino acid sequences of VH and VL of the humanized MAK-195 which were subjected to the affinity maturation selection protocol. Amino acid residues of individual CDRs of each VH and VL sequence are indicated in bold.

Table 19. List of amino acid sequences of affinity matured hMAK195 VH variants

Clone	SEQ ID NO:	VH
rHC1_B8	496	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVSIIRGDGSTDYASTLKSRFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_H12	497	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRGDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E1	498	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AYGVN**WVRQAPGK GLEWVS**IIWGDGATDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A2	499	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MISSDGFTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_H6	500	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIAADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_D7	501	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGSTDYASSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D9	502	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRDDGSTDYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A10	503	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HIGVS**WVRQAPGK GLEWVS**MISYAGSTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCARLLHKGPIDYWGQGTLVTVSS
H1+H2_A5	504	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWSDGSTDYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_F8	505	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRADGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D1	506	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**MIRGDGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCARPSHHGLIDNWGQGTLVTVSS
rHC2_C2	507	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**ELGVN**WVRQAPGK GLEWVS**YISDVGSTYYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCARDWHHGRFDYWGQGTLVTVSS
rHC1_G4	508	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIRADGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F3	509	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGFTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCARDWQHGPSVYWGQGTLVTVSS
rHC1_B4	510	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRADGVTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G3	511	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVH**WVRQAPGK GLEWVS**MIGADGYTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D7	512	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MISADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D5	513	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRSDGFTDYADSVKG**RFTISRDNSKNTLYLQMNSLR TEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E4	514	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**EYGVN**WVRQAPGK GLEWVS**IIWHDGSTAYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Clone	SEQ ID NO:	VH
rHC1_E10	515	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**LIRGDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B6	516	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVS**WVRQAPGK GLEWVS**MIWGDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_B7	517	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRDDGSTYYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLGY**WGQGTLVTVSS
H1+H2_G8	518	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWAGGSTAYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_G5	519	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIGADGSTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAREWQYGPLAYWGQGTLVTVSS
H1+H2_F1	520	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIEGDGGTHYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC19	521	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPAAY**WGQGTLVTVSS
H1+H2_A10	522	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAXGK GLEWVS**MISADGTTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_B9	523	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRGDGTTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLGY**WGQGTLVTVSS
H1+H2_F7	524	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HYGVG**WVRQAPGK GLEWVS**MIWGAGSTNYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B1	525	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**SFGVN**WVRQAPGK GLEWVS**MIWADGTTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_H9	526	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**VIGGDGYTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_A12	527	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGX GLEWVS**MISSDGYTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_G8	528	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWSDGSTHYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_B4	529	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**QLGVT**WVRQAPGK GLEWVS**TISDAGSTYYASSVKG**RFTIIRINSKNTLYLQMNSLR AEDTAVYYCAR**DWHHGRFAY**WGQGTLVTVSS
H1+H2_G5	530	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRGDGSTYYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_C6	531	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**MIRDDGSTSYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F5	532	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRGDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_B4	533	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AYGVN**WVRQAPGK GLEWVS**MISGDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_F6	534	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HFGVT**WVRQAPGK GLEWVS**NIWASGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

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rHC1_B6	535	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
H1+H2_A3	536	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVN**WVRQAPGK GLEWVS**VIWGDGSTAYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D10	537	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC18	538	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWSDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-18	539	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC2_E6	540	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIRGDGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D4	541	EVQLVESGGGLVQPGGSLRISCAASGFTFS**AFGVS**WVRQAPGK GLEWVS**MIWGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_F8	542	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DLGVN**WVRQAPGK GLEWVS**TISDIGSTYYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCARDWHNGRFDYWGQGTLVTVSS
rHC1_F10	543	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRGDGFTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C12	544	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C11	545	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HFGVN**WVRQAPGK GLEWVS**IIWGDGSTAYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_C4	546	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVE**WVRQAPGK GLEWVS**KIWADGSTDYADSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_E12	547	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**LIWGDGTTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C4	548	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**YFGVS**WVRQAPGK GLEWVS**MIWGDGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F9	549	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRSDGSTDYADTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_B5	550	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**IIWSDGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
S4-34	551	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_C2	552	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**EFGVN**WVRQAPGK GLEWVS**MIWGNGATDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_F11	553	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWGDGTTAYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_E9	554	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

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H1+H2_B2	555	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWGDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E9	556	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVN**WVRQAXGK GLEWVS**MIWGDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A6	557	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIGSDGFTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_C8	558	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQTPGK GLEWVS**MIRGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C5	559	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVS**WVRQAPGK GLEWVS**QIWGDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_D5	560	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**QLGVT**WVRQAPGK GLEWVS**TISDAGSTYYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWHHGRFAY**WGQGTLVTVSS
rHC1_C7	561	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWQHGPLGY**WGQGTLVTVSS
H1+H2_C3	562	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AYGVH**WVRQAPGK GLEWVS**MIWGDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_G7	563	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGTTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWQHGPIGY**WGQGTLVTVSS
rHC1_A5	564	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGYTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_G9	565	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVE**WVRQAPGK GLEWVS**KIWGDGTTDYADTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E2	566	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIGGEGRTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_C9	567	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NLGVN**WVRQAPGK GLEWVS**MIWDVGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWHHGLFDY**WGQGTLVTVSS
rHC1_G6	568	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIMGDGYTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_C1	569	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRDDGATDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC1_C2	570	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MISGDGYTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_C1	571	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRGDGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B10	572	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVN**WVRQAPGX GLEWVS**MIWADGSTDYASTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E3	573	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AFGVC**WVRQAPGK GLEWVS**MIWADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

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rHC1_H4	574	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRSDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWQHGPEGY**WGQGTLVTVSS
rHC2_A1	575	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G11	576	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIRSDGSTHYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D8	577	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRGDGYTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A3	578	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-31	579	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**GIGADGSTAYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHSGLAY**WGQGTLVTVSS
rHC36	580	EVQLVESGGGLVQPGGSLILSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNFKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC2_G3	581	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRGDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_C10	582	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIAADGSTAYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC14	583	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC1_D4	584	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGSTDYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_D11	585	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IISGDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_E11	586	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DWGVH**WMRQAPGK GLEWVS**TIWDDGSTYYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**HGHHGPFVY**WGQGTLVTVSS
H1+H2_E7	587	EVQLVESGGGLVQPGGSLRLSCAASXFTFS**NFGVN**WVRQAPGK GLEWVS**MIWGDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A8	588	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**VYGVN**WVRQAPGK GLEWVS**MIGDEGSTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**HWHHGAVDY**WGQGTLVTVSS
H1+H2_B9	589	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWADGSTHYADSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
S4-19	590	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVE**WVRQAPGK GLEWVS**GIWADGSTHYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-74	591	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC1_H2	592	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS

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rHC1_E3	593	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGYTSYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC34	594	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPSAY**WGQGTLVTVSS
H1+H2_F2	595	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRADGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D9	596	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGTTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
H1+H2_E6	597	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVH**WVRQAPGK GLEWVS**MIWADGSTVYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_F3	598	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIGSDGSTYYADSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_G11	599	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLGY**WGQGTLVTVSS
H1+H2_D3	600	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWGDGHTAYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B12	601	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWAHGATHYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B11	602	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**LIRDDGSTDYASTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_A8	603	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWGDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
S4-24	604	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTHYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_F11	605	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MISADGYTDYADSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_D10	606	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_D6	607	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIGADGYTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G4	608	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AFGVS**WVRQAPGK GLEWVS**MIWADGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D11	609	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**LIRGDGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_E9	610	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGTTYYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC1_A12	611	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**RISGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Clone	SEQ ID NO:	VH
H1+H2_A2	612	EVQLVESGGGLVQPGGSLRLSCAASGFSFS**NFGVN**WVRQAPGK GLEWVS**MIWADGSTNYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B7	613	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AYGVS**WVRQAPGK GLEWVS**IISADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_H8	614	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_F12	615	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIGADGYTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_E5	616	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRGDGSTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_A11	617	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWGSGATDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D6	618	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MISADGFTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC2_G10	619	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIAADGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_H3	620	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**LIAADGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_F10	621	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIRGDGSTAYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C7	622	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIWGDGNTGYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_A9	623	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_E5	624	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWGDGSTEYADTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC62	625	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
H1+H2_F4	626	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVY**WVRQAPGK GLEWVS**MIWDDGSTEYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_H8	627	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**QLGVT**WVRQAPGK GLEWVS**TISDAGSTYYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**DWHHGRFAY**WGQGTLVTVSS
rHC2_F4	628	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**GPGVN**WVRQAPGK GLEWVS**SIWDDGSTYYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**HSHDGRFDY**WGQGTLVTVSS
S4-50	629	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVE**WVRQAPGK GLEWVS**GIWADGSTHYADTVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
H1+H2_F12	630	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWGEGSTGYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Clone	SEQ ID NO:	VH
rHC1_E6	631	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRDDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F2	632	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIGGDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
H1+H2_G6	633	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DFGVN**WVRQAPGK GLEWVS**MIWADGTTDYDDSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC2_F5	634	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**GISADGSTAYDSSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D6	635	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**SYGVS**WVRQAPGK GLEWVS**LIRGDGSTYYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_A9	636	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVN**WVRQAPGK GLEWVS**MIWGDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_A1	637	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HFGVN**WVRQAPGK GLEWVS**MIWADGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC60	638	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC1_C8	639	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVH**WVRQAPGK GLEWVS**MIAGDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
rHC44	640	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYADTLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_G9	641	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**IIGADGATDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLGY**WGQGTLVTVSS
H1+H2_A6	642	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**GITGDGITAYASTLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G2	643	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MISGDGFTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G7	644	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**NIWGDGSTDYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E10	645	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRADGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_E2	646	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_A4	647	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**AYGVS**WVRQAPGK GLEWVS**MIWRDGSTDYADSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_H3	648	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVH**WVRQAPGK GLEWVS**MIWGDGSTHYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_G1	649	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVH**WVRQAPGK GLEWVS**GISADGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Clone	SEQ ID NO:	VH
H1+H2_E8	650	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HYGVN**WVRQAPGK GLEWVS**MIGGDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_C9	651	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRADGSTDYASSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F7	652	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**VISADGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_F6	653	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIGADGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
rHC22	654	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTDYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC2_G5	655	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIRGDGYTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_C12	656	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HYGVS**WVRQAPGK GLEWVS**VIRADGVTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
rHC3	657	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIWADGSTHYASSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC1_F1	658	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVQ**WVRQAPGK GLEWVS**RINGDGSTDYASTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_E11	659	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIRSDGFTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B8	660	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NFGVN**WVRQAPGK GLEWVS**MIWVDGSTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G1	661	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGK GLEWVS**MIWGDGSTYYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_B3	662	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HYGVS**WVRQAPGK GLEWVS**MIRSDGFTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D2	663	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MITGDGYTDYADTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC1_E12	664	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRADGLTDYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_B5	665	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**LIRSDGSTDYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_D11	666	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGSTDYADSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPLAY**WGQGTLVTVSS
H1+H2_A7	667	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVI**WVRQAPGK GLEWVS**MIGGDGSTYYDSSLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_G3	668	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVN**WVRQAPGK GLEWVS**MIGSDGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Clone	SEQ ID NO:	VH
H1+H2_D5	669	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**YYGVH**WVRQAPGK GLEWVS**GISGEGSTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_D1	670	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRGDGSTYYASSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WVKGTLVTVSS
rHC1_E7	671	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**IIRGDGSTDYASSLKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
rHC1_E11	672	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIRADGTTDYASSVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
S4-55	673	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVT**WVRQAPGK GLEWVS**MIWADGSTDYASTVKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWQHGPVGY**WGQGTLVTVSS
H1+H2_C10	674	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**NYGVS**WVRQAPGK GLEWVS**MIRGDGSTYYADTLKG**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS
H1+H2_G10	675	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**HFGVN**WVRQAPGK GLEWVS**MIWADGSTSYADSVKS**RFTISRDNSKNTLYLQMNSLR AEDTAVYYCAR**EWHHGPVAY**WGQGTLVTVSS

Table 20 provides a list of amino acid sequences of VL regions of affinity matured fully human TNF antibodies derived from hMAK195. Amino acid residues of individual CDRs of each VH sequence are indicated in bold.

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Table 20. List of amino acid sequences of affinity matured hMAK195 VL variants

Clone	SEQ ID NO:	VL
S3_92	676	DIQMTQSPSSLSASVGDRVTITC**RASQKVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYHTPYT**FGQGTKLEIK
S3_79	677	DIQMTQSPSSLSASVGDRVTITC**KASQAVSTEVA**WYQQK PGKAPKLLIY**CASTRQT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQSYSAPYT**FGQGTKLEIK
S3_68	678	DIQMTQSPSSLSASVGDRVTITC**RASQVVSSAVA**WYQQK PGKAPKLLIY**WASKRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_60	679	DIQMTQSPSSLSASVGDRVTITC**RASQAVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S4-63	680	DIQMTQSPSSLSASVGDRVTITC**KASQKVSSALA**WYQQK PGKAPKLLIY**WASALHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRPPFT**FGQGTKLEIK
S3_5	681	DIQMTQSPSSLSASVGDRVTITC**RASQGVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQHYTTPFTFGQGTKLEIK
S3_44	682	DIQMTQSPSSLSASVGDRVTITC**RASQGVSRALA**WYQQK PGKAPKLLIY**WASTLHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRAPFT**FGQGTKLEIK
S3_53	683	DIQMTQSPSSLSASVGDRVTITC**RASQAVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQHYHTPFTFGQGTKLEIK
S3_91	684	DIQMTQSPSSLSASVGDRVTITC**KASQGVSSALA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK

S3_59	685	DIQMTQSPSSLSASVGDRVTITC**KASQGVSSALA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPYT**FGQGTKLEIK
S3_47	686	DIQMTQSPSSLSASVGDRVTITC**KASQWVSSAVA**WYQQK PGKAPKLLIY**WASTRQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRIPFT**FGQGTKLEIK
S3_70	687	DIQMTQSPSSLSASVGDRVTITC**KASQAVSSALA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPYT**FGQGTKLEIK
S3_56	688	DIQMTQSPSSLSASVGDRVTITC**KASQRVSSAVA**WYQQK PGKAPKLLIY**WASTLHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPYT**FGQGTKLEIK
S3_37	689	DIQMTQSPSSLSASVGDRVTITC**KASQGVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYNTPFT**FGQGTKLEIK
S3_36	690	DIQMTQSPSSLSASVGDRVTITC**KASQKVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_67	691	DIQMTQSPSSLSASVGDRVTITC**KASQTVXRAVA**WYQQK PGKAPKLLIY**WASTRQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQSYSTPFT**FGQGTKLEIK
S3_40	692	DIQMTQSPSSLSASVGDRVTITC**RASQRVSSAVA**WSQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYTTPYT**FGQGTKLEIK
S3_73	693	DIQMTQSPSSLSASVGDRVTITC**KASQAVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S4-50	694	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASALHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSSPYT**FGQGTKLEIK
S4-6	695	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_19	696	DIQMTQSPSSLSASVGDRVTITC**KASQKVSSAVA**WYQQK PGKAPKLLIY**WASARHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRSPFT**FGQGTKLEIK
S3_83	697	DIQMTQSPSSLSASVGDRVTITC**RASQAVSTALA**WYQQK PGKAPKLLIY**SASTLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRSPFT**FGQGTKLEIK
S3_78	698	DIQMTQSPSSLSASVGDRVTITC**KASQYVGGAVA**WYQQK PGKAPKLLIY**QASTLQT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHISKPFT**FGQGTKLEIK
S4-19	699	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASTLHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_58	700	DIQMTQSPSSLSASVGDRVTITC**KASQSVNGALA**WYQQK PGKAPKLLIY**RASTRQT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSIPFT**FGQGTKLEIK
S4-31	701	DIQMTQSPSSLSASVGDRVTITC**RASQGVSSALA**WYQQK PGKAPKLLIY**WASALHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSAPFT**FGQGTKLEIK
S3_31	702	DIQMTQSPSSLSASVGDRVTITC**KASQAVSSSVA**WYQQK PGKAPKLLIY**GASTLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYNEPYT**FGQGTKLEIK
S3_13	703	DIQMTQSPSSLSASVGDRVTITC**KASQKVSSAVA**WYQQK PGKAPKLLIY**WASARHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPYT**FGQGTKLEIK
S4-40	704	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFS**FGQGTKLEIK
S3_26	705	DIQMTQSPSSLSASVGDRVTITC**RASQAVSSAVA**WYQQK

		PGKAPKLLIY**WASKRQT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYISPYT**FGQGTKLEIK
S3_33	706	DIQMTQSPSSLSASVGDRVTITC**KASQGVRSALA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQSYSAPYT**FGQGTKLEIK
S3_28	707	DIQMTQSPSSLSASVGDRVTITC**KASQTVSNAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S4-74	708	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_84	709	DIQMTQSPSSLSASVGDRVTITC**KASQPVRSAVA**WYQQK PGKAPKLLIY**SASTRQT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQSYSIPFT**FGQGTKLEIK
S4-54	710	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYKTPFS**FGQGTKLEIK
S3_23	711	DIQMTQSPSSLSASVGDRVTITC**RASQAVSSAVA**WYQQK PGKAPKLLIY**WASSRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_55	712	DIQMTQSPSSLSASVGDRVTITC**KASQTVGRAVA**WYQQK PGKAPKLLIY**WASTRQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQSYSTPFT**FGQGTKLEIK
S4-34	713	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_76	714	DIQMTQSPSSLSASVGDRVTITC**RASQKVSNAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYNSPFT**FGQGTKLEIK
S4-12	715	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYKTPFT**FGQGTKLEIK
S3_86	716	DIQMTQSPSSLSASVGDRVTITC**RASQRVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYTTPYT**FGQGTKLEIK
S3_61	717	DIQMTQSPSSLSASVGDRVTITC**KASQRVSSAVA**WYQQK PGKAPKLLIY**WASNRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_18	718	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSALA**WYQQK PGKAPKLLIY**WASTRQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_72	719	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSALA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRNPFT**FGQGTKLEIK
S3_41	720	DIQMTQSPSSLSASVGDRVTITC**KASQAVSSALA**WYQQK PXKAPKLLIY**WASSRQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S4-24	721	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTLHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S4-17	722	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_90	723	DIQMTQSPSSLSASVGDRVTITC**KASQPVSGAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRASYT**FGQGTKLEIK
S3_87	724	DIQMTQSPSSLSASVGDRVTITC**RASQKVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPYT**FGQGTKLEIK
S3_66	725	DIQMTQSPSSLSASVGDRVTITC**RASQRVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL

		QPEDFATYYC**QQHYTTPYT**FGQGTKLEIK
S4-18	726	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTLHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_4	727	DIQMTQSPSSLSASVGDRVTITC**RASQAVSSAVA**WYQQK PGKAPKLLIY**WASARHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSSPYT**FGQGTKLEIK
S3_64	728	DIQMTQSPSSLSASVGDRVTITC**KASQPVSSAVA**WYQQK PGKAPKLLIY**WASTLHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPFT**FGQGTKLEIK
S3_62	729	DIQMTQSPSSLSASVGDRVTITC**RASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPYT**FGQGTNLEIK
S3_29	730	DIQMTQSPSSLSASVGDIVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRTPYT**FGQGTKLEIK
S3_65	731	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASMRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSSPFT**FGQGTKLEIK
S3_81	732	DIQMTQSPSSLSASVGDRVTITC**KASQTVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYRAPYT**FGQGTKLEIK
S3_39	733	DIQMTQSPSSLSASVGDRVTITC**KASQRVSSALA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_49	734	DIQMTQSPSSLSASVGDRVTITC**RASQLVSNAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSSPFT**FGQGTKLEIK
S3_85	735	DIQMTQSPSSLSASVGDRVTITCRASQLVSSAVAWYQQK PGKAPKLLIY**WASARHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK
S3_82	736	DIQMTQSPSSLSASVGDRVTITC**KASQLVSSAVA**WYQQK PGKAPKLLIY**WASTRHS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYTTPFT**FGQGTKLEIK
S3_93	737	DIQMTQSPSSLSASVGDRVTITC**KASQRVSSAVA**WYQQK PGKAPKLLIY**WASTRHT**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQHYSTPFT**FGQGTKLEIK

Table 21. Amino acid residues observed in affinity matured hMAK-195.

hMAK195 Heavy chain variable region (SEQ ID NO: 1075)	
hMAK195VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**DYGVN**WVRQAPGKGLEWVS**MIWGDGS** **TD** NFS T I RAG T A HLN S V GSE F H YS H L SDA A V IR Q R AEV Y S Y K LVG W N S NY G

	YDSTLKSRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREWHHGPVAYWGQGTLVT VSS ADSV G HSQQRTLDS QLRPASGVF LCLLVQDGC YRYNWAETN DFPYEKW P NDARS R I TYVTP P H PPDDI A AICA I SG C R
hMAK195 Light chain variable region (SEQ ID NO: 1076)	
hMAK195VL	DIQMTQSPSSLSASVGDRVTITC**KASQAVSSAVA**WYQQKPGKAPKLLIY**WASTRHT** G R S RRPL S SLQS V TNT R I T G IGG L L A D NCV C K E T CTS Q A F P KIR G R
	VPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQHYSTPFT**FGQGTKLEIK SNRSTY FGPR DTML GIIQ HCAA S

The tables below provide a list of humanized MAK-195 antibodies that were converted into IgG proteins for characterization.

Table 22. VH sequences of IgG converted clones

Protein region		SEQ ID NO:	**Sequence**
			123456789**0**123456789**0**1234567890
A8 VH		**738**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVN**WVRQAPGKGLEWVS**MIAADGFTDYA** **SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWHHGPVAY**WGQGTLVTVSS
A8 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 738	**NYGVN**
A8 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 738	**MIAADGFTDYASSVKG**
A8 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 738	**EWHHGPVAY**
B5 VH		**739**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**LIRGDGSTDYA** **SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWHHGPVAY**WGQGTLVTVSS
B5 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 739	**NYGVS**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
B5 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 739	**LIRGDGSTDYASSLKG**
B5 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 739	**EWHHGPVAY**
rHC44 VH		**740**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA DTLKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC44 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 740	**NYGVS**
rHC44 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 740	**MIWADGSTHYADTLKS**
rHC44 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 740	**EWQHGPVAY**
rHC22 VH		**741**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTDYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC22 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 741	**NYGVT**
rHC22 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 741	**MIWADGSTDYADTVKG**
rHC22 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 741	**EWQHGPVAY**
rHC81 VH		**742**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA DSVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
rHC81 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 742	**NYGVT**
rHC81 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 742	**MIWADGSTHYADSVKS**
rHC81 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 742	**EWQHGPLAY**
rHC18 VH		**743**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWSDGSTDYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC18 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 743	**NYGVT**
rHC18 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 743	**MIWSDGSTDYASSVKG**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
rHC18 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.: 743	**EWQHGPVAY**
rHC14 VH		**744**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC14 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.: 744	**NYGVT**
rHC14 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.: 744	**MIWADGSTHYASSLKG**
rHC14 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.: 744	**EWQHGPAAY**
rHC3 VH		**745**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC3 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.: 745	**NYGVS**
rHC3 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.: 745	**MIWADGSTHYASSLKG**
rHC3 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.: 745	**EWQHGPVAY**
rHC19 VH		**746**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPAAY**WGQGTLVTVSS
rHC19 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.: 746	**NYGVT**
rHC19 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.: 746	**MIWADGSTHYASSVKG**
rHC19 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.: 746	**EWQHGPAAY**
rHC34 VH		**747**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPSAY**WGQGTLVTVSS
rHC34 VH	**CDR-H1**	Residues 31–35 of SEQ ID NO.: 747	**NYGVT**
rHC34 VH	**CDR-H2**	Residues 50–65 of SEQ ID NO.: 747	**MIWADGSTHYASSVKG**
rHC34 VH	**CDR-H3**	Residues 98 – 106 of SEQ ID NO.: 747	**EWQHGPSAY**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
rHC83 VH		**748**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
rHC83 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 748	**NYGVT**
rHC83 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 748	**MIWADGSTHYASSVKG**
rHC83 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 748	**EWQHGPVAY**
S4-19 VH		**749**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-19 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 749	**NYGVE**
S4-19 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 749	**GIWADGSTHYADTVKS**
S4-19 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 749	**EWQHGPVAY**
S4-50 VH		**750**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS
S4-50 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 750	**NYGVE**
S4-50 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 750	**GIWADGSTHYADTVKS**
S4-50 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 750	**EWQHGPVGY**
S4-63 VH		**751**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVE**WVRQAPGKGLEWVS**GIWADGSTHYA DTVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS
S4-63 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 751	**NYGVE**
S4-63 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 751	**GIWADGSTHYADTVKS**
S4-63 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 751	**EWQHGPVGY**
S4-55 VH		**752**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTDYA STVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVGY**WGQGTLVTVSS

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-55 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 752	**NYGVT**
S4-55 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 752	**MIWADGSTDYASTVKG**
S4-55 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 752	**EWQHGPVGY**
S4-6 VH		**753**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-6 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 753	**NYGVT**
S4-6 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 753	**MIWADGSTHYASSVKG**
S4-6 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 753	**EWQHGPVAY**
S4-18 VH		**754**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA DSVKS**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-18 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 754	**NYGVT**
S4-18 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 754	**MIWADGSTHYADSVKS**
S4-18 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 754	**EWQHGPLAY**
S4-31 VH		**755**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVQ**WVRQAPGKGLEWVS**GIGADGSTAYA SSLKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHSGLAY**WGQGTLVTVSS
S4-31 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 755	**NYGVQ**
S4-31 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 755	**GIGADGSTAYASSLKG**
S4-31 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 755	**EWQHSGLAY**
S4-34 VH		**756**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVS**WVRQAPGKGLEWVS**MIWADGSTHYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-34 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 756	**NYGVS**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-34 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 756	**MIWADGSTHYADTVKG**
S4-34 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 756	**EWQHGPLAY**
S4-74 VH		**757**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA DTVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPLAY**WGQGTLVTVSS
S4-74 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 757	**NYGVT**
S4-74 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 757	**MIWADGSTHYADTVKG**
S4-74 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 757	**EWQHGPLAY**
S4-12 VH		**758**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-12 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 758	**NYGVT**
S4-12 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 758	**MIWADGSTHYASSVKG**
S4-12 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 758	**EWQHGPVAY**
S4-54 VH		**759**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-54 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 759	**NYGVT**
S4-54 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 759	**MIWADGSTHYASSVKG**
S4-54 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 759	**EWQHGPVAY**
S4-17 VH		**760**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-17 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 760	**NYGVT**
S4-17 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 760	**MIWADGSTHYASSVKG**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-17 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 760	**EWQHGPVAY**
S4-40 VH		**761**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-40 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 761	**NYGVT**
S4-40 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 761	**MIWADGSTHYASSVKG**
S4-40 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 761	**EWQHGPVAY**
S4-24 VH		**762**	EVQLVESGGGLVQPGGSLRLSCAASGFTFS **NYGVT**WVRQAPGKGLEWVS**MIWADGSTHYA SSVKG**RFTISRDNSKNTLYLQMNSLRAEDT AVYYCAR**EWQHGPVAY**WGQGTLVTVSS
S4-24 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 762	**NYGVT**
S4-24 VH	**CDR-H2**	Residues 50-65 of SEQ ID NO.: 762	**MIWADGSTHYASSVKG**
S4-24 VH	**CDR-H3**	Residues 98 - 106 of SEQ ID NO.: 762	**EWQHGPVAY**

Table 23. VL sequences of IgG converted clones

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
hMAK195 VL.1 VL		**763**	DIQMTQSPSSLSASVGDRVTITC**KASQAVS SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPFT**FGQGTKLEIKR
hMAK195 VL.1 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 763	**KASQAVSSAVA**
hMAK195 VL.1 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 763	**WASTRHT**
hMAK195 VL.1 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 763	**QQHYSTPFT**
S4-24 VL		**764**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-24 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 764	**RASQLVSSAVA**
S4-24 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 764	**WASTLHT**
S4-24 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 764	**QQHYRTPFT**
S4-40 VL		**765**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFS**FGQGTKLEIKR
S4-40 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 765	**RASQLVSSAVA**
S4-40 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 765	**WASTRHS**
S4-40 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 765	**QQHYRTPFS**
S4-17 VL		**766**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-17 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 766	**RASQLVSSAVA**
S4-17 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 766	**WASTRHS**
S4-17 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 766	**QQHYRTPFT**
S4-54 VL		**767**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYKTPFS**FGQGTKLEIKR
S4-54 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 767	**RASQLVSSAVA**
S4-54 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 767	**WASARHT**
S4-54 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 767	**QQHYKTPFS**
S4-12 VL		**768**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYKTPFT**FGQGTKLEIKR
S4-12 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 768	**RASQLVSSAVA**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-12 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 768	**WASARHT**
S4-12 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 768	**QQHYKTPFT**
S4-74 VL		**769**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASARHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-74 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 769	**RASQLVSSAVA**
S4-74 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 769	**WASARHT**
S4-74 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 769	**QQHYRTPFT**
S4-34 VL		**770**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-34 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 770	**RASQLVSSAVA**
S4-34 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 770	**WASTRHT**
S4-34 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 770	**QQHYRTPFT**
S4-31 VL		**771**	DIQMTQSPSSLSASVGDRVTITC**RASQGVS SALA**WYQQKPGKAPKLLIY**WASALHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSAPFT**FGQGTKLEIKR
S4-31 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 771	**RASQGVSSALA**
S4-31 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 771	**WASALHS**
S4-31 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 771	**QQHYSAPFT**
S4-18 VL		**772**	DIQMTQSPSSLSASVGDRVTITC**RASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPFT**FGQGTKLEIKR
S4-18 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 772	**RASQLVSSAVA**
S4-18 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 772	**WASTLHS**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-18 VL	**CDR-L3**	Residues 89 – 97 of SEQ ID NO.: 772	**QQHYSTPFT**
S4-6 VL		**773**	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTRHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPFT**FGQGTKLEIKR
S4-6 VL	**CDR-L1**	Residues 24–34 of SEQ ID NO.: 773	**KASQLVSSAVA**
S4-6 VL	**CDR-L2**	Residues 50–56 of SEQ ID NO.: 773	**WASTRHT**
S4-6 VL	**CDR-L3**	Residues 89 – 97 of SEQ ID NO.: 773	**QQHYSTPFT**
S4-55 VL		**774**	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-55 VL	**CDR-L1**	Residues 24–34 of SEQ ID NO.: 774	**KASQLVSSAVA**
S4-55 VL	**CDR-L2**	Residues 50–56 of SEQ ID NO.: 774	**WASTLHT**
S4-55 VL	**CDR-L3**	Residues 89 – 97 of SEQ ID NO.: 774	**QQHYRTPFT**
S4-63 VL		**775**	DIQMTQSPSSLSASVGDRVTITC**KASQKVS SALA**WYQQKPGKAPKLLIY**WASALHS**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRPPFT**FGQGTKLEIKR
S4-63 VL	**CDR-L1**	Residues 24–34 of SEQ ID NO.: 775	**KASQKVSSALA**
S4-63 VL	**CDR-L2**	Residues 50–56 of SEQ ID NO.: 775	**WASALHS**
S4-63 VL	**CDR-L3**	Residues 89 – 97 of SEQ ID NO.: 775	**QQHYRPPFT**
S4-50 VL		776	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASALHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSSPYT**FGQGTKLEIKR
S4-50 VL	**CDR-L1**	Residues 24–34 of SEQ ID NO.: 776	**KASQLVSSAVA**
S4-50 VL	**CDR-L2**	Residues 50–56 of SEQ ID NO.: 776	**WASALHT**
S4-50 VL	**CDR-L3**	Residues 89 – 97 of SEQ ID NO.: 776	**QQHYSSPYT**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
S4-19 VL		777	DIQMTQSPSSLSASVGDRVTITC**KASQLVS SAVA**WYQQKPGKAPKLLIY**WASTLHT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYRTPFT**FGQGTKLEIKR
S4-19 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 777	**KASQLVSSAVA**
S4-19 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 777	**WASTLHT**
S4-19 VL	**CDR-L3**	Residues 89 - 97 of SEQ ID NO.: 777	**QQHYRTPFT**

Table 24. Heavy and light chain pairs of hMAK195 affinity matured clones

Clone name	HC	LC	Protein name
A8	hMAK195-A8	hMAK195 VL.1	hMAK195-AM11
B5	hMAK195-B5	hMAK195 VL.1	hMAK195-AM13
rHC3	hMAK195 rHC3	hMAK195 VL.1	hMAK195-AM14
rHC18	hMAK195 rHC18	hMAK195 VL.1	hMAK195-AM15
rHC19	hMAK195 rHC19	hMAK195 VL.1	hMAK195-AM16
rHC22	hMAK195 rHC22	hMAK195 VL.1	hMAK195-AM17
rHC34	hMAK195 rHC34	hMAK195 VL.1	hMAK195-AM18
rHC60	hMAK195 rHC60	hMAK195 VL.1	hMAK195-AM19
S4-6	hMAK195 S4-6	hMAK195 S4-6	hMAK195-AM20
S4-12	hMAK195 S4-12	hMAK195 S4-12	hMAK195-AM21
S4-17	hMAK195 S4-17	hMAK195 S4-17	hMAK195-AM22
S4-18	hMAK195 S4-18	hMAK195 S4-18	hMAK195-AM23
S4-19	hMAK195 S4-19	hMAK195 S4-19	hMAK195-AM24
S4-24	hMAK195 S4-24	hMAK195 S4-24	hMAK195-AM25
S4-34	hMAK195 S4-34	hMAK195 S4-34	hMAK195-AM26

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2.1 TNF enzyme-linked immunosorbent assay result

Table 25

IgG Name	EC50 in hTNFa ELISA (nM)
hMAK195-AM11	0.2
hMAK195-AM13	0.2
hMAK195-AM14	0.051
hMAK195-AM15	0.052
hMAK195-AM16	0.056
hMAK195-AM17	0.056
hMAK195-AM18	0.052
hMAK195-AM19	0.057
hMAK195-AM20	0.043

hMAK195-AM21	0.042
hMAK195-AM22	0.052
hMAK195-AM23	0.055
hMAK195-AM24	0.053
hMAK195-AM25	0.052
hMAK195-AM26	0.061

2.2 TNF neutralization potency of TNF antibodies by L929 bioassay

Table 26

IgG Name	hu TNF neutralization IC50 (nM)	rhesus TNF neutralization IC50 (nM)
hMAK195-AM11	0.259	>25
hMAK195-AM13	1.218	4.64
hMAK195-AM14	0.0401	4.61
hMAK195-AM15	0.036	>150
hMAK195-AM16	0.0105	0.803
hMAK195-AM17	0.0031	>25
hMAK195-AM18	0.0145	0.4412
hMAK195-AM19	0.0126	1.206
hMAK195-AM20	0.0037	0.596
hMAK195-AM21	0.009	0.09
hMAK195-AM22	0.00345	0.2705
hMAK195-AM23	0.0468	2.627
hMAK195-AM24	0.015	0.557
hMAK195-AM25	0.0114	0.262
hMAK195-AM26	0.0061	0.2495

Example 3: Affinity maturation of a humanized anti-human TNF antibody hMAK-199

The mouse anti-human TNF antibody MAK-199 was humanized and affinity-matured to generate a panel of humanized MAK195 variants that have improved affinity and binding kinetics against both human and cyno TNF. Several libraries were made according to specifications below:

Three HC libraries were made after the V2I back-mutation was first introduced and confirmed that it did not impact scFv affinity to TNF.

H1+H2 (DDK) library:

- Limited mutagenesis at 7 residues (T30, N31, N35, T52a, T54, E56, T58)
- Germline toggle: M34I and F63L

H1+H2 (QKQ) library:

- Limited mutagenesis at 7 residues (T30, N31, N35, T52a, T54, E56, T58)
- Germline toggle: M34I and F63L
- Germline back-mutations: D61Q, D62K, K64Q, F67V, F69M, L71T

H3 library:

- Limited mutagenesis at 12 residues 95-100, 100a-100f

- Germline toggle: F91Y

LC library: library

- Limited mutagenesis at 11 residues 28, 30-32, 50, 53, 91-94, 96

- Germline toggles: T51A, Y71F, F87Y, and T43A/V44P (these two co-evolve)

Recombined libraries:

VH libraries will be recombined with and without VL library after library diversity is reduced after at least 3 rounds of selection.

All four libraries were selected separately for the ability to bind human or cynomolgus monkey TNF in the presence of decreasing concentrations of biotinylated human or cynomolgus monkey TNF antigens. All mutated CDR sequences recovered from library selections were recombined into additional libraries and the recombined libraries were subjected to more stringent selection conditions before individual antibodies are identified.

Table 27 provides a list of amino acid sequences of VH of the hMAK-199 antibody which were subjected to the affinity maturation selection protocol. Amino acid residues of individual CDRs of each VH sequence are indicated in bold.

Table 27. List of amino acid sequences of affinity matured hMAK199 VH variants

Clone	SEQ ID NO:	VH
J644M2S1-10VH	778	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**DYGIT**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-11VH	779	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-12VH	780	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIS**WVRQ APGQGLEWMG**WINTYTGEPHYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-13VH	781	EVQLVQSGAEVKKPGASVKVSCKASGYTFD**NYGIQ**WVRQ APGQGLEWMG**WINTYTGAPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-14VH	782	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIN**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-15VH	783	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGMN**WVRQ APGQGLEWMG**WINTYTGESTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-16VH	784	EVQLVQSGAEVKKPGASVKVSCKASGYTFK**NYGMT**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J644M2S1-17VH	785	EVQLVQSGAEVKKPGASVKVSCKASGYAFT**DYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-18VH	786	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPAYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-1VH	787	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-22VH	788	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-23VH	789	EVQLVQSGAEVKKPGASVKVSCKASGYTFK**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-24VH	790	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-25VH	791	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-27VH	792	EVQLVQSGAEVKKPGASVKVSCKASGYTFK**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-28VH	793	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-2VH	794	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIX**WVRQ APGQGLEWMG**WINTYXGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-31VH	795	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPHYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-33VH	796	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**HYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-34VH	797	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**HYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-35VH	798	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIT**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-36VH	799	EVQLVQSGAEVKKPGASVKVSCKASGYTFG**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J644M2S1-37VH	800	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGRPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-38VH	801	EVQLVQSGAEVKKPGASVKVSCKASGYTFK**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPHYAQGFTG**RVTMTTDTSTST AYIELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-3VH	802	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-40VH	803	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-41VH	804	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIG**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-43VH	805	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-44VH	806	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIA**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-45VH	807	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPHYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-46VH	808	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIX**WVRQ APGQGLEWMG**WINTYTGEPXYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-47VH	809	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-48VH	810	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-4VH	811	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIT**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-50VH	812	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPQYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-51VH	813	EVQLVQSGAEVKKPGASVKVSCKASGYTFQ**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-53VH	814	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**QYGIN**WVRQ APGQGLEWMG**WINTYTGDPHYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

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J644M2S1-54VH	815	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGLPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-55VH	816	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYNGKPMYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-56VH	817	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**NYGIT**WVRQ APGQGLEWMG**WINTYTGEPAYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-59VH	818	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**HYGIN**WVRQ APGQGLEWMG**WINTYTGRPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-5VH	819	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-60VH	820	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-64VH	821	EVQLVQSGAEVKKPGASVKVSCKASGYTFD**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-65VH	822	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**DYGII**WVRQ APGQGLEWMG**WINTYTGKPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-66VH	823	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-67VH	824	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**NYGMN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-68VH	825	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPSYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-6VH	826	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-71VH	827	EVQLVQSGAEVKKPGASVKVSCKASGYTFD**HYGMN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-72VH	828	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIG**WVRQ APGQGLEWMG**WINTYTGKPSYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-73VH	829	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

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J644M2S1-74VH	830	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGMN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-75VH	831	EVQLVQSGAEVKKPGASVKVSCKASGYTFD**NYGMN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-76VH	832	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**SYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-77VH	833	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIT**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-79VH	834	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYNGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-7VH	835	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGII**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-81VH	836	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-82VH	837	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**DYGIQ**WVRQ APGQGLEWMG**WINTYTGRPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-83VH	838	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIS**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-84VH	839	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIQ**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-85VH	840	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-87VH	841	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYSGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-88VH	842	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-8VH	843	EVQLVQSGAEVKKPGASVKVSCKASGYTFP**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-90VH	844	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGKTNYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

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J644M2S1-91VH	845	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPNYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-92VH	846	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIT**WVRQ APGQGLEWMG**WINTYTGEPHYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-93VH	847	EVQLVQSGAEVKKPGASVKVSCKASGYTFK**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-94VH	848	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGIPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-95VH	849	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-96VH	850	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYSGVPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J644M2S1-9VH	851	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2-11VH	852	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFWRTVVGTDNAMDY**WGQG TTVTVSS
J647M2-12VH	853	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYSTTVVVTDYAMDY**WGQG TTVTVSS
J647M2-13VH	854	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDSAMDY**WGQG TTVTVSS
J647M2-15VH	855	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFMTTMAVTDFAMDY**WGQG TTVTVSS
J647M2-16VH	856	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLTTVVATDNAMDY**WGQG TTVTVSS
J647M2-17VH	857	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVIVTDNAMDY**WGQG TTVTVSS
J647M2-19VH	858	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFFTPVVVTDNAMDY**WGQG TTVTVSS
J647M2-1VH	859	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLMTTVVVTDHAMDY**WGQG TTVTVSS

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J647M2-20VH	860	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KYLTTVVVTDSAMDY**WGQG TTVTVSS
J647M2-21VH	861	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFRSSVAVTDNAMDY**WGQG TTVTVSS
J647M2-22VH	862	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLFTTVVVTDSAMDY**WGQG TTVTVSS
J647M2-23VH	863	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYLMPVVVTDYAMDY**WGQG TTVTVSS
J647M2-24VH	864	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KLLDAVMVTDYAMDY**WGQG TTVTVSS
J647M2-26VH	865	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVVVNDYAMDY**WGQG TTVTVSS
J647M2-44VH	866	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLTTVAVTDYAMDY**WGQG TTVTVSS
J647M2-45VH	867	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLKTVVATDDAMDY**WGQG TTVTVSS
J647M2-47VH	868	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLNTAVVTDYAMDY**WGQG TTVTVSS
J647M2-48VH	869	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**RFLTTVDVTDNAMDY**WGQG TTVTVSS
J647M2-4VH	870	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYLTPVVATDFAMDY**WGQG TTVTVSS
J647M2-51VH	871	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KCMTTIVETDNAMDY**WGQG TTVTVSS
J647M2-52VH	872	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFMNTVDVTDNAMDY**WGQG TTVTVSS
J647M2-53VH	873	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLFTTVVVTDDAMDY**WGQG TTVTVSS
J647M2-54VH	874	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLMTTVVVTDYAMDY**WGQG TTVTVSS

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J647M2-55VH	875	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLPTVVVTDYAMDY**WGQG TTVTVSS
J647M2-56VH	876	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KLLTTVVVTDNAMDY**WGQG TTVTVSS
J647M2-58VH	877	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KILTTVVVTDNAMDY**WGQG TTVTVSS
J647M2-70VH	878	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KVMATEVVTDYAMDY**WGQG TTVTVSS
J647M2-71VH	879	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLVTTVVVTDYAMDY**WGQG TTVTVSS
J647M2-72VH	880	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFRKPVSVTDYAMDY**WGQG TTVTVSS
J647M2-73VH	881	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLWTTVVVTDNAMDY**WGQG TTVTVSS
J647M2-74VH	882	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLTPVVVTDYAMDY**WGQG TTVTVSS
J647M2-75VH	883	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFRTTVVETDYCMDY**WGQG TTVTVSS
J647M2-76VH	884	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYFTTVAVTDYAMDY**WGQG TTVTVSS
J647M2-78VH	885	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**RFLTTVEVTDLAMDY**WGQG TTVTVSS
J647M2-79VH	886	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLRTEVMTDYAMDY**WGQG TTVTVSS
J647M2-7VH	887	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLSTVAVTDSAMDY**WGQG TTVTVSS
J647M2-80VH	888	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KVLNTVVVTDYAMDY**WGQG TTVTVSS
J647M2-83VH	889	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFMNTAMVTDYAMDY**WGQG TTVTVSS

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J647M2-84VH	890	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFSTTVVVTDYAMDY**WGQG TTVTVSS
J647M2-85VH	891	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYFTTVVVTDYAMDY**WGQG TTVTVSS
J647M2-86VH	892	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLNTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-12VH	893	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFMPTVVETDYAMDY**WGQG TTVTVSS
J647M2S1-13VH	894	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGNPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-14VH	895	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**DYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-15VH	896	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVVVTDCAMDY**WGQG TTVTVSS
J647M2S1-17VH	897	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-18VH	898	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVVVTDNAMDY**WGQG TTVTVSS
J647M2S1-19VH	899	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLNTVVGTDYAMDY**WGQG TTVTVSS
J647M2S1-21VH	900	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KLLTTEAVTDYAMDY**WGQG TTVTVSS
J647M2S1-22VH	901	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KYSTPVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-23VH	902	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-26VH	903	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KCLNTVAVTEHRMDY**WGQG TTVTVSS
J647M2S1-28VH	904	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVVHTDYAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J647M2S1-30VH	905	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-31VH	906	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-32VH	907	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-33VH	908	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFRTTVVLTDSAMDY**WGQG TTVTVSS
J647M2S1-35VH	909	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-36VH	910	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFQTPVVDTDYAMDY**WGQG TTVTVSS
J647M2S1-39VH	911	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFMKTRVVTDNAMDY**WGQG TTVTVSS
J647M2S1-40VH	912	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIV**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-41VH	913	EVQLVQSGAEVKKPGASVKVSCKASGYTFP**NYGIS**WVRQ APGQGLEWMG**WINTYTGEPSYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-43VH	914	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPSYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-45VH	915	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**KYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-47VH	916	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KYLTTVVATDYAMDY**WGQG TTVTVSS
J647M2S1-48VH	917	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLNTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-65VH	918	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTPVVVTDCAMDY**WGQG TTVTVSS
J647M2S1-66VH	919	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPRYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J647M2S1-67VH	920	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**DYGIN**WVRQ APGQGLEWMG**WINTYTGLPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-69VH	921	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFWTTIVVTDYAMDY**WGQG TTVTVSS
J647M2S1-6VH	922	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KLLTTVSATDNAMDY**WGQG TTVTVSS
J647M2S1-70VH	923	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLNTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-72VH	924	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**DYGIN**WVRQ APGQGLEWMG**WINTYNGEPSYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-75VH	925	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**TYGIA**WVRQ APGQGLEWMG**WINTYSGVPKYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-76VH	926	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFRTTAVPTDNAMDY**WGQG TTVTVSS
J647M2S1-77VH	927	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFLTTVVNTDSAMDY**WGQG TTVTVSS
J647M2S1-78VH	928	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDYWGRG TTVTVSS**
J647M2S1-79VH	929	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLKTRVVTDYAMDY**WGQG TTVTVSS
J647M2S1-7VH	930	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-80VH	931	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLTTVVATDYAMDY**WGQG TTVTVSS
J647M2S1-84VH	932	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-85VH	933	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPTYAQGFTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-87VH	934	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFFPTMVVTDYAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J647M2S1-88VH	935	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KFVTTMVVTDYAMDY**WGQG TTVTVSS
J647M2S1-8VH	936	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYAQGLTG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFLTTVVVTDYAMDY**WGQG TTVTVSS
J647M2S1-92VH	937	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYFCAR**KLLTTIVATDNAMDY**WGQG TTVTVSS
J647M2S1-93VH	938	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLMSTVVETDNAMDY**WGQG TTVTVSS
J647M2S1-94VH	939	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLFTVVQTDYAMDY**WGQG TTVTVSS
J647M2S1-96VH	940	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQ APGQGLEWMG**WINTYTGEPTYADDFKG**RFTFTLDTSTST AYMELSSLRSEDTAVYYCAR**KLLNTVVDTDYAMDY**WGQG TTVTVSS
J662M2S3-14VH	941	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGII**WVRQ APGQGLEWMG**WINTYTGEPHYAQKLQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFTVEDVTDCAMDY**WGQG TTVTVSS
J662M2S3-18VH	942	EVQLVQSGAEVKKPGASVKVSCKASGYTFD**NYGMN**WVRQ APGQGLEWMG**WINTYNGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFLVEAVTDYAMDY**WGQG TTVTVSS
J662M2S3-28VH	943	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFTTVDVTDNAMDY**WGQG TTVTVSS
J662M2S3-29VH	944	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYTGVPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFNTVDVTDNAMDY**WGQG TTVTVSS
J662M2S3-30VH	945	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYTGEPHYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFKTMAVTDAAMDY**WGQG TTVTVSS
J662M2S3-34VH	946	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFRNTVAVTDYAMDY**WGQG TTVTVSS
J662M2S3-3VH	947	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFNTVAVTDNAMDY**WGQG TTVTVSS
J662M2S3-41VH	948	EVQLVQSGAEVKKPGASVKVSCKASGYTFT**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFFTEDVTDYAMDY**WGQG TTVTVSS
J662M2S3-45VH	949	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGIN**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KFFTPVVVTDNAMDY**WGQG TTVTVSS

Clone	SEQ ID NO:	VH
J662M2S3-55VH	950	EVQLVQSGAEVKKPGASVKVSCKASGYTFR**NYGIT**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFTTMDVTDNAMDY**WGQG TTVTVSS
J662M2S3-5VH	951	EVQLVQSGAEVKKPGASVKVSCKASGYTFA**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFTTMDVTDNAMDY**WGQG TTVTVSS
J662M2S3-65VH	952	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQKLQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFNTVDVTDNAMDY**WGQG TTVTVSS
J662M2S3-78VH	953	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGII**WVRQ APGQGLEWMG**WINTYTGKPSYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFNTVDVTDNAMDY**WGQG TTVTVSS
J662M2S3-84VH	954	EVQLVQSGAEVKKPGASVKVSCKASGYTFS**NYGIN**WVRQ APGQGLEWMG**WINTYTGQPSYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KLFKTEAVTDYAMDY**WGQG TTVTVSS
J662M2S3-87VH	955	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYSGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYFCAR**KLFTTMDVTDNAMDY**WGQG TTVTVSS
J662M2S3-96VH	956	EVQLVQSGAEVKKPGASVKVSCKASGYTFN**NYGII**WVRQ APGQGLEWMG**WINTYTGKPTYAQKFQG**RVTMTTDTSTST AYMELSSLRSEDTAVYYCAR**KFFTTMAVTDNAMDY**WGQG TTVTVSS

Table 28 provides a list of amino acid sequences of VL regions of affinity matured fully human TNF antibodies derived from hMAK199. Amino acid residues of individual CDRs of each VL sequence are indicated in bold.

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Table 28. List of amino acid sequences of affinity matured hMAK199 VL variants

Clone	SEQ ID NO:	VL
J644M2S1-11Vk	957	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J644M2S1-73Vk	958	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2-11Vk	959	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKTVKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-10Vk	960	DIQMTQSPSSLSASVGDRVTITC**RASQDIWNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNRYPPT**FGQGTKLEIK
J647M2S1-16Vk	961	DIQMTQSPSSLSASVGDRVTITC**RASQDICTYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNSPPPT**FGQGTKLEIK
J647M2S1-1Vk	962	DIQMTQSPSSLSASVGDRVTITC**RASQAIGNYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-20Vk	963	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL

		QPEDFATYFC**QQGNTRPPT**FGQGTKLEIK
J647M2S1-24Vk	964	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSLLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTGPPT**FGQGTKLEIK
J647M2S1-25Vk	965	DIQMTQSPSSLSASVGDRVTITC**RASQDIYNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-29Vk	966	DIQMTQSPSSLSASVGDRVTITC**RASQDISHYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPAT**FGQGTKLEIK
J647M2S1-2Vk	967	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQK PGKTVKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTPPPT**FGQGTKLEIK
J647M2S1-34Vk	968	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-37Vk	969	DIQMTQSPSSLSASVGDRVTITC**RASQEISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTMPTT**FGQGTKLEIK
J647M2S1-38Vk	970	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**FASRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTPPTT**FGQGTKLEIK
J647M2S1-3Vk	971	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPST**FGQGTKLEIK
J647M2S1-42Vk	972	DIQMTQSPSSLSASVGDRVTITC**RASQVISNTLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNALPPT**FGQGTKLEIK
J647M2S1-44Vk	973	DIQMTQSPSSLSASVGDRVTITC**RASQDISTYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTPPPT**FGQGTKLEIK
J647M2S1-46Vk	974	DIQMTQSPSSLSASVGDRVTITC**RASQDISQYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-50Vk	975	DIQMTQSPSSLSASVGDRVTITC**RASQDITNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTAPPT**FGQGTKLEIK
J647M2S1-52Vk	976	DIQMTQSPSSLSASVGDRVTITC**RASQGISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK
J647M2S1-56Vk	977	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-59Vk	978	DIQMTQSPSSLSASVGDRVTITC**RASQDISKYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTRPPT**FGQGTKLEIK
J647M2S1-71Vk	979	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSLLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTQPPT**FGQGTKLEIK
J647M2S1-74Vk	980	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNSQPPT**FGQGTKLEIK
J647M2S1-78Vk	981	DIQMTQSPSSLSASVGDRVTITC**RASQDISKYLN**WYQQK PGKAPKLLIY**NASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J647M2S1-7Vk	982	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSLLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNIWPPT**FGQGTKLEIK
J647M2S1-9Vk	983	DIQMTQSPSSLSASVGDRVTITC**RASQDISHYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK

J652M2S1-10Vk	984	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTFPPT**FGQGTKLEIK
J652M2S1-13Vk	985	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-14Vk	986	DIQMTQSPSSLSASVGDRVTITC**RASQDISNVLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-15Vk	987	DIQMTQSPSSLSASVGDRVTITC**RASQDIYKYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTMPPT**FGQGTKLEIK
J652M2S1-17Vk	988	DIQMTQSPSSLSASVGDRVTITC**RASQEIFSYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNMGPPT**FGQGTKLEIK
J652M2S1-18Vk	989	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-1Vk	990	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTWPPT**FGQGTKLEIK
J652M2S1-22Vk	991	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTRPPT**FGQGTKLEIK
J652M2S1-23Vk	992	DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTFPPT**FGQGTKLEIK
J652M2S1-25Vk	993	DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTRPPT**FGQGTKLEIK
J652M2S1-26Vk	994	DIQMTQSPSSLSASVGDRVTITC**RASQDINNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-27Vk	995	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YASGLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J652M2S1-28Vk	996	DIQMTQSPSSLSASVGDRVTITC**RASQDISRYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-29Vk	997	DIQMTQSPSSLSASVGDRVTITC**RASQDIATYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK
J652M2S1-31Vk	998	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTFPPT**FGQGTKLEIK
J652M2S1-33Vk	999	DIQMTQSPSSLSASVGDRVTITC**RASQRIGNYLN**WYQQK PGKTVKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-34Vk	1000	DIQMTQSPSSLSASVGDRVTITC**RASQEISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNSQPPT**FGQGTKLEIK
J652M2S1-35Vk	1001	DIQMTQSPSSLSASVGDRVTITC**RASQDIANYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-37Vk	1002	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTFPPT**FGQGTKLEIK
J652M2S1-38Vk	1003	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-3Vk	1004	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK

		PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTPPPT**FGQGTKLEIK
J652M2S1-40Vk	1005	DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-41Vk	1006	DIQMTQSPSSLSASVGDRVTITC**RASQDIGNFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTRPPT**FGQGTKLEIK
J652M2S1-42Vk	1007	DIQMTQSPSSLSASVGDRVTITC**RASQDITNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTPPPT**FGQGTKLEIK
J652M2S1-45Vk	1008	DIQMTQSPSSLSASVGDRVTITC**RASQDISDYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNMWPPT**FGQGTKLEIK
J652M2S1-47Vk	1009	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK
J652M2S1-48Vk	1010	DIQMTQSPSSLSASVGDRVTITC**RASQDISHYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-49Vk	1011	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK
J652M2S1-51Vk	1012	DIQMTQSPSSLSASVGDRVTITC**RASQDISQYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTRPPT**FGQGTKLEIK
J652M2S1-52Vk	1013	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNMRPPT**FGQGTKLEIK
J652M2S1-53Vk	1014	DIQMTQSPSSLSASVGDRVTITC**RASQDISTYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-55Vk	1015	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTGPPT**FGQGTKLEIK
J652M2S1-56Vk	1016	DIQMTQSPSSLSASVGDRVTITC**RASQNINNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK
J652M2S1-57Vk	1017	DIQMTQSPSSLSASVGDRVTITC**RASQDISKYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTPPPT**FGQGTKLEIK
J652M2S1-61Vk	1018	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTVPPT**FGQGTKLEIK
J652M2S1-62Vk	1019	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSKLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNIFPPT**FGQGTKLEIK
J652M2S1-64Vk	1020	DIQMTQSPSSLSASVGDRVTITC**RASQGIYNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-67Vk	1021	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-69Vk	1022	DIQMTQSPSSLSASVGDRVTITC**RASQEISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTGPPT**FGQGTKLEIK
J652M2S1-6Vk	1023	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTPPPT**FGQGTKLEIK
J652M2S1-71Vk	1024	DIQMTQSPSSLSASVGDRVTITC**RASQDISDYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL

		QPEDFATYYC**QQGNTWPPT**FGQGTKLEIK
J652M2S1-73Vk	1025	DIQMTQSPSSLSASVGDRVTITC**RASQDIWKYLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-75Vk	1026	DIQMTQSPSSLSASVGDRVTITC**RASQDISTYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTWPPT**FGQGTKLEIK
J652M2S1-77Vk	1027	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTPPPT**FGQGTKLEIK
J652M2S1-78Vk	1028	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNAPPPT**FGQGTKLEIK
J652M2S1-79Vk	1029	DIQMTQSPSSLSASVGDRVTITC**RASQDIYKFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-80Vk	1030	DIQMTQSPSSLSASVGDRVTITC**RASQDIFNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-82Vk	1031	DIQMTQSPSSLSASVGDRVTITC**RASQDISNTLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTLPPT**FGQGTKLEIK
J652M2S1-84Vk	1032	DIQMTQSPSSLSASVGDRVTITC**RASQHISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-86Vk	1033	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNMPPPT**FGQGTKLEIK
J652M2S1-87Vk	1034	DIQMTQSPSSLSASVGDRVTITC**RASQDITNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTVPPT**FGQGTKLEIK
J652M2S1-8Vk	1035	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**FTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGNTQPPT**FGQGTKLEIK
J652M2S1-90Vk	1036	DIQMTQSPSSLSASVGDRVTITC**RASQDISKFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYYC**QQGNTRPPT**FGQGTKLEIK
J652M2S1-91Vk	1037	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTFPPT**FGQGTKLEIK
J652M2S1-92Vk	1038	DIQMTQSPSSLSASVGDRVTITC**RASQDIYNVLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGITLPPT**FGQGTKLEIK
J652M2S1-93Vk	1039	DIQMTQSPSSLSASVGDRVTITC**RASQHISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J652M2S1-95Vk	1040	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTQPST**FGQGTKLEIK
J652M2S1-9Vk	1041	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3-13Vk	1042	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNSWPPT**FGQGTKLEIK
J662M2S3-15Vk	1043	DIQMTQSPSSLSASVGDRVTITC**RASQDIYNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3-21Vk	1044	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTWPPT**FGQGTKLEIK

J662M2S3-22Vk	1045	DIQMTQSPSSLSASVGDRVTITC**RASQDISQYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3-34Vk	1046	DIQMTQSPSSLSASVGDRVTITC**RASQDIYDVLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYYC**QQGITLPPT**FGQGTKLEIK
J662M2S3-3Vk	1047	DIQMTQSPSSLSASVGDRVTITC**RASQDIENYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3-41Vk	1048	DIQMTQSPSSLSASVGDRVTITC**RASQNIENFLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3-56Vk	1049	DIQMTQSPSSLSASVGDRVTITC**RASQDIYNYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTPPPT**FGQGTKLEIK
J662M2S3-64Vk	1050	DIQMTQSPSSLSASVGDRVTITC**RASQDIASYLN**WYQQK PGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3-78Vk	1051	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQK PGKVPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSL QPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3-84Vk	1052	DIQMTQSPSSLSASVGDRVTITC**RASQNIYNVLN**WYQQK PGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSL QPEDFATYFC**QQGNTMPPT**FGQGTKLEIK

Table 29. Amino acid residues observed in affinity matured hMAK-199 antibodies

MAK199 Heavy chain variable region (SEQ ID NO: 1077)	
MAK 199VH.2 a	12345678901234567890123456789012345678901234567890123456789012a345678901 **EI**QLVQSGAEVKKPGASVKVSCKASGYTFT**NYGMN**WVRQAPGQGLEWMG**WINTYTGEPTYAD** V ND II N K S Q AH T S V H ST Q Q N RS S R M DQ G L K KK A S A P V N R Q I Q M D D G A E
	23456789012345678901 2abc345678901234567890abcdefg1234567890123 **DFKG**R**F**T**F**T**L**DTSTSTAYMEL**S**SLRS**E**DTAVY**F**CAR**KFLTTVVVTDYAMDY**WGQGTTVTVSS GLT V M T Y RLFNPMDASENT K Q NYMKVEAEM SR IRSSAEMN CC VSRARSD H CWL IMG D QP QII I VF GPQ F ND D P V GM N L CA L A H

Mak199 Light chain variable region (SEQ ID NO: 1078)	
Mak199Vk.1a	1234567890123456789012345678901234567890123456789012345678901 DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQKPGK**TV**KLLIY**YTSRLQS**GVPSR N YQV AP FA L E ESF V N K H AKT G G TT V WH R GD A NR F C
	23456789012345678901234567890123456789012345678901234567890123456a FSGSGSGTD**Y**TLTISSLQPEDFATY**F**C**QQGNTLPPT**FGQGTKLEIK F Y ISW T MQ S IP A AM RR F G V Y A

Table 30. Individual hMAK-199 VH sequences from converted clones

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3 #10 **VH**		**1053**	EVQLVQSGAEVKKPGASVKVSCKASGYTFA **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY** **AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 10 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1053	**NYGII**
J662M2S3# 10 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1053	**WINTYTGKPTYAQKFQG**
J662M2S3# 10 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1053	**RASQDISQYLN**
J662M2S3# 13 **VH**		**1054**	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY** **AQKLQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFNTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3# 13 **VH**	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1054	**NYGII**
J662M2S3# 13 **VH**	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1054	**WINTYTGKPTYAQKLQG**
J662M2S3# 13 **VH**	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1054	**KLFNTVDVTDNAMD**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#15 VH		**1055**	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGVPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFNTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3#15 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1055	**NYGII**
J662M2S3#15 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1055	**WINTYTGVPTYAQKFQG**
J662M2S3#15 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1055	**KLFNTVDVTDNAMD**
J662M2S3#16 VH		**1056**	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFNTVAVTDNAMD**YWGQGTTV TVSS
J662M2S3#16 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1056	**NYGII**
J662M2S3#16 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1056	**WINTYTGKPTYAQKFQG**
J662M2S3#16 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1056	**KLFNTVAVTDNAMD**
J662M2S3#21 VH		**1057**	EVQLVQSGAEVKKPGASVKVSCKASGYTFR **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTVDVTDNAMD**YWGQGTTV TVSS
J662M2S3#21 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1057	**NYGII**
J662M2S3#21 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1057	**WINTYTGKPTYAQKFQG**
J662M2S3#21 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1057	**KLFTTVDVTDNAMD**
J662M2S3#34 VH		**1058**	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGIN**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KFRNTVAVTDYAMD**YWGQGTTV TVSS
J662M2S3#34 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1058	**NYGIN**
J662M2S3#34 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1058	**WINTYTGKPTYAQKFQG**
J662M2S3#34 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1058	**KFRNTVAVTDYAMD**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#36 VH		**1059**	EVQLVQSGAEVKKPGASVKVSCKASGYTFR **NYGIT**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3#36 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1059	**NYGIT**
J662M2S3#36 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1059	**WINTYTGKPTYAQKFQG**
J662M2S3#36 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1059	**KLFTTMDVTDNAMD**
J662M2S3#45 VH		**1060**	EVQLVQSGAEVKKPGASVKVSCKASGYTFA **NYGII**WVRQAPGQGLEWMG**WINTYTGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3#45 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1060	**NYGII**
J662M2S3#45 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1060	**WINTYTGKPTYAQKFQG**
J662M2S3#45 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1060	**KLFTTMDVTDNAMD**
J662M2S3#58 VH		**1061**	EVQLVQSGAEVKKPGASVKVSCKASGYTFS **NYGIN**WVRQAPGQGLEWMG**WINTYTGQPSY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYYCAR**KLFKTEAVTDYAMD**YWGQGTTV TVSS
J662M2S3#58 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1061	**NYGIN**
J662M2S3#58 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1061	**WINTYTGQPSYAQKFQG**
J662M2S3#58 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1061	**KLFKTEAVTDYAMD**
J662M2S3#72 VH		**1062**	EVQLVQSGAEVKKPGASVKVSCKASGYTFN **NYGII**WVRQAPGQGLEWMG**WINTYSGKPTY AQKFQG**RVTMTTDTSTSTAYMELSSLRSED TAVYFCAR**KLFTTMDVTDNAMD**YWGQGTTV TVSS
J662M2S3#72 VH	**CDR-H1**	Residues 31-35 of SEQ ID NO.: 1062	**NYGII**
J662M2S3#72 VH	**CDR-H2**	Residues 50-66 of SEQ ID NO.: 1062	**WINTYSGKPTYAQKFQG**
J662M2S3#72 VH	**CDR-H3**	Residues 99-112 of SEQ ID NO.: 1062	**KLFTTMDVTDNAMD**

Table 31. Individual hMAK-199 clones VL sequences

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#10 VL		**1063**	DIQMTQSPSSLSASVGDRVTITC**RASQDISQYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3#10 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1063	**RASQDISQYLN**
J662M2S3#10 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1063	**YTSRLQS**
J662M2S3#10 VL	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1063	**QQGNTWPPT**
J662M2S3#13 VL		**1064**	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSLQPEDFATYFC**QQGNSWPPT**FGQGTKLEIK
J662M2S3#13 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1064	**RASQDISNYLN**
J662M2S3#13 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1064	**YTSRLQS**
J662M2S3#13 VL	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1064	**QQGNSWPPT**
J662M2S3#15 VL		**1065**	DIQMTQSPSSLSASVGDRVTITC**RASQDIYNYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSLQPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3#15 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1065	**RASQDIYNYLN**
J662M2S3#15 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1065	**YTSRLQS**
J662M2S3#15 VL	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1065	**QQGNTQPPT**
J662M2S3#16 VL		**1066**	DIQMTQSPSSLSASVGDRVTITC**RASQDIENYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGNTQPPT**FGQGTKLEIK
J662M2S3#16 VL	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1066	**RASQDIENYLN**
J662M2S3#16 VL	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1066	**YTSRLQS**
J662M2S3#16 VL	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1066	**QQGNTQPPT**

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#21 **VL**		**1067**	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSLQPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3#21 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1067	**RASQDISNYLN**
J662M2S3#21 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1067	**YTSRLQS**
J662M2S3#21 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1067	**QQGNTWPPT**
J662M2S3#34 **VL**		**1068**	DIQMTQSPSSLSASVGDRVTITC**RASQDIYDVLN**WYQQKPGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGITLPPT**FGQGTKLEIK
J662M2S3#34 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1068	**RASQDIYDVLN**
J662M2S3#34 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1068	**YASRLQS**
J662M2S3#34 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1068	**QQGITLPPT**
J662M2S3#36 **VL**		**1069**	DIQMTQSPSSLSASVGDRVTITC**RASQDISNYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDYTLTISSLQPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3#36 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1069	**RASQDISNYLN**
J662M2S3#36 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1069	**YTSRLQS**
J662M2S3#36 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1069	**QQGNTWPPT**
J662M2S3#45 **VL**		**1070**	DIQMTQSPSSLSASVGDRVTITC**RASQDISQYLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGNTWPPT**FGQGTKLEIK
J662M2S3#45 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1070	**RASQDISQYLN**
J662M2S3#45 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1070	**YTSRLQS**
J662M2S3#45 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1070	**QQGNTWPPT**
J662M2S3#58 **VL**		**1071**	DIQMTQSPSSLSASVGDRVTITC**RASQNIYNVLN**WYQQKPGKAPKLLIY**YASRLQS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGNTMPPT**FGQGTKLEIK

Protein region		SEQ ID NO:	Sequence
			123456789**0**123456789**0**1234567890
J662M2S3#58 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1071	**RASQNIYNVLN**
J662M2S3#58 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1071	**YASRLQS**
J662M2S3#58 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1071	**QQGNTMPPT**
J662M2S3#72 **VL**		**1072**	DIQMTQSPSSLSASVGDRVTITC**RASQDIS NFLN**WYQQKPGKAPKLLIY**YTSRLQS**GVPS RFSGSGSGTDYTLTISSLQPEDFATYFC**QQ GNTQPPT**FGQGTKLEIK
J662M2S3#72 **VL**	**CDR-L1**	Residues 24-34 of SEQ ID NO.: 1072	**RASQDISNFLN**
J662M2S3#72 **VL**	**CDR-L2**	Residues 50-56 of SEQ ID NO.: 1072	**YTSRLQS**
J662M2S3#72 **VL**	**CDR-L3**	Residues 89-97 of SEQ ID NO.: 1072	**QQGNTQPPT**

Table 32. hMAK199 affinity matured scFv clones converted to full length IgG

ScFv clone name	HC plasmid	LC plasmid	Full length IgG (protein) name
J662M2S3#10	pHybE-hCg1,z,non-a V2 J662M2S3#10	pHybE-hCk V3 J662 M2S3#10	hMAK199-AM1
J662M2S3#13	pHybE-hCg1,z,non-a V2 J662M2S3#13	pHybE-hCk V3 J662 M2S3#13	hMAK199-AM2
J662M2S3#15	pHybE-hCg1,z,non-a V2 J662M2S3#15	pHybE-hCk V3 J662 M2S3#15	hMAK199-AM3
J662M2S3#16	pHybE-hCg1,z,non-a V2 J662M2S3#16	pHybE-hCk V3 J662 M2S3#16	hMAK199-AM4
J662M2S3#21	pHybE-hCg1,z,non-a V2 J662M2S3#21	pHybE-hCk V3 J662 M2S3#21	hMAK199-AM5
J662M2S3#34	pHybE-hCg1,z,non-a V2 J662M2S3#34	pHybE-hCk V3 J662 M2S3#34	hMAK199-AM6
J662M2S3#36	pHybE-hCg1,z,non-a V2 J662M2S3#36	pHybE-hCk V3 J662 M2S3#36	hMAK199-AM7
J662M2S3#45	pHybE-hCg1,z,non-a V2 J662M2S3#45	pHybE-hCk V3 J662 M2S3#45	hMAK199-AM8
J662M2S3#58	pHybE-hCg1,z,non-a V2 J662M2S3#58	pHybE-hCk V3 J662 M2S3#58	hMAK199-AM9
J662M2S3#72	pHybE-hCg1,z,non-a V2 J662M2S3#72	pHybE-hCk V3 J662 M2S3#72	hMAK199-AM10

5 **3.1 TNF enzyme-linked immunosorbent assay result**

Table 33. hMAK199 affinity matured full length IgG

IgG Name	EC50 in hTNFa ELISA(nM)
hMAK199-AM1	0.016
hMAK199-AM2	0.016
hMAK199-AM3	0.019
hMAK199-AM4	0.050
hMAK199-AM5	0.078
hMAK199-AM6	0.035
hMAK199-AM7	0.100
hMAK199-AM8	0.219
hMAK199-AM9	0.032
hMAK199-AM10	0.014

3.2 TNF neutralization potency of TNF antibodies by L929 bioassay

Table 34

IgG Name	hu TNF neutralization IC50 (nM)	rhesus TNF neutralization IC50 (nM)
hMAK199-AM1	0.054	0.012
hMAK199-AM2	0.029	0.010
hMAK199-AM3	0.051	0.019
hMAK199-AM4	0.028	0.005
hMAK199-AM5	0.087	0.020
hMAK199-AM6	0.033	0.004
hMAK199-AM7	0.095	0.051
hMAK199-AM8	0.247	0.204
hMAK199-AM9	0.163	0.089
hMAK199-AM10	0.048	0.034

Example 4

Example 4.4: Affinity Determination Using BIACORE Technology

Table 35: Reagent for Biacore Analyses

Antigen	Vendor Designation	Vendor	Catalog #
TNFα	Recombinant Human TNF-α/TNFSF1A	R&D systems	210-TA

BIACORE Methods:

The BIACORE assay (Biacore, Inc. Piscataway, NJ) determines the affinity of binding proteins with kinetic measurements of on-rate and off-rate constants. Binding of binding proteins to a target antigen (for example, a purified recombinant target antigen) is determined by surface plasmon resonance-based measurements with a Biacore® 1000 or 3000 instrument (Biacore® AB, Uppsala, Sweden) using running HBS-EP (10 mM HEPES [pH 7.4], 150 mM NaCl, 3 mM EDTA, and 0.005% surfactant P20) at 25°C. All chemicals are obtained from Biacore® AB (Uppsala, Sweden) or otherwise from a different source as described in the text. For example, approximately 5000 RU of goat anti-mouse IgG, (Fcγ), fragment specific

polyclonal antibody (Pierce Biotechnology Inc, Rockford, Ill., US) diluted in 10 mM sodium acetate (pH 4.5) is directly immobilized across a CM5 research grade biosensor chip using a standard amine coupling kit according to manufacturer's instructions and procedures at 25 µg/ml. Unreacted moieties on the biosensor surface are blocked with ethanolamine. Modified carboxymethyl dextran surface in flowcell 2 and 4 is used as a reaction surface. Unmodified carboxymethyl dextran without goat anti-mouse IgG in flow cell 1 and 3 is used as the reference surface. For kinetic analysis, rate equations derived from the 1:1 Langmuir binding model are fitted simultaneously to association and dissociation phases of all eight injections (using global fit analysis) with the use of Biaevaluation 4.0.1 software. Purified antibodies are diluted in HEPES-buffered saline for capture across goat anti-mouse IgG specific reaction surfaces. Antibodies to be captured as a ligand (25 µg/ml) are injected over reaction matrices at a flow rate of 5 µl/minute. The association and dissociation rate constants, k_{on} ($M^{-1}s^{-1}$) and k_{off} (s^{-1}), are determined under a continuous flow rate of 25 µl/minute. Rate constants are derived by making kinetic binding measurements at different antigen concentrations ranging from 10 - 200 nM. The equilibrium dissociation constant (M) of the reaction between antibodies and the target antigen is then calculated from the kinetic rate constants by the following formula: $K_D = k_{off}/k_{on}$. Binding is recorded as a function of time and kinetic rate constants are calculated. In this assay, on-rates as fast as 10^6 $M^{-1}s^{-1}$ and off-rates as slow as 10^{-6} s^{-1} can be measured.

The binding proteins herein are expected to have beneficial properties in this regard, including high affinity, slow off rate, and high neutralizing capacity.

Example 4.5: Neutralization of Human TNF-α

L929 cells are grown to a semi-confluent density and harvested using 0.25% trypsin (Gibco#25300). The cells are washed with PBS, counted and resuspended at 1E6 cells/mL in assay media containing 4 µg/mL actinomycin D. The cells are seeded in a 96-well plate (Costar#3599) at a volume of 100 µL and 5E4 cells/well. The binding proteins and control IgG are diluted to a 4X concentration in assay media and serial 1:4 dilutions are performed. The huTNF-α is diluted to 400 pg/mL in assay media. Binding protein sample (200 µL) is added to the huTNF-α (200 µL) in a 1:2 dilution scheme and allowed to incubate for 0.5 hour at room temperature.

The binding protein/human TNF-α solution is added to the plated cells at 100 µL for a final concentration of 100 pg/mL huTNF-α and 150 nM - 0.0001 nM binding protein. The plates are incubated for 20 hours at 37°C, 5% CO_2. To quantitate viability, 100 µL is removed from the wells and 10 µL of WST-1 reagent (Roche cat# 11644807001) is added. Plates are incubated under assay conditions for 3.5 hours. The plates are read at OD 420-600 nm on a Spectromax 190 ELISA plate reader.

The binding proteins herein are expected to have beneficial properties in this regard, including high affinity, slow off rate, and high neutralizing capacity.

Example 4.6: Treatment

A patient requiring treatment with a TNF-α binding protein may have a disease with immune and inflammatory elements, such as autoimmune diseases, particularly those assocated with inflammation, including Crohn's disease, psoriasis (including plaque psoriasis), arthritis (including rheumatoid arthritis, psoratic arthritis, osteoarthritis, or juvenile idiopathic arthritis), multiple sclerosis, and ankylosing spondylitis. Therefore, the binding proteins herein may be used to treat these disorders.

Administration of the TNF-α binding protein may occur by subcutaneous injection. If the patient has rheumatoid arthritis, psoratic arthritis, or ankylosing spondyitis, the patient may receive 40 mg every other week as a starting dose and 40 mg every week, if necessary to achieve treatment goals. If the patient has juvenile idiopathic arthritis and weighs from 15 kg to <30 kg, the patient may receive 20 mg every other week, and if ≥ 30 kg, 40 mg every other week. If the patient has Crohn's disease, the patient may receive an initial dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) followed by 80 mg two weeks later, and another two weeks later begin a maintenance dose of 40 mg every other week. If the patient has plaque psoriasis, the patient may receive an 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

The binding protein may be provided in a single-use prefilled pen (40 mg/0.8 mL), a single-use prefilled glass syringe (40 mg/0.8 mL or 20 mg/ 0.4 mL).

Incorporation by Reference

The contents of all cited references (including literature references, patents, patent applications, and websites) that are cited throughout this application are hereby expressly incorporated by reference in their entirety, as are the references cited therein. The practice disclosed herein will employ, unless otherwise indicated, conventional techniques of immunology, molecular biology and cell biology, which are well known in the art.

Equivalents

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting of the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are therefore intended to be embraced herein.

Claims

We claim:

1. A binding protein comprising at least one heavy chain variable region (VH region) comprising:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077; or

(b) any one of SEQ ID NOS: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077.

2. A binding protein comprising at least one light chain variable regions (VL region) comprising:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078; or

(b) any one of SEQ ID NOS: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, 1078.

3. A binding protein comprising at least one heavy chain variable region (VH region) and at least one light chain variable region (VL region), wherein the VH region comprises:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077; or

(b) any one of SEQ ID NOS: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077; and

the VL region comprises:

(c) three CDRs from any one of SEQ ID NOS: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078; or

(d) any one of SEQ ID NOS: 23, 25, 27, 29, 31, 33, 59-73, 84-93 , 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, 1078.

4. The binding protein of claim 3, wherein the binding protein comprises two VH regions and two VL regions.

5. The binding protein of claim 3, wherein the binding protein comprises at least one VH region and at least one VL region comprising a set of amino acid sequences selected from the

group consisting of SEQ ID NOS: 22 and 23; 24 and 25; 26 and 27; 28 and 29; 30 and 31; and 32 and 33.

6. The binding protein of claim 4, wherein the binding protein:

(a) modulates a biological function of TNF-α;

(b) neutralizes TNF-α;

(c) diminishes the ability of TNF-α to bind to its receptor;

(d) diminishes the ability of pro-human TNF-α, mature-human TNF-α, or truncated-human TNF-α to bind to its receptor; and/or

(e) reduces one or more of TNF-dependent cytokine production, TNF-dependent cell killing, TNF-dependent inflammation, TNF-dependent bone erosion, and TNF-dependent cartilage damage.

7. The binding protein of claim 4, wherein the binding protein has an on rate constant (Kon) of at least about $10^2M^{-1}s^{-1}$; at least about $10^3M^{-1}s^{-1}$; at least about $10^4M^{-1}s^{-1}$; at least about $10^5M^{-1}s^{-1}$; or at least about $10^6M^{-1}s^{-1}$, as measured by surface plasmon resonance.

8. The binding protein of claim 4, wherein the binding protein has an off rate constant (Koff) of at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about 10^{-5}s-1; or at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

9. The binding protein of claim 4, wherein the binding protein has a dissociation constant (KD) of at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; or at most 10^{-13} M.

10. A binding protein capable of binding human TNF-α, the binding protein comprising:

(a) a heavy chain constant region comprising an amino acid sequence of SEQ ID NO:2 or SEQ ID NO: 3;

(b) a light chain constant region comprising an amino acid sequence of SEQ ID NO:4 or SEQ ID NO: 5;

(c) a heavy chain variable region (VH region) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 22, 24, 26, 28, 30, 32, 34-58, 74-83, 94-266, 478-486, 496-675, 738-762, 778-956, 1053-1062, 1073, 1075, and 1077; and

(d) a light chain variable region (VL region) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 23, 25, 27, 29, 31, 33, 59-73, 84-93, 267-477, 487-495, 676-737, 763-777, 957-1052, 1063-1072, 1074, 1076, and 1078.

11. The binding protein of claim 3, wherein the binding protein comprises an immunoglobulin molecule, an Fv, a disulfide linked Fv, a monoclonal antibody, an scFv, a chimeric binding protein, a single domain binding protein, a CDR-grafted binding protein, a diabody, a humanized binding protein, a multispecific binding protein, an Fab, a dual specific binding protein, an Fab' fragment, a bispecific binding protein, an F(ab')2 fragment, a DVD-Ig™, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region, a Fd fragment consisting of the VH and CH1 domains, a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment, an isolated complementarity determining region (CDR), or a single chain binding protein.

12. The binding protein of claim 4, wherein the binding protein is conjugated to an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

13. The binding protein of claim 4, wherein the binding protein further comprises a therapeutic or cytotoxic agent selected from the group consisting of an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, an apoptotic agent, and at least one additional therapeutic agent for treating a disorder in which TNF-α activity is detrimental.

14. An isolated nucleic acid encoding a binding protein comprising the amino acid sequence of claim 3.

15. A vector comprising the isolated nucleic acid of claim 14.

16. A host cell comprising the vector of claim 15.

17. A method for producing a protein that binds TNF-α, the method comprising the steps of culturing the host cell of claim 16 in a culture medium under conditions sufficient to produce a binding protein that binds TNF-α.

18. A pharmaceutical composition comprising the binding protein of claim 3, and a pharmaceutically acceptable carrier.

19. A method for treating a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 18.

20. A method for reducing human TNF-α activity, the method comprising contacting human TNF-α with the binding protein of claim 3 such that human TNF-α activity is reduced.

21. A method for reducing human TNF-α activity in a human subject suffering from a disorder in which TNF-α activity is detrimental, the method comprising administering to the human subject the binding protein of claim 3 such that human TNF-α activity in the human subject is reduced and/or treatment is achieved.

22. A method for treating a patient suffering from a disorder in which TNF-α is detrimental comprising administering to the patient the binding protein of claim 3 either before, concurrent, or after the administration to the patient of a second agent, wherein the second agent is selected from the group consisting of an antibody, or fragment thereof, capable of binding human IL-12; PGE2; LPA; NGF; CGRP; SubP; RAGE; histamine; a histamine receptor blocker; bradykinin; IL-1alpha; IL-1beta; VEGF; PLGF; methotrexate; a corticosteroid, a glucocorticoid receptor modulator; cyclosporin, rapamycin, FK506, and a non-steroidal anti-inflammatory agent.

23. The method of claim 21 or 22, wherein the disorder is an autoimmune and/or inflammatory disorder.

24. The method of claims 23, wherein the disorder is selected from the group consisting of Crohn's disease, psoriasis, plaque psoriasis, arthritis, rheumatoid arthritis, psoratic arthritis, osteoarthritis, or juvenile idiopathic arthritis, multiple sclerosis, and ankylosing spondylitis.

25. The method of claim 23, wherein the disorder is selected from the group consisting of a respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs; inflammatory bowel diseases (IBD); ulcerative colitis; Crohn's disease; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma;

glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, and suppression of expression of a protective type 1 immune response during vaccination.

26. A method for determining the presence of TNF-α or a fragment thereof in a test sample by an immunoassay, wherein the immunoassay comprises contacting the test sample with at least one binding protein or fragment thereof according to claim 3, and at least one detectable label.

27. The method of claim 26, wherein the method further comprises:
(i) contacting the test sample with the at least one binding protein or fragment thereof, wherein the binding protein binds to an epitope on the TNF-α or fragment thereof so as to form a first complex;
(ii) contacting the complex with the at least one detectable label, wherein the detectable label binds to an epitope on the first complex, or on the TNF-α or fragment thereof, that is not bound by the binding protein or fragment thereof, to form a second complex; and
(iii) detecting the presence of the TNF-α or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the TNF-α or fragment thereof is directly correlated with the signal generated by the detectable label.

28. The method of claim 26, wherein the method further comprises:
(i) contacting the test sample with the at least one binding protein or fragment thereof, wherein the binding protein or fragment thereof binds to an epitope on the TNF-α or fragment thereof so as to form a first complex;
(ii) contacting the complex with the at least one detectable label, wherein the detectable label competes with the TNF-α or fragment thereof for binding to the binding protein or fragment thereof so as to form a second complex; and
(iii) detecting the presence of the TNF-α or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the TNF-α or fragment thereof is indirectly correlated with the signal generated by the detectable label.

29. The method of claim 26, wherein the method optionally further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient.