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(54) Title: IL-6 BINDING MOLECULES

(57) Abstract: The present invention provides binding molecules (e.g., antibodies or antigen binding fragments thereof) that specifically bind to and inhibit the biological activity of IL-6 (e.g., human, mouse and non-human primate IL-6). In a preferred embodiment, the antibodies or antigen binding fragments of the invention bind to IL-6 and inhibit its binding to an IL-6 receptor. Such antibodies or antigen binding fragments are particularly useful for treating IL-6- associated diseases or disorders (e.g., inflammatory disease and cancer).

IL-6 BINDING MOLECULES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 61/650,883, filed May 23, 2012, U.S. Provisional Application Serial No. 61/720,102, filed October 30, 2012, and PCT/IB2012/056424, filed on November 14, 2012, all of which are herein incorporated by reference in their entireties.

BACKGROUND

Interleukin-6 (IL-6) is a major proinflammatory cytokine. It is responsible for the proliferation and differentiation of immunocompetent and hematopoietic cells. Human IL-6 is a single glycoprotein consisting of 212 amino acids with two N-linked glycosylation sites, and has a molecular weight of about 26kDa. The structure of IL-6 comprises four α-helical domains with a motif of four cysteine residues which are necessary for its tertiary structure. IL-6 signalling is mediated by the binding of IL-6 to either soluble or surface bound IL-6 receptor alpha chain (IL-6Rα), enabling interaction of the complex with the cell surface transmembrane gp130 subunit that mediates intracellular signalling.

IL-6 is implicated in the pathogenesis of inflammatory diseases, including inflammatory autoimmune diseases such as rheumatoid arthritis (RA), spondylosing arthropathy, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and Castleman's disease. IL-6 is also implicated in the pathogenesis of cancers, including prostate cancer, diffuse large cell lymphoma, multiple myeloma, and renal cell cancer. A role for IL-6 in promoting cancer-related anorexia, oral mucositis and cachexia has also been reported.

Although IL-6 binding molecules derived from immunization of non-human animals are known in the art, these molecules have typically required extensive antibody engineering (e.g., CDR grafting and humanization) to reduce their immunogenicity. Moreover, the resulting humanized variants typically suffer from sub-optimal binding affinity to the IL-6 target and require extensive antibody engineering and affinity maturation in an attempt to restore IL-6 binding affinity. The end result is that most IL-6 antibodies exhibit sub-optimal binding affinity to the IL-6 target.

Therefore, given the importance of IL-6 in disease pathogenesis and the shortcomings of known IL-6 antibodies, there is clearly a need in the art for improved (e.g., minimally engineered) IL-6 agents that can inhibit the biological activity of IL-6, and hence treat diseases associated with IL-6 activity.

SUMMARY OF THE INVENTION

The present invention improves upon the state of the art by providing binding molecules (e.g., antibodies or antigen binding fragments thereof) with improved binding profiles that specifically bind to IL-6 (e.g., human and non-human primate IL-6) with high binding affinity (e.g., picomolar binding affinity) and potently inhibit its biological activity (e.g., binding to an IL-6 receptor). In certain exemplary embodiments, the IL-6 binding molecules of the invention are derived from the conventional antibody repertoire of a camelid species (e.g., llama) that has been subjected to active immunization with the IL-6 antigen. For example, the camelid-derived IL-6 binding molecules of the invention may comprise paired VH/VL domains or other alternative frameworks wherein one or more hypervariable loops (e.g., H1, H2, H3, L1, L2 and/or L3) of the VH or VL domains are derived from the camelid species. Moreover, in certain embodiments, at least one of the hypervariable loops adopt a canonical fold (or combination of canonical folds) that is identical or substantially identical to that of a human antibody. Such binding molecules exhibit high human homology (sequence and structure) and are therefore particularly useful for treating IL-6-associated diseases or disorders (e.g., inflammatory disease and cancer) due to their low immunogenicity. Surprisingly, the IL-6 antibodies of the invention exhibit high binding affinity, manufacturability and thermal stability without the need for extensive and time-consuming antibody engineering and affinity maturation that is typically required of known IL-6 antibodies.

Accordingly, in one aspect, the invention provides, a binding molecule that specifically binds to IL-6, the binding molecule comprising at least one antibody CDR, wherein the CDR comprises at least one amino acid residue that is buried in the F229 cavity or the F279 cavity on IL-6 when the binding molecule is bound to IL-6. In certain embodiments, the binding molecule comprises a VH domain, the VH domain having an amino acid at position 98, according to Kabat, that is buried in the F229 cavity on IL-6 when the antibody or fragment is bound to IL-6. In one particular embodiment, the amino acid at position 98 is a tryptophan. In certain embodiments, the binding molecule comprises a VL

domain, the VL domain having an amino acid at position 30, according to Kabat, that is buried in the F229 cavity on IL-6 when the antibody or fragment is bound to IL-6. In one particular embodiment, the amino acid at position 30 is a tyrosine. In certain embodiments, the binding molecule comprises a VH domain, the VH domain having an amino acid at position 99, according to Kabat, that is buried in the F279 cavity on IL-6 when the antibody or fragment is bound to IL-6. In one particular embodiment, the amino acid at position 99 is a valine.

In certain embodiments, the binding molecule comprises a VH domain and a VL domain, said VH domain comprising hypervariable loops H1, H2 and H3, wherein said VH domain polypeptide is paired with a VL domain comprising hypervariable loops L1, L2 and L3 wherein at least one of hypervariable loops H1-H3 and L1-L3 are obtained from a conventional antibody of a *Lama* species by active immunization of the *Lama* species with the IL-6 antigen. In one particular embodiment, at least one of the hypervariable loops H1, H2, L1, L2 and L3 exhibits a predicted or actual canonical fold structure which is identical or substantially identical to a corresponding canonical fold structure of a H1, H2, L1, L2 or L3 hypervariable loop which occurs in a human antibody.

In one particular embodiment, at least one of the hypervariable loops H1 and H2 each exhibit a predicted or actual canonical fold structure which is identical or substantially identical to the corresponding human canonical fold structure. In one particular embodiment, at least one of the hypervariable loops L1, L2 and L3 each exhibit a predicted or actual canonical fold structure which is identical or substantially identical to the corresponding human canonical fold structure. In one particular embodiment, at least one of the hypervariable loops H1 and H2 form a combination of predicted or actual canonical fold structures which is identical or substantially identical to a corresponding combination of canonical fold structures known to occur in a human germline VH domain. In one particular embodiment, at least one of the hypervariable loops H1 and H2 form a combination of canonical fold structures corresponding to a combination of human canonical fold structures selected from the group consisting of 1-1, 1-2, 1-3, 1-4, 1-6, 2-1, 3-1 and 3-5.

In one particular embodiment, at least one of the hypervariable loops L1 and L2 form a combination of predicted or actual canonical fold structures which is identical or substantially identical to a corresponding combination of canonical fold structures known to occur in human germline VL domains. In one particular embodiment, at least one of the hypervariable loops L1 and L2 form a combination of canonical fold structures corresponding

to a combination of human canonical fold structures selected from the group consisting of 11-7, 13-7(A,B,C), 14-7 (A,B), 12-11, 14-11, 12-12, 2-1, 3-1, 4-1 and 6-1.

In certain embodiments, the binding molecule comprises a VH domain and a VL domain, wherein the VH domain and/or VL domain of the binding molecule exhibits a sequence identity of 90% or greater, with one or more corresponding human VH or VL domains across framework regions FR1, FR2, FR3 and FR4. In certain embodiments, the binding molecule comprises a VH domain and a VL domain and is a germlined variant of a parental binding molecule, wherein one or both of the VH domain and VL domain of the binding molecule comprise a total of between 1 and 10 amino acid substitutions across the framework regions as compared to the corresponding VH domain and VL domain of the parental non-human antibody. In one particular embodiment the parental binding molecule is a conventional camelid antibody. In certain embodiments, the binding molecule is an antibody or antigen binding fragment thereof.

In certain embodiments, the binding molecule comprises a VH domain, the VH domain comprising the HCDR3 amino acid sequence set forth in SEQ ID NO: 500 [X_1PDVVTGFHYDX_2], or sequence variant thereof, wherein:

X_1 is any amino acid, preferably D or Y;

X_2 is any amino acid, preferably Y or N; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR3 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 497-499.

In certain embodiments, the VH domain further comprises the HCDR2 amino acid sequence set forth in SEQ ID NO: 507 [VIX_1Y$X_2$$X_3$DTYYSPSL$X_4$S], or sequence variant thereof, wherein:

X1 is any amino acid, preferably D, Y or N;

X2 is any amino acid, preferably D or E;

X3 is any amino acid, preferably A or G;

X4 is any amino acid, preferably E or K; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR2 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 501-506.

In certain embodiments, the VH domain further comprises the HCDR1 amino acid sequence set forth in SEQ ID NO: 512 [$X_1X_2YYX_3WX_4$], or sequence variant thereof, wherein:

X1 is any amino acid, preferably T, S or P;

X2 is any amino acid, preferably R or S;

X3 is any amino acid, preferably A or V;

X4 is any amino acid, preferably S or T; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR1 amino acid sequence is selected from the group consisting of SEQ ID NO: 508-511.

In certain embodiments, the binding molecule comprises a VH domain comprising the HCDR3, HCDR2 and HCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 497, 501 and 508, respectively.

In certain embodiments, the binding molecule further comprises a VL domain, wherein the VL domain comprises the LCDR3 amino acid sequence set forth in SEQ ID NO: 524 [$ASYX_1X_2X_3X_4X_5X_6X_7$], or sequence variant thereof, wherein:

X1 is any amino acid, preferably R or K;

X2 is any amino acid, preferably N, H, R, S, D, T or Y;

X3 is any amino acid, preferably F, Y, T, S or R;

X4 is any amino acid, preferably N or I;

X5 is any amino acid, preferably N or D;

X6 is any amino acid, preferably V, N, G or A;

X7 is any amino acid, preferably V or I; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the LCDR3 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 513-523.

In certain embodiments, the VL domain further comprises the LCDR2 amino acid sequence set forth in SEQ ID NO: 535 [$X_1VX_2X_3RX_4S$], or sequence variant thereof, wherein:

X1 is any amino acid, preferably R, K, D, A or E;

X2 is any amino acid, preferably S, N or T;

X3 is any amino acid, preferably T, K or Y;

X4 is any amino acid, preferably A, T or V; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the LCDR2 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 525-534.

In certain embodiments, the VL domain further comprises the LCDR1 amino acid sequence set forth in SEQ ID NO: 542 [$AGX_1X_2X_3DX_4GX_5X_6X_7YVS$], or sequence variant thereof, wherein

X1 is any amino acid, preferably A or T;

X2 is any amino acid, preferably S or N;

X3 is any amino acid, preferably S, E or N;

X4 is any amino acid, preferably V or I;

X5 is any amino acid, preferably G, Y, T or F;

X6 is any amino acid, preferably G or Y;

X7 is any amino acid, preferably N, D or A; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence.

In one particular embodiment, the LCDR1 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 538-541. In certain embodiments, the binding molecule comprises a VL domain comprising the comprising the LCDR3, LCDR2 and LCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 513, 525 and 536, respectively. In certain embodiments, the binding molecule comprises: a VH domain having the HCDR3, HCDR2 and HCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 497, 501 and 508, respectively; and a VL domain having the LCDR3, LCDR2 and LCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 513, 525 and 536, respectively.

In certain embodiments, the binding molecule comprises a VH domain with at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 152. In certain embodiments, the binding molecule comprises a VH domain amino acid sequence is selected from the group consisting of SEQ ID NO: 127-232 and 569-571. In certain embodiments, the binding molecule comprises a VH domain amino acid sequence is SEQ ID NO: 152. In certain embodiments, the binding molecule comprises a VL domain with at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 416. In certain embodiments, the binding molecule comprises a VL domain amino acid sequence is selected from the group consisting of SEQ ID NO: 391-496. In certain embodiments, the binding molecule comprises a VL domain amino acid sequence is SEQ ID NO: 416. In certain

embodiments, the binding molecule comprises: a VH domain having the amino acid sequences set forth in SEQ ID NO: 152; and a VL domain having the amino acid sequence set forth in SEQ ID NO: 416.

In certain embodiments, the binding molecule comprises the H1 and H2 loops form a combination of canonical fold structures corresponding to the 3-1 combination of human canonical fold structures as found in a human 1ACY antibody structure.

In certain embodiments, the binding molecule comprises the L1 and L2 loops form a combination of canonical fold structures corresponding to the 6λ-1 combination of human canonical fold structures as found in a human 3MUG antibody structure. In certain embodiments, the binding molecule comprises the L1, L2 and L3 loops form a combination of canonical fold structures corresponding to the 6λ-1-5 combination of human canonical fold structures as found in the human 3MUG antibody structure.

In certain embodiments, the binding molecule comprises a VH domain, the VH domain comprising the HCDR3 amino acid sequence set forth in SEQ ID NO: 544 [$RAGX_1GX_2G$], or sequence variant thereof, wherein:

X_1 is any amino acid, preferably W;

X_2 is any amino acid, preferably M, A, L, S or N; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR3 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 543, SEQ ID NO: 566, SEQ ID NO:567, and SEQ ID NO:568.

In certain embodiments, the VH domain further comprises the HCDR2 amino acid sequence set forth in SEQ ID NO: 554 [$X_1ISX_2X_3GX_4SX_5X_6YX_7DSVKG$], or sequence variant thereof, wherein:

X1 is any amino acid, preferably A, P or R;

X2 is any amino acid, preferably A or S;

X3 is any amino acid, preferably S or G;

X4 is any amino acid, preferably G or V;

X5 is any amino acid, preferably A or T;

X6 is any amino acid, preferably Y, N or S;

X7 is any amino acid, preferably G, A or T; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR2 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 545-553.

In certain embodiments, the VH domain further comprises the HCDR1 amino acid sequence set forth in SEQ ID NO: 562 [$X_1X_2X_3X_4$ X_5], or sequence variant thereof, wherein:

X1 is any amino acid, preferably S or T;

X2 is any amino acid, preferably H or Y;

X3 is any amino acid, preferably A or R;

X4 is any amino acid, preferably M or L;

X5 is any amino acid, preferably S or Y; and

wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In one particular embodiment, the HCDR1 amino acid amino acid sequence is selected from the group consisting of SEQ ID NO: 555-561.

In certain embodiments, the VH domain comprises a HCDR3 having an amino acid amino acid sequence selected from the group consisting of SEQ ID NO:543, 566, 567, and 568, and the HCDR2 and HCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 545 and 555, respectively. In certain embodiments, the binding molecule further comprises a VL domain, wherein the VL domain comprises the LCDR3 amino acid sequence set forth in SEQ ID NO: 563, or sequence variant thereof, wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In certain embodiments, the VL domain further comprises the LCDR2 amino acid sequence set forth in SEQ ID NO: 564, or sequence variant thereof, wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In certain embodiments, the VL domain further comprises the LCDR1 amino acid sequence set forth in SEQ ID NO: 565, or sequence variant thereof, wherein the sequence variant comprises one, two or three amino acid substitutions in the recited sequence. In certain embodiments, the VL domain comprises the LCDR3, LCDR2 and LCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 563, 564 and 565, respectively. In certain embodiments, the binding molecule comprises a VH domain having the HCDR3, HCDR2 and HCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 544, 545 and 555, respectively; and a VL domain having the LCDR3, LCDR2 and LCDR1 amino acid amino acid sequences set forth in SEQ ID NO: 563, 564 and 565, respectively. In certain embodiments, the binding molecule comprises a VH domain with at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 86. In

certain embodiments, the binding molecule comprises a VH domain having the amino acid sequence is selected from the group consisting of SEQ ID NO: 39-126 and 569-571. In certain embodiments, the binding molecule comprises a VH domain having the amino acid sequence is selected from SEQ ID NO: 86, SEQ ID NO:569, SEQ ID NO:570 and SEQ ID NO:571. In certain embodiments, the binding molecule comprises a VL domain with at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 350. In certain embodiments, the binding molecule comprises a VL domain having the amino acid sequence is selected from the group consisting of SEQ ID NO: 303-390. In certain embodiments, the binding molecule comprises a VL domain having the amino acid sequence is SEQ ID NO: 350. In certain embodiments, the binding molecule comprises: a VH domain having the amino acid sequences set forth in SEQ ID NO: 86, SEQ ID NO:569, SEQ ID NO:570 or SEQ ID NO:571; and a VL domain having the amino acid sequences set forth in SEQ ID NO: 350.

In certain embodiments, the binding molecule comprises the H1 and H2 loops form a combination of canonical fold structures corresponding to the 1-3 combination of human canonical fold structures as found in a human 1DFB antibody structure. In certain embodiments, the binding molecule comprises the L1 and L2 loops form a combination of canonical fold structures corresponding to the 7λ-1 combination of human canonical fold structures as found in a human 1MFA antibody structure. In certain embodiments, the binding molecule comprises the L1, L2 and L3 loops form a combination of canonical fold structures corresponding to the 7λ-1-4 combination of human canonical fold structures as found in the human 3MUG antibody structure.

In certain embodiments, the binding molecule is a Fab fragment which binds to human IL-6 with an off-rate (k_{off} measured by surface Plasmon resonance) of less than 2 x 10^{-5} s^{-1}. In certain embodiments, the binding molecule binds to the human IL-6 antigen with sub-picomolar binding affinity. In certain embodiments, the binding molecule binds to the human IL-6 antigen with single digit femtomolar binding affinity. In certain embodiments, the binding molecule comprises the hypervariable loops are obtained from the conventional antibody of the Lama without subsequent affinity maturation. In certain embodiments, the binding molecule inhibits IL-6-induced proliferation of B9 hybridoma cells with an IC50 of less than 0.1 pM.

In certain embodiments, the binding molecule exhibits a melting temperature (Tm) of greater than 65 °C. In certain embodiments, the binding molecule is a germlined variant of a

parental camelid antibody, said germlined variant having a higher melting temperature than the parental camelid antibody. In certain embodiments, the binding molecule is expressed at the level of at least 20 mg/ml following transient expression in a HEK293 cell. In certain embodiments, the binding molecule is characterized by an EpiBase® score of less than about 10.0, e.g., less than about 6.0. In certain embodiments, the binding molecule inhibits binding of IL-6 to an IL-6 receptor. In certain embodiments, the binding molecule inhibits binding of gp130 to an IL-6 receptor. In certain embodiments, the binding molecule binds specifically to human and cynomologus monkey IL-6. In certain embodiments, the binding molecule comprises at least one CDR from a camelid antibody that specifically binds to IL-6.

In another aspect, the invention provides, a pharmaceutical composition comprising the binding molecule of any of the preceding claims and one or more pharmaceutically acceptable carrier.

In another aspect, the invention provides, a method of treating an IL-6-associated disease or disorder, comprising administering to a subject in need of treatment thereof an effective amount of the pharmaceutical composition of the invention.

In another aspect, the invention provides, an isolated nucleic acid encoding a binding molecule disclosed herein.

In another aspect, the invention provides, a recombinant expression vector comprising a nucleic acid molecule of the invention.

In another aspect, the invention provides a host cell comprising a recombinant expression vector of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the results of cell proliferation assays measuring the *in vitro* IL-6 neutralizing activity of antibodies of the invention.

Figure 2 depicts the results of epithelial ovarian cancer mouse tumor xenograph experiments measuring the *in vivo* efficacy of antibodies of the invention.

Figures 3A-B show that camelid-derived hypervariable loops (L1-L3, H1 and H2) of the 61H7 antibody of the invention adopts predicted canonical folds and canonical fold combinations of human antibodies.

Figures 4A-B show that camelid-derived hypervariable loops (L1-L3, H1 and H2) of the 68F2 antibody of the invention and its germlined variant (129D3) adopt predicted canonical folds and canonical fold combinations of human antibodies.

Figure 5 depicts a space-fill model of IL-6 overlaid with: (A) F229 of the IL-6 receptor; (B) F229 of the IL-6 receptor and W98 of the 61H7 VH, (C) F229 of the IL-6 receptor and Y30 of the 68F2 VL; and (D) F229 of the IL-6 receptor, W98 of the 61H7 VH and V99 of the 68F2 VH, according to Kabat numbering.

Figure 6 depicts a space-fill model of the two surface binding cavities on IL-6 important for IL-6 receptor binding overlaid with residues F229 and F279 of the IL-6 receptor, and residues Y30 of the 68F2 VL and V99 of the 68F2 VH, according to Kabat numbering (Y32 and V104 in the structure).

Figures 7A-B depicts the thermal stability of 68F2 and its germlined variant 129D3 as measured in Biacore with immobilized glycosylated human IL-6 with respect to (A) other germlined variant IL-6 antibodies of the invention and (B) other reference antibodies. The upper part of each figure depicts the melting curves, while the lower part lists the Tm value for each antibody.

Figure 8 depicts the serum stability of antibody clones 68F2, 129D3 (a germlined variant of 68F2), and 103A1 (a variant of 61H7). Also included is the reference antibody GL 18.

Figure 9 depicts the low immunogenicity (Epibase) scores for IL-6 antibodies of the invention as compared to reference antibodies (shown in bold), including the fully human antibody adalimumab (Humira).

Figure 10A-B depicts an alignment of the VH and VL (A) 68F2 and (B) 61H7 depicting the high level of sequence homology with the framework regions of their respective germlined variants 129D3 and 111A7. The minimal number of framework alterations introduced into each molecule (13 total) is also shown.

Figure 11A-B depicts an alignment of the VH and VK of (A) CNTO328 and (B) VH_rabbit (ALD518) depicting the high level of sequence homology with the framework regions of their respective germlined variants CNTO136 and VH_human(ALD518). The minimal number of framework alterations introduced into each molecule (36 and 46 in total) is also shown.

Figure 12 depicts the pharmacokinetic profiles of 129D3 IgG1 antibodies and variants thereof in cynomolgus monkeys.

Figure 13 depicts the results of serum amyloid A (SAA) mouse model experiments measuring the *in vivo* efficacy of antibodies of the invention.

Figure 14 depicts the results of mouse psoriasis xenograph experiments measuring the *in vivo* efficacy of antibodies of the invention.

Figure 15 depicts tumor growth data observed in experiments measuring the *in vivo* efficacy of antibodies of the invention in a renal cell cancer mouse tumor xenograph model.

Figure 16 depicts Kaplan-Meier plot of survival data observed in experiments measuring the *in vivo* efficacy of antibodies of the invention in a renal cell cancer mouse tumor xenograph model.

Figure 17 depicts tumor growth data observed in experiments measuring the *in vivo* efficacy of antibodies of the invention in a renal cell cancer mouse tumor xenograph model with all agents dosed at 3 mg/kg.

Figure 18 depicts Kaplan-Meier plot of survival data observed in experiments measuring the *in vivo* efficacy of antibodies of the invention in a renal cell cancer mouse tumor xenograph model with all agents dosed at 3 mg/kg.

DESCRIPTION OF THE INVENTION

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined.

As used herein, the term "IL-6" refers to interleukin-6. IL-6 nucleotide and polypeptide sequences are well known in the art. An exemplary human IL-6 amino sequence is set forth in GenBank deposit GI: 10834984 and an exemplary mouse IL-6 amino sequence is set forth in GenBank deposit GI: 13624311.

As used herein, the term "antibody" refers to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated VL) and a light chain constant region. The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR).

As used herein, the term "antigen-binding fragment" of an antibody includes any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Non-limiting examples of antigen-binding portions include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR)). Other engineered molecules, such as diabodies, triabodies, tetrabodies and minibodies, are also encompassed within the expression "antigen-binding portion."

As used herein, the terms "variable region" or "variable domain" refer to the fact that certain portions of the variable domains VH and VL differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its target antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called "hypervariable loops" in each of the VL domain and the VH domain which form part of the antigen binding site. The first, second and third hypervariable loops of the VLambda light chain domain are referred to herein as L1(λ), L2(λ) and L3(λ) and may be defined as comprising residues 24-33 (L1(λ), consisting of 9, 10 or 11 amino acid residues), 49-53 (L2(λ), consisting of 3 residues) and 90-96 (L3(λ), consisting of 5 residues) in the VL domain (Morea et al., Methods 20:267-279 (2000)). The first, second and third hypervariable loops of the VKappa light chain domain are referred to herein as L1(κ), L2(κ) and L3(κ) and may be defined as comprising residues 25-33 (L1(κ), consisting of 6, 7, 8, 11, 12 or 13 residues), 49-53 (L2(κ), consisting of 3 residues) and 90-97 (L3(κ), consisting of 6 residues) in the VL domain (Morea et al., Methods 20:267-279 (2000)). The first, second and third hypervariable loops of the VH domain are referred to herein as H1, H2 and H3 and may be defined as comprising residues 25-33 (H1, consisting of 7, 8 or 9 residues), 52-56 (H2, consisting of 3 or 4 residues) and 91-105 (H3, highly variable in length) in the VH domain (Morea et al., Methods 20:267-279 (2000)).

Unless otherwise indicated, the terms L1, L2 and L3 respectively refer to the first, second and third hypervariable loops of a VL domain, and encompass hypervariable loops

obtained from both Vkappa and Vlambda isotypes. The terms H1, H2 and H3 respectively refer to the first, second and third hypervariable loops of the VH domain, and encompass hypervariable loops obtained from any of the known heavy chain isotypes, including γ, ε, δ, α or μ.

The hypervariable loops L1, L2, L3, H1, H2 and H3 may each comprise part of a "complementarity determining region" or "CDR", as defined below. The terms "hypervariable loop" and "complementarity determining region" are not strictly synonymous, since the hypervariable loops (HVs) are defined on the basis of structure, whereas complementarity determining regions (CDRs) are defined based on sequence variability (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD., 1983) and the limits of the HVs and the CDRs may be different in some VH and VL domains.

The CDRs of the VL and VH domains can typically be defined as comprising the following amino acids: residues 24-34 (CDRL1), 50-56 (CDRL2) and 89-97 (CDRL3) in the light chain variable domain, and residues 31-35 or 31-35b (CDRH1), 50-65 (CDRH2) and 95-102 (CDRH3) in the heavy chain variable domain; (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). Thus, the HVs may be comprised within the corresponding CDRs and references herein to the "hypervariable loops" of VH and VL domains should be interpreted as also encompassing the corresponding CDRs, and vice versa, unless otherwise indicated.

The more highly conserved portions of variable domains are called the framework region (FR), as defined below. The variable domains of native heavy and light chains each comprise four FRs (FR1, FR2, FR3 and FR4, respectively), largely adopting a β-sheet configuration, connected by the three hypervariable loops. The hypervariable loops in each chain are held together in close proximity by the FRs and, with the hypervariable loops from the other chain, contribute to the formation of the antigen-binding site of antibodies. Structural analysis of antibodies revealed the relationship between the sequence and the shape of the binding site formed by the complementarity determining regions (Chothia et al., J. Mol. Biol. 227: 799-817 (1992)); Tramontano et al., J. Mol. Biol, 215:175-182 (1990)). Despite their high sequence variability, five of the six loops adopt just a small repertoire of main-chain conformations, called “canonical structures”. These conformations are first of all determined by the length of the loops and secondly by the presence of key residues at certain

positions in the loops and in the framework regions that determine the conformation through their packing, hydrogen bonding or the ability to assume unusual main-chain conformations.

As used herein, the terms "complementarity determining region" or "CDR" refer to the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest. (1991), and by Chothia et al., J. Mol. Biol. 196:901-917 (1987) and by MacCallum et al., J. Mol. Biol. 262:732-745 (1996) where the definitions include overlapping or subsets of amino acid residues when compared against each other. The amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth for comparison. Preferably, the term “CDR” is a CDR as defined by Kabat based on sequence comparisons.

Table 1: CDR definitions

	CDR Definitions		
	Kabat[1]	Chothia[2]	MacCallum[3]
V_H CDR1	31-35	26-32	30-35
V_H CDR2	50-65	53-55	47-58
V_H CDR3	95-102	96-101	93-101
V_L CDR1	24-34	26-32	30-36
V_L CDR2	50-56	50-52	46-55
V_L CDR3	89-97	91-96	89-96

[1]Residue numbering follows the nomenclature of Kabat et al., supra

[2]Residue numbering follows the nomenclature of Chothia et al., supra

[3]Residue numbering follows the nomenclature of MacCallum et al., supra

As used herein he terms “framework region” or “FR region” include the amino acid residues that are part of the variable region, but are not part of the CDRs (e.g., using the Kabat definition of CDRs). Therefore, a variable region framework is between about 100-120 amino acids in length but includes only those amino acids outside of the CDRs. For the specific example of a heavy chain variable region and for the CDRs as defined by Kabat et al., framework region 1 corresponds to the domain of the variable region encompassing

amino acids 1-30; framework region 2 corresponds to the domain of the variable region encompassing amino acids 36-49; framework region 3 corresponds to the domain of the variable region encompassing amino acids 66-94, and framework region 4 corresponds to the domain of the variable region from amino acids 103 to the end of the variable region. The framework regions for the light chain are similarly separated by each of the light chain variable region CDRs. Similarly, using the definition of CDRs by Chothia et al. or McCallum et al. the framework region boundaries are separated by the respective CDR termini as described above. In preferred embodiments the CDRs are as defined by Kabat.

In naturally occurring antibodies, the six CDRs present on each monomeric antibody are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen binding site as the antibody assumes its three dimensional configuration in an aqueous environment. The remainder of the heavy and light variable domains show less inter-molecular variability in amino acid sequence and are termed the framework regions. The framework regions largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, these framework regions act to form a scaffold that provides for positioning the six CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen binding site formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to the immunoreactive antigen epitope. The position of CDRs can be readily identified by one of ordinary skill in the art.

As used herein, the term "F229 cavity" refers to the surface cavity of human IL-6 that is occupied by the phenylalanine 229 residue of the human IL-6 receptor in the IL-6/IL-6 receptor complex set forth in Boulanger et al., 2003, Science 27, 2101-2104, which is incorporated by reference herein in its entirety.

As used herein, the term "F279 cavity" refers to the surface cavity of human IL-6 that is occupied by the phenylalanine 279 residue of the human IL-6 receptor in the IL-6/IL-6 receptor complex set forth in Boulanger et al., 2003, Science 27, 2101-2104, which is incorporated by reference herein in its entirety.

As used herein, the term "camelid-derived" refers to antibody variable region amino acid sequences (e.g., framework or CDR sequences) naturally present in antibody molecules of a camelid (e.g., llama). Camelid-derived antibodies may be obtained from any camelid species, including, without limitation, llama, dromedary, alpaca, vicuna, guanaco or camel.

In certain embodiments, the camelid (e.g., llama) has been actively immunised with IL-6 (e.g., human IL-6). In certain embodiments, the term "camelid-derived" is limited to antibody sequences that are derived from the conventional antibody repertoire of a camelid and specifically excludes antibody sequences derived from the heavy chain-only antibody (VHH) repertoire of the camelid.

As used herein, the term "conventional antibody" refers to antibodies of any isotype, including IgA, IgG, IgD, IgE or IgM. Native or naturally occurring "conventional" camelid antibodies are usually heterotetrameric glycoproteins, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end (N-terminal) a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain (VL) at one end (N-terminal) and a constant domain (CL) at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

As used herein, the term "specifically binds to" refers to the ability of an antibody or antigen binding fragment thereof to bind to an IL-6 with an KD of at least about 1×10^{-6} (e.g, 1×10^{-6} M, 1×10^{-7} M, 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-11} M, 1×10^{-12} M, 1×10^{-13} M, 1×10^{-14} M, 1×10^{-15} M or more), preferably between 1×10^{-12} M and 1×10^{-15} M or more and/or bind to IL-6 with an affinity that is at least two-fold greater than its affinity for a non-specific antigen. It shall be understood, however, that an antibody or antigen binding fragment thereof is capable of specifically binding to two or more antigens which are related in sequence. For example, the antibodies or antigen binding fragments thereof disclosed herein can specifically bind to both human and a non-human (e.g., mouse or non-human primate) IL-6.

As used herein, the term "antigen" refers to the binding site or epitope recognized by an antibody variable region.

As used herein, the term "treat," "treating," and "treatment" refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration to a subject, an antibody or antigen binding fragment thereof of the present invention, for

example, a subject having an IL-6-associated disease or disorder (e.g. inflammation and cancer) or predisposed to having such a disease or disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disease or disorder or recurring disease or disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

As used herein, the term "IL6-associated disease or disorder" includes disease states and/or symptoms associated with IL-6 activity. Exemplary IL6-associated diseases or disorders include, but are not limited to, inflammatory diseases (e.g., inflammatory autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus), cancer (e.g., prostate cancer, diffuse large cell lymphoma, multiple myeloma, and renal cell cancer), and cancer-related disorders (e.g., anorexia and cachexia).

As used herein, the term "effective amount" refers to that amount of an antibody or antigen binding fragment thereof that is sufficient to effect treatment, prognosis or diagnosis of an IL-6-associated disease or disorder, as described herein, when administered to a subject. A therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The dosages for administration can range from, for example, about 1 ng to about 10,000 mg, about 1 ug to about 5,000 mg, about 1 mg to about 1,000 mg, about 10 mg to about 100 mg, of an antibody or antigen binding fragment thereof according to the invention. Dosage regiments may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (i.e., side effects) of a binding polypeptide are minimized and/or outweighed by the beneficial effects.

As used herein, the term "subject" includes any human or non-human animal.

As used herein, the term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

As used herein, the term "K_D" refers to the equilibrium dissociation constant of a particular binding polypeptide/antigen interaction.

As used herein, the term "off-rate" is refers to the dissociation rate (K_{off}) for a particular binding interaction.

II. IL-6 Binding Molecules

In one aspect, the invention provides binding molecules (antibodies or antigen binding fragments thereof) that specifically bind to and inhibit the activity of IL-6. Such binding molecules generally comprise at least one CDR region amino acid sequence set forth in Tables 13-18, herein.

Analysis of the crystal structure of human IL-6 in complex with the human IL-6 receptor has shown that 2 residues of the IL-6 receptor, F229 and F279, are critical for the IL-6/ IL-6 receptor interaction (see e.g., Boulanger et al., 2003, Science 27, 2101-2104, which is incorporated by reference herein in its entirety). In the IL-6/ IL-6 receptor complex, F229 and F279 are buried in separate cavities on the surface of IL-6. In certain embodiments, the binding molecules of the invention utilize these cavities on IL-6 to achieve high affinity binding. In one particular embodiment, binding molecules of the invention comprise an antibody CDR region, wherein the CDR region comprises an amino acid residue that is buried in the F229 cavity or the F279 cavity on IL-6 when the binding molecule to bound to IL-6.

In general, the binding molecules of the invention inhibit IL-6 activity (e.g., by antagonizing the binding of IL-6 to an IL-6 receptor). In certain embodiments, the binding molecules also inhibit binding of gp130 to an IL-6 receptor. However, in other embodiments, the binding molecules can bind to IL-6 without inhibiting binding of gp130 to an IL-6 receptor.

Binding molecules of the invention generally have a high affinity for IL-6 and are generally highly potent at inhibiting IL-6 activity *in vivo* and *in vitro*. In certain embodiments, the binding molecules of the invention bind to human IL-6 with an off-rate (k_{off} measured by surface Plasmon resonance) of less than about 1×10^{-4} s^{-1} (e.g., about 9×10^{-5}, 8×10^{-5}, $7x\ 10^{-5}$, 6×10^{-5}, 5×10^{-5}, 4×10^{-5}, 3×10^{-5}, 2×10^{-5}, and 1×10^{-5}). In other embodiments, the binding molecules of the invention inhibit IL-6-induced proliferation of B9 hybridoma cells with an IC50 of less than 0.1 pM. In certain other embodiments, the binding molecules of the invention compete with a predetermined antibody binding to IL-6 wherein such predetermined antibody containing a VH sequence and a VL sequence selected from VH and VL amino acid sequences set forth in Table 13-18. In certain other embodiments, the binding molecules of the invention compete away at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the binding of the predetermined antibody binding to IL-6. In certain other embodiments, the binding molecules of the invention compete with the binding of 20A4,

24D10, 68F2, 61H7, 129D3 or 111A7 to IL-6, e.g., compete away at least 50%, 60%, 70%, 80% or 90% of the binding of one of these antibodies to IL-6. In certain other embodiments, the binding molecules of the invention compete with the binding of 17F10, 24C9, 18C11, 29B11, 28A6, or 126A3 to IL-6, e.g., compete away at least 50%, 60%, 70%, 80% or 90% of the binding of one of these antibodies to IL-6.

In general, the binding molecules of the invention also exhibit high thermal stability. In certain embodiments, the binding molecules exhibit a melting temperature (Tm) of greater than 55˚C (e.g., at least 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75 C or higher). In certain exemplary embodiments, the IL-6 binding molecules of the invention are germlined variants which exhibit a thermal stability that is comparable to, or higher than, their parental, camelid-derived counterparts. In certain exemplary embodiments, thermal stability is measured following incubation in a suitable buffer (e.g., PBS) at a concentration of 100 μg/ml for 1 hour. In other exemplary, embodiments the thermal stability of the IL-6 binding molecule is that exhibited in a full-length IgG format (e.g., comprising an IgG1 or IgG4 Fc region).

The binding molecules of the invention are also characterized by high expression levels of functional antibody, with low levels of non-functional contaminants such as high or low-molecular weight aggregates. For example, IL-6 binding molecules of the invention may be characterized by production levels of at least 20 mg/L (e.g., at least 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 mg/L or higher). In certain exemplary embodiments, the IL-6 binding molecules are germlined variants which exhibit an expression level that is comparable to, or higher than, their parental, camelid counterparts. In other exemplary embodiments, the expression level is determined using the full-length IgG format of an IL-6 binding molecule of the invention, e.g., by transient expression in a HEK293 cell.

Binding molecules of the invention are also generally characterized by low predicted immunogenicity. For example, IL-6 binding molecules of the invention exhibit EpiBase® scores (e.g., total DRB1 scores) of less than 15.0, least than about 12.0, or less than about 10.0. In certain exemplary embodiments, the binding molecules exhibit immunogenicity scores of about 9.0, about 8.0, about 7.0, or about 6.0. In yet other embodiments, the immunogenicity score is less than the immunogenicity score of Humira®, e.g., about 6.0, about 5.0, or about 4.0.

Binding molecules of the invention can bind to any IL-6 including, without limitation, human and cynomolgus monkey IL-6. Preferably, binding molecules can bind to both human and cynomolgus monkey IL-6.

i) IL-6 Antibodies or Antigen Binding Fragments Thereof

In certain embodiments, the invention provides antibodies or antigen binding fragments thereof that specifically bind to IL-6 (e.g., human IL-6) and antagonize the binding of IL-6 to an IL-6 receptor. The VH, VL and CDR sequences of exemplary Fab clones of the invention are set forth in Tables 13-18. Antibodies of the invention can comprise any of the framework and/or CDR amino acid sequences of these Fab clones.

Antibodies of the invention can comprise a CDR region sequence with an amino acid residue (e.g., an aromatic amino acid, such as tryptophan or tyrosine) that is buried in the F229 cavity on IL-6 when the antibody or fragment to bound to IL-6. Exemplary antibodies comprise a VH domain with a tryptophan at position 98 and/or VL domain with a tyrosine at position 30, according to Kabat. Such antibodies have particularly high affinity for IL-6.

Additionally or alternatively, antibodies of the invention can comprise a CDR region sequence with an amino acid residue that is buried in the F279 cavity on IL-6 when the antibody or fragment to bound to IL-6. Exemplary antibodies comprise a VH domain with a valine at position 99, according to Kabat.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VH comprising 1, 2, or 3 CDR amino acid sequences from a VH set forth in Tables 13-16.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VL comprising 1, 2, or 3 CDR amino acid sequences from a VL set forth in Tables 13-16.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise: a VH comprising 1, 2, or 3 CDR amino acid sequences from a VH set forth in Tables 13-18; and a VL comprising 1, 2, or 3 CDR amino acid sequences from a VL set forth in Tables 13-18. In a preferred embodiment all six CDRs are from the same Fab clone.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VH set forth in Tables 13-16.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VL set forth in Tables 13-16.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VH and VL set forth in Tables 13-16.

In certain embodiments, the anti-IL-6 antibodies or fragments of the invention comprise a VH and VL from a single Fab clone set forth in Tables 13-16.

In certain embodiments, the invention provides antibodies or antigen binding fragments thereof that specifically bind to IL-6, the antibodies or fragments comprising a sequence variant of a CDR, VH, and VL amino acid sequences set forth in Tables 13-18.

In certain embodiments, the sequence variant comprises a VH and/or VL amino acid sequence with about 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to a VH or VL region amino acid sequences set forth in Tables 13-16.

In other embodiments, the sequence variant comprises a VH, VL, or CDR amino acid sequence selected from Tables 13-18 which has been altered by the introduction of one or more conservative amino acid substitutions. Conservative amino acid substitutions include the substitution of an amino acid in one class by an amino acid of the same class, where a class is defined by common physicochemical amino acid side chain properties and high substitution frequencies in homologous proteins found in nature, as determined, for example, by a standard Dayhoff frequency exchange matrix or BLOSUM matrix. Six general classes of amino acid side chains have been categorized and include: Class I (Cys); Class II (Ser, Thr, Pro, Ala, Gly); Class III (Asn, Asp, Gln, Glu); Class IV (His, Arg, Lys); Class V (Ile, Leu, Val, Met); and Class VI (Phe, Tyr, Trp). For example, substitution of an Asp for another class III residue such as Asn, Gln, or Glu, is a conservative substitution. Thus, a predicted nonessential amino acid residue in an IL-6 antibody or antigen binding fragment thereof is preferably replaced with another amino acid residue from the same class. Methods of identifying amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, e.g., Brummell *et al.*, Biochem. 32:1180-1187 (1993); Kobayashi *et al.* Protein Eng. 12(10):879-884 (1999); and Burks *et al.* Proc. Natl. Acad. Sci. USA 94:412-417 (1997)).

In other embodiments, the sequence variant comprises a VH, VL or CDR amino acid sequence selected from Tables 13-18 which has been altered to improve antibody production and/or manufacturing, e.g., exchange of a methionine to alanine, serine or leucine. In certain other embodiments, the sequence variant comprises a VH, VL or CDR amino acid sequence selected from Tables 13-18 which has been altered to improve antibody production, e.g.,

exchange of glutamine to glutamic acid or asparagine to alanine or related amino acids. In exemplary embodiments, one or more glutamines outside of CDR regions of VH amino acid sequences of Table 16 have been changed to glutamic acid(s), e.g., one or more glutamines at position 1, 3, 5, or 16 or any combination thereof of SEQ ID NO. 152 have been changed to glutamic acid(s) to improve antibody production or stability. In one particular embodiment, glutamine at position 1 of SEQ ID NO. 152 has been changed to glutamic acid.

ii) IL-6 Binding Molecules with High Human Homology

In certain aspects, the IL-6 binding molecules of the invention are antibodies (or antigen binding fragments) with high human homology. An antibody will be considered as having "high human homology" if the VH domains and the VL domains, taken together, exhibit at least 90% amino acid sequence identity to the closest matching human germline VH and VL sequences. Antibodies having high human homology may include antibodies comprising VH and VL domains of native non-human antibodies which exhibit sufficiently high % sequence identity human germline sequences, including for example antibodies comprising VH and VL domains of camelid conventional antibodies, as well as engineered, especially humanised, variants of such antibodies and also “fully human” antibodies.

In one embodiment the VH domain of the antibody with high human homology may exhibit an amino acid sequence identity or sequence homology of 80% or greater with one or more human VH domains across the framework regions FR1, FR2, FR3 and FR4. In other embodiments the amino acid sequence identity or sequence homology between the VH domain of the polypeptide of the invention and the closest matching human germline VH domain sequence may be 85% or greater, 90% or greater, 95% or greater, 97% or greater, or up to 99% or even 100%.

In one embodiment the VH domain of the antibody with high human homology may contain fewer than 10 (e.g. 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1) amino acid sequence substitutions across the framework regions FR1, FR2, FR3 and FR4, in comparison to the closest matched human VH sequence.

In another embodiment the VL domain of the antibody with high human homology may exhibit a sequence identity or sequence homology of 80% or greater with one or more human VL domains across the framework regions FR1, FR2, FR3 and FR4. In other embodiments the amino acid sequence identity or sequence homology between the VL domain of the polypeptide of the invention and the closest matching human germline VL

domain sequence may be 85% or greater 90% or greater, 95% or greater, 97% or greater, or up to 99% or even 100%.

In one embodiment the VL domain of the antibody with high human homology may contain fewer than 10 (e.g. 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1) amino acid sequence substitutions across the framework regions FR1, FR2, FR3 and FR4, in comparison to the closest matched human VL sequence.

Antibodies with high human homology may also comprise hypervariable loops or CDRs having human or human-like canonical folds, as discussed in detail below. In one embodiment at least one hypervariable loop or CDR in either the VH domain or the VL domain of the antibody with high human homology may be obtained or derived from a VH or VL domain of a non-human antibody, for example a conventional antibody from a species of Camelidae, yet exhibit a predicted or actual canonical fold structure which is substantially identical to a canonical fold structure which occurs in human antibodies.

It should be noted that antibodies with high human homology do not necessarily possess human or human-like canonical folds structures. For example, primate antibodies have high sequence homology to human antibodies yet often do not possess human or human-like canonical folds structures.

It is well established in the art that although the primary amino acid sequences of hypervariable loops present in both VH domains and VL domains encoded by the human germline are, by definition, highly variable, all hypervariable loops, except CDR H3 of the VH domain, adopt only a few distinct structural conformations, termed canonical folds (Chothia et al., J. Mol. Biol. 196:901-917 (1987); Tramontano et al. Proteins 6:382-94 (1989)), which depend on both the length of the hypervariable loop and presence of the so-called canonical amino acid residues (Chothia et al., J. Mol. Biol. 196:901-917 (1987)). Actual canonical structures of the hypervariable loops in intact VH or VL domains can be determined by structural analysis (e.g. X-ray crystallography), but it is also possible to predict canonical structure on the basis of key amino acid residues which are characteristic of a particular structure (discussed further below). In essence, the specific pattern of residues that determines each canonical structure forms a "signature" which enables the canonical structure to be recognised in hypervariable loops of a VH or VL domain of unknown structure; canonical structures can therefore be predicted on the basis of primary amino acid sequence alone.

The predicted canonical fold structures for the hypervariable loops of any given VH or VL sequence in an antibody with high human homology can be analysed using algorithms which are publicly available from www.bioinf.org.uk/abs/chothia.html, www.biochem.ucl.ac.uk/~martin/antibodies.html and www.bioc.unizh.ch/antibody/Sequences/Germlines/Vbase_hVk.html. These tools permit query VH or VL sequences to be aligned against human VH or VL domain sequences of known canonical structure, and a prediction of canonical structure made for the hypervariable loops of the query sequence.

In the case of the VH domain, H1 and H2 loops may be scored as having a canonical fold structure "substantially identical" to a canonical fold structure known to occur in human antibodies if at least the first, and preferable both, of the following criteria are fulfilled:

1. An identical length, determined by the number of residues, to the closest matching human canonical structural class.

2. At least 33% identity, preferably at least 50% identity with the key amino acid residues described for the corresponding human H1 and H2 canonical structural classes.

(note for the purposes of the foregoing analysis the H1 and H2 loops are treated separately and each compared against its closest matching human canonical structural class)

The foregoing analysis relies on prediction of the canonical structure of the H1 and H2 loops of the antibody of interest. If the actual structures of the H1 and H2 loops in the antibody of interest are known, for example based on X-ray crystallography, then the H1 and H2 loops in the antibody of interest may also be scored as having a canonical fold structure "substantially identical" to a canonical fold structure known to occur in human antibodies if the length of the loop differs from that of the closest matching human canonical structural class (typically by ±1 or ±2 amino acids) but the actual structure of the H1 and H2 loops in the antibody of interest matches the structure of a human canonical fold.

Key amino acid residues found in the human canonical structural classes for the first and second hypervariable loops of human VH domains (H1 and H2) are described by Chothia et al., J. Mol. Biol. 227:799-817 (1992), the contents of which are incorporated herein in their entirety by reference. In particular, Table 3 on page 802 of Chothia et al., which is

specifically incorporated herein by reference, lists preferred amino acid residues at key sites for H1 canonical structures found in the human germline, whereas Table 4 on page 803, also specifically incorporated by reference, lists preferred amino acid residues at key sites for CDR H2 canonical structures found in the human germline.

In one embodiment, both H1 and H2 in the VH domain of the antibody with high human homology exhibit a predicted or actual canonical fold structure which is substantially identical to a canonical fold structure which occurs in human antibodies.

Antibodies with high human homology may comprise a VH domain in which the hypervariable loops H1 and H2 form a combination of canonical fold structures which is identical to a combination of canonical structures known to occur in at least one human germline VH domain. It has been observed that only certain combinations of canonical fold structures at H1 and H2 actually occur in VH domains encoded by the human germline. In an embodiment H1 and H2 in the VH domain of the antibody with high human homology may be obtained from a VH domain of a non-human species, e.g. a Camelidae species, yet form a combination of predicted or actual canonical fold structures which is identical to a combination of canonical fold structures known to occur in a human germline or somatically mutated VH domain. In non-limiting embodiments H1 and H2 in the VH domain of the antibody with high human homology may be obtained from a VH domain of a non-human species, e.g. a Camelidae species, and form one of the following canonical fold combinations: 1-1, 1-2, 1-3, 1-6, 1-4, 2-1, 3-1 and 3-5.

An antibody with high human homology may contain a VH domain which exhibits both high sequence identity/sequence homology with human VH, and which contains hypervariable loops exhibiting structural homology with human VH.

It may be advantageous for the canonical folds present at H1 and H2 in the VH domain of the antibody with high human homology, and the combination thereof, to be "correct" for the human VH germline sequence which represents the closest match with the VH domain of the antibody with high human homology in terms of overall primary amino acid sequence identity. By way of example, if the closest sequence match is with a human germline VH3 domain, then it may be advantageous for H1 and H2 to form a combination of canonical folds which also occurs naturally in a human VH3 domain. This may be particularly important in the case of antibodies with high human homology which are derived from non-human species, e.g. antibodies containing VH and VL domains which are derived

from camelid conventional antibodies, especially antibodies containing humanised camelid VH and VL domains.

Thus, in one embodiment the VH domain of the IL-6 antibody with high human homology may exhibit a sequence identity or sequence homology of 80% or greater, 85% or greater, 90% or greater, 95% or greater, 97% or greater, or up to 99% or even 100% with a human VH domain across the framework regions FR1, FR2 , FR3 and FR4, and in addition H1 and H2 in the same antibody are obtained from a non-human VH domain (e.g. derived from a Camelidae species), but form a combination of predicted or actual canonical fold structures which is the same as a canonical fold combination known to occur naturally in the same human VH domain.

For example, in one exemplary embodiment, the H1 and H2 loops of an IL-6 antibody of the invention (e.g., 61H7) may comprise the 1-2 combination human canonical fold structures as found, for example, in the human antibody structure 1DFB. In another exemplary embodiment, the H1 and H2 of an IL-6 antibody of the invention (e.g., 68F2 or its germlined variant 129D3) loops may comprise the 3-1 combination of human canonical fold structures as found, for example, in the human antibody structure 1ACY.

In other embodiments, L1 and L2 in the VL domain of the antibody with high human homology are each obtained from a VL domain of a non-human species (e.g. a camelid-derived VL domain), and each exhibits a predicted or actual canonical fold structure which is substantially identical to a canonical fold structure which occurs in human antibodies.

As with the VH domains, the hypervariable loops of VL domains of both VLambda and VKappa types can adopt a limited number of conformations or canonical structures, determined in part by length and also by the presence of key amino acid residues at certain canonical positions.

Within an antibody of interest having high human homology, L1, L2 and L3 loops obtained from a VL domain of a non-human species, e.g. a *Camelidae* species, may be scored as having a canonical fold structure "substantially identical" to a canonical fold structure known to occur in human antibodies if at least the first, and preferable both, of the following criteria are fulfilled:

1. An identical length, determined by the number of amino acid residues, to the closest matching human structural class.

2. At least 33% identity, preferably at least 50% identity with the key amino acid residues described for the corresponding human L1 or L2 canonical structural classes, from either the VLambda or the VKappa repertoire.

(note for the purposes of the foregoing analysis the L1 and L2 loops are treated separately and each compared against its closest matching human canonical structural class).

The foregoing analysis relies on prediction of the canonical structure of the L1, L2 and L3 loops in the VL domain of the antibody of interest. If the actual structure of the L1, L2 and L3 loops is known, for example based on X-ray crystallography, then L1, L2 or L3 loops derived from the antibody of interest may also be scored as having a canonical fold structure "substantially identical" to a canonical fold structure known to occur in human antibodies if the length of the loop differs from that of the closest matching human canonical structural class (typically by ±1 or ±2 amino acids) but the actual structure of the Camelidae loops matches a human canonical fold.

Key amino acid residues found in the human canonical structural classes for the CDRs of human VLambda and VKappa domains are described by Morea et al. Methods, 20: 267-279 (2000) and Martin et al., J. Mol. Biol., 263:800-815 (1996). The structural repertoire of the human VKappa domain is also described by Tomlinson et al. EMBO J. 14:4628-4638 (1995), and that of the VLambda domain by Williams et al. J. Mol. Biol., 264:220-232 (1996). The contents of all these documents are to be incorporated herein by reference.

L1 and L2 in the VL domain of an antibody with high human homology may form a combination of predicted or actual canonical fold structures which is identical to a combination of canonical fold structures known to occur in a human germline VL domain. In non-limiting embodiments L1 and L2 in the VLambda domain of an antibody with high human homology (e.g. an antibody containing a camelid-derived VL domain or a humanised variant thereof) may form one of the following canonical fold combinations: 11-7, 13-7(A,B,C), 14-7(A,B), 12-11, 14-11 and 12-12 (as defined in Williams et al. J. Mol. Biol. 264:220 -32 (1996) and as shown on http://www.bioc.uzh.ch/antibody/Sequences/Germlines/VBase_hVL.html). In non-limiting embodiments L1 and L2 in the Vkappa domain may form one of the following canonical fold combinations: 2-1, 3-1, 4-1 and 6-1 (as defined in Tomlinson et al. EMBO J. 14:4628-38 (1995) and as shown on http://www.bioc.uzh.ch/antibody/Sequences/Germlines/VBase_hVK.html). For example, in

one exemplary embodiment, the L1 and L2 loops of an IL-6 antibody of the invention (e.g., 61H7) may comprise the 7λ-1 combination human canonical fold structures as found, for example, in the human antibody structure 1MFA. In another exemplary embodiment, the L1 and L2 of an IL-6 antibody of the invention (e.g., 68F2 or its germlined variant 129D3) loops may comprise the 6λ-1 combination of human canonical fold structures as found, for example, in the human antibody structure 3MUG.

In a further embodiment, all three of L1, L2 and L3 in the VL domain of an antibody with high human homology may exhibit a substantially human structure. It is preferred that the VL domain of the antibody with high human homology exhibits both high sequence identity/sequence homology with human VL, and also that the hypervariable loops in the VL domain exhibit structural homology with human VL. For example, in one exemplary embodiment, loops L1-L3 of an IL-6 antibody of the invention (e.g., 61H7) may comprise the 7λ-1-4 combination human canonical fold structures as found, for example, in the human antibody structure 1MFA. In another exemplary embodiment, the L1-L3 of an IL-6 antibody of the invention (e.g., 68F2 or its germlined variant 129D3) loops may comprise the 6λ-1-5 combination of human canonical fold structures as found, for example, in the human antibody structure 3MUG.

In one embodiment, the VL domain of a IL-6 antibody with high human homology may exhibit a sequence identity of 80% or greater, 85% or greater, 90% or greater, 95% or greater, 97% or greater, or up to 99% or even 100% with a human VL domain across the framework regions FR1, FR2 , FR3 and FR4, and in addition hypervariable loop L1 and hypervariable loop L2 may form a combination of predicted or actual canonical fold structures which is the same as a canonical fold combination known to occur naturally in the same human VL domain.

It is, of course, envisaged that VH domains exhibiting high sequence identity/sequence homology with human VH, and also structural homology with hypervariable loops of human VH will be combined with VL domains exhibiting high sequence identity/sequence homology with human VL, and also structural homology with hypervariable loops of human VL to provide antibodies with high human homology containing VH/VL pairings (e.g camelid-derived VH/VL pairings) with maximal sequence and structural homology to human-encoded VH/VL pairings.

iii). Non-immunoglobulin Binding Molecules

In a further aspect, the invention provides non-immunoglobulin binding molecules that specifically bind to IL-6. As used herein, the term "non-immunoglobulin binding molecules" are binding molecules whose binding sites comprise a portion (e.g., a scaffold or framework) derived from a polypeptide other than an immunoglobulin, but which may be engineered (e.g., by the addition of CDR region sequences) to confer a desired binding specificity to the binding molecule. The non-immunoglobulin binding molecules of the invention generally comprise one or more of the CDR regions set forth in Tables 13-18 grafted into a non-immunoglobulin polypeptide.

In certain embodiments, non-immunoglobulin binding molecules comprise binding site portions that are derived from a member of the immunoglobulin superfamily that is not an immunoglobulin (e.g. a T-cell receptor or a cell-adhesion protein (e.g., CTLA-4, N-CAM, telokin)). Such binding molecules comprise a binding site portion which retains the conformation of an immunoglobulin fold and is capable of specifically binding to IL-6 when modified to include one or more of the CDR region set forth in Tables 13-18. In other embodiments, non-immunoglobulin binding molecules of the invention comprise a binding site with a protein topology that is not based on the immunoglobulin fold (e.g. ankyrin repeat proteins, tetranectins, and fibronectins) but which nonetheless are capable of specifically binding to a target (e.g. IL-6) when modified to include one or more of the CDR region set forth in Tables 13-18.

In one embodiment, a binding molecule of the invention comprises a tetranectin molecule. Tetranectins are plasma proteins of trivalent structure. Each monomer of the tetranectin trimer comprises five distinct amino-acid loops that can be can be replaced by or engineered to contain antibody CDR sequences (e.g., CDR regions set forth in Tables 13-18). Methods for making tetranectin binding polypeptides are described, for example, in US20110086770, which is incorporated by reference herein in its entirety.

In one embodiment, a binding molecule of the invention comprises a fibronectin molecule. Fibronectin binding molecules (e.g., molecules comprising the Fibronectin type I, II, or III domains) display CDR-like loops which can be replaced by or engineered to contain antibody CDR sequences (e.g., CDR regions set forth in Tables 13-18). Methods for making fibronectin binding polypeptides are described, for example, in WO 01/64942 and in U.S. Pat. Nos. 6,673,901, 6,703,199, 7,078,490, and 7,119,171, which are each incorporated herein by reference in their entirety.

In another embodiment, a binding molecule of the invention comprises a binding site

from an affibody. Affibodies are derived from the immunoglobulin binding domains of staphylococcal Protein A (SPA) (see e.g., Nord et al., Nat. Biotechnol., 15: 772-777 (1997)). Affibody binding sites employed in the invention may be synthesized by mutagenizing an SPA-related protein (e.g., Protein Z) derived from a domain of SPA (e.g., domain B) and selecting for mutant SPA-related polypeptides having binding affinity for IL-6. Other methods for making affibody binding sites are described in U.S. Pat. Nos. 6,740,734 and 6,602,977 and in WO 00/63243, each of which is incorporated herein by reference.

In another embodiment, a binding molecule of the invention comprises a binding site from an anticalin. Anticalins (also known as lipocalins) are members of a diverse beta-barrel protein family whose function is to bind target molecules in their barrel/loop region. Lipocalin binding sites may be engineered to bind IL-6 by randomizing loop sequences connecting the strands of the barrel (see e.g., Schlehuber et al., Drug Discov. Today, 10: 23-33 (2005); Beste et al., PNAS, 96: 1898-1903 (1999). Anticalin binding sites employed in the binding molecules of the invention may be obtainable starting from polypeptides of the lipocalin family which are mutated in four segments that correspond to the sequence positions of the linear polypeptide sequence comprising amino acid positions 28 to 45, 58 to 69, 86 to 99 and 114 to 129 of the Bilin-binding protein (BBP) of Pieris brassica. Other methods for making anticalin binding sites are described in WO99/16873 and WO 05/019254, each of which is incorporated herein by reference.

In another embodiment, a binding molecule of the invention comprises a binding site from a cysteine-rich polypeptide. Cysteine-rich domains employed in the practice of the present invention typically do not form an alpha-helix, a beta-sheet, or a beta-barrel structure. Typically, the disulfide bonds promote folding of the domain into a three-dimensional structure. Usually, cysteine-rich domains have at least two disulfide bonds, more typically at least three disulfide bonds. An exemplary cysteine-rich polypeptide is an A domain protein. A-domains (sometimes called "complement-type repeats") contain about 30-50 or 30-65 amino acids. In some embodiments, the domains comprise about 35-45 amino acids and in some cases about 40 amino acids. Within the 30-50 amino acids, there are about 6 cysteine residues. Of the six cysteines, disulfide bonds typically are found between the following cysteines: C1 and C3, C2 and C5, C4 and C6. The A domain constitutes a ligand binding moiety. The cysteine residues of the domain are disulfide linked to form a compact, stable, functionally independent moiety. Clusters of these repeats make up a ligand binding domain, and differential clustering can impart specificity with respect to the ligand binding.

Exemplary proteins containing A-domains include, e.g., complement components (e.g., C6, C7, C8, C9, and Factor I), serine proteases (e.g., enteropeptidase, matriptase, and corin), transmembrane proteins (e.g., ST7, LRP3, LRP5 and LRP6) and endocytic receptors (e.g., Sortilin-related receptor, LDL-receptor, VLDLR, LRP1, LRP2, and ApoER2). Methods for making A domain proteins of a desired binding specificity are disclosed, for example, in WO 02/088171 and WO 04/044011, each of which is incorporated herein by reference.

In other embodiments, a binding molecule of the invention comprises a binding site from a repeat protein. Repeat proteins are proteins that contain consecutive copies of small (e.g., about 20 to about 40 amino acid residues) structural units or repeats that stack together to form contiguous domains. Repeat proteins can be modified to suit a particular target binding site by adjusting the number of repeats in the protein. Exemplary repeat proteins include designed ankyrin repeat proteins (i.e., a DARPins) (see e.g., Binz et al., Nat. Biotechnol., 22: 575-582 (2004)) or leucine-rich repeat proteins (i.e., LRRPs) (see e.g., Pancer et al., Nature, 430: 174-180 (2004)). All so far determined tertiary structures of ankyrin repeat units share a characteristic composed of a beta-hairpin followed by two antiparallel alpha-helices and ending with a loop connecting the repeat unit with the next one. Domains built of ankyrin repeat units are formed by stacking the repeat units to an extended and curved structure. LRRP binding sites from part of the adaptive immune system of sea lampreys and other jawless fishes and resemble antibodies in that they are formed by recombination of a suite of leucine-rich repeat genes during lymphocyte maturation. Methods for making DARpin or LRRP binding sites are described in WO 02/20565 and WO 06/083275, each of which is incorporated herein by reference.

Other non-immunoglobulin binding sites which may be employed in binding molecules of the invention include binding sites derived from Src homology domains (e.g. SH2 or SH3 domains), PDZ domains, beta-lactamase, high affinity protease inhibitors, or small disulfide binding protein scaffolds such as scorpion toxins. Methods for making binding sites derived from these molecules have been disclosed in the art, see e.g., Panni et al, J. Biol. Chem., 277: 21666-21674 (2002), Schneider et al., Nat. Biotechnol., 17: 170-175 (1999); Legendre et al., Protein Sci., 11:1506-1518 (2002); Stoop et al., Nat. Biotechnol., 21: 1063-1068 (2003); and Vita et al., PNAS, 92: 6404-6408 (1995). Yet other binding sites may be derived from a binding domain selected from the group consisting of an EGF-like domain, a Kringle-domain, a PAN domain, a Gla domain, a SRCR domain, a Kunitz/Bovine pancreatic trypsin Inhibitor domain, a Kazal-type serine protease inhibitor domain, a Trefoil

(P-type) domain, a von Willebrand factor type C domain, an Anaphylatoxin-like domain, a CUB domain, a thyroglobulin type I repeat, LDL-receptor class A domain, a Sushi domain, a Link domain, a Thrombospondin type I domain, an Immunoglobulin-like domain, a C-type lectin domain, a MAM domain, a von Willebrand factor type A domain, a Somatomedin B domain, a WAP-type four disulfide core domain, a F5/8 type C domain, a Hemopexin domain, a Laminin-type EGF-like domain, a C2 domain, and other such domains known to those of ordinary skill in the art, as well as derivatives and/or variants thereof.

Non-immunoglobulin binding molecules may be identified by selection or isolation of a target-binding variant from a library of binding molecules having artificially diversified binding sites. Diversified libraries can be generated incorporation of a library of CDR sequences (e.g., selected from those CDR sequences set forth in **Tables 13-18**) and/or completely random approaches (e.g., error-prone PCR, exon shuffling, or directed evolution) and/or aided by art-recognized design strategies. For example, amino acid positions that are usually involved when the binding site interacts with its cognate target molecule can be randomized by insertion of degenerate codons, trinucleotides, random peptides, or entire loops at corresponding positions within the nucleic acid which encodes the binding site (see e.g., U.S. Pub. No. 20040132028). The location of the amino acid positions can be identified by investigation of the crystal structure of the binding site in complex with the target molecule. Candidate positions for incorporation of CDR sequences (e.g., selected from those CDR sequences set forth in **Tables 13-18**) and/or randomization include loops, flat surfaces, helices, and binding cavities of the binding site. In certain embodiments, amino acids within the binding site that are likely candidates for diversification can be identified by their homology with the immunoglobulin fold. For example, residues within the CDR-like loops of fibronectin may be randomized to generate a library of fibronectin binding molecules (see, e.g., Koide et al., J. Mol. Biol., 284: 1141-1151 (1998)). Following incorporation of CDR sequences (e.g., selected from those CDR sequences set forth in Table 2-6) and/or randomization, the diversified library may then be subjected to a selection or screening procedure to obtain binding molecules with the desired binding characteristics, e.g. specific binding to IL-6. Selection can be achieved by art-recognized methods such as phage display, yeast display, or nucleic acid display.

iv. Germlining of Camelid-Derived VH and VL Domains

Camelid conventional antibodies provide an advantageous starting point for the preparation of antibodies with utility as human therapeutic agents due to the following factors (discussed in US 12/497,239, which is incorporated herein by reference in its entirety):

1) High % sequence homology between camelid VH and VL domains and their human counterparts;

2) High degree of structural homology between CDRs of camelid VH and VL domains and their human counterparts (i.e. human-like canonical fold structures and human-like combinations of canonical folds).

The camelid (e.g. llama) platform also provides a significant advantage in terms of the functional diversity of the IL-6 antibodies which can be obtained.

The utility of IL-6 antibodies comprising camelid VH and/or camelid VL domains for human therapy can be improved still further by "germlining" of natural camelid VH and VL domains, for example to render them less immunogenic in a human host. The overall aim of germlining is to produce a molecule in which the VH and VL domains exhibit minimal immunogenicity when introduced into a human subject, while retaining the specificity and affinity of the antigen binding site formed by the parental VH and VL domains.

Determination of homology between a camelid VH (or VL) domain and human VH (or VL) domains is a critical step in the germlining process, both for selection of camelid amino acid residues to be changed (in a given VH or VL domain) and for selecting the appropriate replacement amino acid residue(s).

An approach to germlining of camelid conventional antibodies has been developed based on alignment of a large number of novel camelid VH (and VL) domain sequences, typically somatically mutated VH (or VL) domains which are known to bind a target antigen, with human germline VH (or VL) sequences, human VH (and VL) consensus sequences, as well as germline sequence information available for llama pacos.

The following passages outline the principles which can be applied to (i) select "camelid" amino acid residues for replacement in a camelid-derived VH or VL domain or a CDR thereof, and (ii) select replacement "human" amino acid residues to substitute in, when germlining any given camelid VH (or VL) domain. This approach can be used to prepare germlined variants of the VH and VL sequences set forth in **Tables 13-16**, herein.

Step 1. Select human (germline) family and member of this family that shows highest homology/identity to the mature camelid sequence to be germlined. A general procedure for

identifying the closest matching human germline for any given camelid VH (or VL) domain is outlined below.

Step 2. Select specific human germline family member used to germline against. Preferably this is the germline with the highest homology or another germline family member from the same family.

Step 3. Identify the preferred positions considered for germlining on the basis of the table of amino acid utilisation for the camelid germline that is closest to the selected human germline.

Step 4. Try to change amino acids in the camelid germline that deviate from the closest human germline; germlining of FR residues is preferred over CDR residues.

a. Preferred are positions that are deviating from the selected human germline used to germline against, for which the amino acid found in the camelid sequence does not match with the selected germline and is not found in other germlines of the same subclass (both for V as well as for J encoded FR amino acids).

b. Positions that are deviating from the selected human germline family member but which are used in other germlines of the same family may also be addressed in the germlining process.

c. Additional mismatches (e.g. due to additional somatic mutations) towards the selected human germline may also be addressed.

The following approach may be used to determine the closest matching human germline for a given camelid VH (or VL) domain:

Before analyzing the percentage sequence identity between Camelidae and human germline VH and VL, the canonical folds may first be determined, which allows the identification of the family of human germline segments with the identical combination of canonical folds for H1 and H2 or L1 and L2 (and L3). Subsequently the human germline family member that has the highest degree of sequence homology with the Camelidae variable region of interest may be chosen for scoring sequence homology. The determination of Chothia canonical classes of hypervariable loops L1, L2, L3, H1 and H2 can be performed with the bioinformatics tools publicly available on webpage www.bioinf.org.uk/abs/chothia.html.page. The output of the program shows the key residue requirements in a datafile. In these datafiles, the key residue positions are shown with the allowed amino acids at each position. The sequence of the variable region of the antibody is

given as input and is first aligned with a consensus antibody sequence to assign the Kabat numbering scheme. The analysis of the canonical folds uses a set of key residue templates derived by an automated method developed by Martin and Thornton (Martin et al., J. Mol. Biol. 263:800-815 (1996)). The boundaries of the individual framework regions may be assigned using the IMGT numbering scheme, which is an adaptation of the numbering scheme of Chothia (Lefranc et al., NAR 27: 209-212 (1999); imgt.cines.fr).

With the particular human germline V segment known, which uses the same combination of canonical folds for H1 and H2 or L1 and L2 (and L3), the best matching family member in terms of sequence homology can be determined. The percentage sequence identity between Camelidae VH and VL domain framework amino acid sequences and corresponding sequences encoded by the human germline can be determined using bioinformatic tools, but manual alignment of the sequences could also be used. Human immunoglobulin sequences can be identified from several protein data bases, such as VBase (vbase.mrc-cpe.cam.ac.uk/) or the Pluckthun/Honegger database (http://www.bioc.unizh.ch/antibody/Sequences/Germlines. To compare the human sequences to the V regions of Camelidae VH or VL domains a sequence alignment algorithm such as available via websites like www.expasy.ch/tools/#align can be used, but also manual alignment can also be performed with a limited set of sequences. Human germline light and heavy chain sequences of the families with the same combinations of canonical folds and with the highest degree of homology with the framework regions 1, 2, and 3 of each chain may be selected and compared with the Camelidae variable region of interest; also the FR4 is checked against the human germline JH and JK or JL regions.

Note that in the calculation of overall percent sequence homology the residues of FR1, FR2 and FR3 are evaluated using the closest match sequence from the human germline family with the identical combination of canonical folds. Only residues different from the closest match or other members of the same family with the same combination of canonical folds are scored (NB - excluding any primer-encoded differences). However, for the purposes of germlining, residues in framework regions identical to members of other human germline families, which do not have the same combination of canonical folds, can be considered for germlining, despite the fact that these are scored “negative” according to the stringent conditions described above. This assumption is based on the "mix and match" approach for germlining, in which each of FR1, FR2, FR3 and FR4 is separately compared to its closest matching human germline sequence and the germlined molecule therefore contains

a combination of different FRs as was done by Qu and colleagues (Qu et la., Clin. Cancer Res. 5:3095-3100 (1999)) and Ono and colleagues (Ono et al., Mol. Immunol. 36:387-395 (1999)).

IV. Modified Binding Molecules

In certain embodiments, binding polypeptides of the invention may comprise one or more modifications. Modified forms of binding polypeptides of the invention can be made using any techniques known in the art.

i) Reducing Immunogenicity Risk

In certain embodiments, binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention are modified to further reduce their immunogenicity risk using art-recognized techniques. For example, antibodies, or fragments thereof, can be germlined according to the methods describe above. Alternatively, binding molecules of the invention can be chimericized, humanized, and/or deimmunized.

In one embodiment, an antibody, or antigen binding fragments thereof, of the invention may be chimeric. A chimeric antibody is an antibody in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a camelid (e.g., llama) monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies, or fragments thereof, are known in the art. See, e.g., Morrison, Science 229:1202 (1985); Oi *et al.*, BioTechniques 4:214 (1986); Gillies *et al.*, J. Immunol. Methods 125:191-202 (1989); U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. Techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger *et al.*, Nature 312:604-608 (1984); Takeda *et al.*, Nature 314:452-454 (1985)) may be employed for the synthesis of said molecules. For example, a genetic sequence encoding a binding specificity of a camelid anti-IL-6 antibody molecule may be fused together with a sequence from a human antibody molecule of appropriate biological activity. As used herein, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a camelid (e.g., llama) monoclonal antibody and a human immunoglobulin constant region, e.g., germlined or humanized antibodies.

In another embodiment, an antibody, or antigen binding portion thereof, of the invention is humanized. Humanized antibodies have a binding specificity comprising one or more complementarity determining regions (CDRs) from a non-human antibody and framework regions from a human antibody molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen *et al.*, U.S. Pat. No. 5,585,089; Riechmann *et al.*, Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka *et al.*, Protein Engineering 7(6):805-814 (1994); Roguska. *et al.*, PNAS 91:969-973 (1994)), and chain shuffling (U.S. Pat. No. 5,565,332).

In some embodiments, de-immunization can be used to further decrease the immunogenicity risk of IL-6 binding molecules (e.g., antibody, or antigen binding portion thereof). As used herein, the term "de-immunization" includes alteration of polypeptide (e.g., an antibody, or antigen binding portion thereof) to modify T cell epitopes (see, e.g., WO9852976A1, WO0034317A2). For example, VH and VL sequences from the starting IL-6-specific antibody, or antigen binding portion thereof, of the invention may be analyzed and a human T cell epitope "map" may be generated from each V region showing the location of epitopes in relation to complementarity-determining regions (CDRs) and other key residues within the sequence. Individual T cell epitopes from the T cell epitope map are analyzed in order to identify alternative amino acid substitutions with a low risk of altering activity of the final antibody. A range of alternative VH and VL sequences are designed comprising combinations of amino acid substitutions and these sequences are subsequently incorporated into a range of IL-6-specific antibodies or fragments thereof for use in the diagnostic and treatment methods disclosed herein, which are then tested for function. Typically, between 12 and 24 variant antibodies are generated and tested. Complete heavy and light chain genes

comprising modified V and human C regions are then cloned into expression vectors and the subsequent plasmids introduced into cell lines for the production of whole antibody. The antibodies are then compared in appropriate biochemical and biological assays, and the optimal variant is identified.

ii) Effector Functions and Fc Modifications

In certain embodiments, binding molecules of the invention may comprise an antibody constant region (e.g. an IgG constant region e.g., a human IgG constant region, e.g., a human IgG1 or IgG4 constant region) which mediates one or more effector functions. For example, binding of the C1 component of complement to an antibody constant region may activate the complement system. Activation of complement is important in the opsonisation and lysis of cell pathogens. The activation of complement also stimulates the inflammatory response and may also be involved in autoimmune hypersensitivity. Further, antibodies bind to receptors on various cells via the Fc region, with a Fc receptor binding site on the antibody Fc region binding to a Fc receptor (FcR) on a cell. There are a number of Fc receptors which are specific for different classes of antibody, including IgG (gamma receptors), IgE (epsilon receptors), IgA (alpha receptors) and IgM (mu receptors). Binding of antibody to Fc receptors on cell surfaces triggers a number of important and diverse biological responses including engulfment and destruction of antibody-coated particles, clearance of immune complexes, lysis of antibody-coated target cells by killer cells (called antibody-dependent cell-mediated cytotoxicity, or ADCC), release of inflammatory mediators, placental transfer and control of immunoglobulin production. In preferred embodiments, the binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention bind to an Fc-gamma receptor. In alternative embodiments, binding molecules of the invention may comprise a constant region which is devoid of one or more effector functions (e.g., ADCC activity) and/or is unable to bind Fcγ receptor.

Certain embodiments of the invention include anti-IL-6 antibodies in which at least one amino acid in one or more of the constant region domains has been deleted or otherwise altered so as to provide desired biochemical characteristics such as reduced or enhanced effector functions, the ability to non-covalently dimerize, increased ability to localize at the site of a tumor, reduced serum half-life, or increased serum half-life when compared with a whole, unaltered antibody of approximately the same immunogenicity. For example, certain

antibodies, or fragments thereof, for use in the diagnostic and treatment methods described herein are domain deleted antibodies which comprise a polypeptide chain similar to an immunoglobulin heavy chain, but which lack at least a portion of one or more heavy chain domains. For instance, in certain antibodies, one entire domain of the constant region of the modified antibody will be deleted, for example, all or part of the CH2 domain will be deleted.

In certain other embodiments, binding molecules comprise constant regions derived from different antibody isotypes (e.g., constant regions from two or more of a human IgG1, IgG2, IgG3, or IgG4). In other embodiments, binding molecules comprises a chimeric hinge (i.e., a hinge comprising hinge portions derived from hinge domains of different antibody isotypes, e.g., an upper hinge domain from an IgG4 molecule and an IgG1 middle hinge domain). In one embodiment, binding molecules comprise an Fc region or portion thereof from a human IgG4 molecule and a Ser228Pro mutation (EU numbering) in the core hinge region of the molecule.

In certain embodiments, the Fc portion may be mutated to increase or decrease effector function using techniques known in the art. For example, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating modified antibody thereby increasing tumor localization. In other cases it may be that constant region modifications consistent with the instant invention moderate complement binding and thus reduce the serum half life and nonspecific association of a conjugated cytotoxin. Yet other modifications of the constant region may be used to modify disulfide linkages or oligosaccharide moieties that allow for enhanced localization due to increased antigen specificity or flexibility. The resulting physiological profile, bioavailability and other biochemical effects of the modifications, such as tumor localization, biodistribution and serum half-life, may easily be measured and quantified using well know immunological techniques without undue experimentation.

In certain embodiments, an Fc domain employed in an antibody of the invention is an Fc variant. As used herein, the term "Fc variant" refers to an Fc domain having at least one amino acid substitution relative to the wild-type Fc domain from which said Fc domain is derived. For example, wherein the Fc domain is derived from a human IgG1 antibody, the Fc variant of said human IgG1 Fc domain comprises at least one amino acid substitution relative to said Fc domain.

The amino acid substitution(s) of an Fc variant may be located at any position (i.e., any EU convention amino acid position) within the Fc domain. In one embodiment, the Fc

variant comprises a substitution at an amino acid position located in a hinge domain or portion thereof. In another embodiment, the Fc variant comprises a substitution at an amino acid position located in a CH2 domain or portion thereof. In another embodiment, the Fc variant comprises a substitution at an amino acid position located in a CH3 domain or portion thereof. In another embodiment, the Fc variant comprises a substitution at an amino acid position located in a CH4 domain or portion thereof.

The binding molecules of the invention may employ any art-recognized Fc variant which is known to impart an improvement (e.g., reduction or enhancement) in effector function and/or FcR binding. Said Fc variants may include, for example, any one of the amino acid substitutions disclosed in International PCT Publications WO88/07089A1, WO96/14339A1, WO98/05787A1, WO98/23289A1, WO99/51642A1, WO99/58572A1, WO00/09560A2, WO00/32767A1, WO00/42072A2, WO02/44215A2, WO02/060919A2, WO03/074569A2, WO04/016750A2, WO04/029207A2, WO04/035752A2, WO04/063351A2, WO04/074455A2, WO04/099249A2, WO05/040217A2, WO05/070963A1, WO05/077981A2, WO05/092925A2, WO05/123780A2, WO06/019447A1, WO06/047350A2, and WO06/085967A2 or U.S. Pat. Nos. 5,648,260; 5,739,277; 5,834,250; 5,869,046; 6,096,871; 6,121,022; 6,194,551; 6,242,195; 6,277,375; 6,528,624; 6,538,124; 6,737,056; 6,821,505; 6,998,253; and 7,083,784, each of which is incorporated by reference herein. In one exemplary embodiment, a binding polypeptide of the invention may comprise an Fc variant comprising an amino acid substitution at EU position 268 (e.g., H268D or H268E). In another exemplary embodiment, a binding polypeptide of the invention may comprise an amino acid substitution at EU position 239 (e.g., S239D or S239E) and/or EU position 332 (e.g., I332D or I332Q).

In certain embodiments, a binding polypeptide of the invention may comprise an Fc variant comprising an amino acid substitution which alters the antigen-independent effector functions of the antibody, in particular the circulating half-life of the binding polypeptide. Such binding molecules exhibit either increased or decreased binding to FcRn when compared to binding molecules lacking these substitutions, therefore, have an increased or decreased half-life in serum, respectively. Fc variants with improved affinity for FcRn are anticipated to have longer serum half-lives, and such molecules have useful applications in methods of treating mammals where long half-life of the administered antibody is desired, e.g., to treat a chronic disease or disorder. In contrast, Fc variants with decreased FcRn binding affinity are expected to have shorter half-lives, and such molecules are also useful,

for example, for administration to a mammal where a shortened circulation time may be advantageous, e.g. for in vivo diagnostic imaging or in situations where the starting antibody has toxic side effects when present in the circulation for prolonged periods. Fc variants with decreased FcRn binding affinity are also less likely to cross the placenta and, thus, are also useful in the treatment of diseases or disorders in pregnant women.

In addition, other applications in which reduced FcRn binding affinity may be desired include those applications in which localization the brain, kidney, and/or liver is desired. In one exemplary embodiment, the altered binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention exhibit reduced transport across the epithelium of kidney glomeruli from the vasculature. In another embodiment, the altered binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention exhibit reduced transport across the blood brain barrier (BBB) from the brain, into the vascular space. In one embodiment, an antibody with altered FcRn binding comprises an Fc domain having one or more amino acid substitutions within the "FcRn binding loop" of an Fc domain. The FcRn binding loop is comprised of amino acid residues 280-299 (according to EU numbering). Exemplary amino acid substitutions which altered FcRn binding activity are disclosed in International PCT Publication No. WO05/047327 which is incorporated by reference herein.

In certain exemplary embodiments, the binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention comprise an Fc domain having one or more of the following substitutions: V284E, H285E, N286D, K290E and S304D (EU numbering). In yet other exemplary embodiments, the binding molecules of the invention comprise a human Fc domain with the double mutation H433K/N434F (see, e.g., US Patent No. 8,163,881). In a particular embodiment, the binding molecules of the invention comprise one or more variable regions selected from Table 16 and a human Fc domain with the double mutation H433K/N434F. In another particular embodiment, the binding molecule of the invention comprise one or more CDR sequences from Table 17 and a human Fc domain with the double mutation H433K/N434F. In yet another particular embodiment, the binding molecule of the invention comprise a VH domain of SEQ ID NO. 152 and a human Fc domain with the double mutation H433K/N434F. In still another particular embodiment, the binding molecule of the invention comprise a VH domain of SEQ ID NO. 152 wherein glutamine at one or more positions, e.g., position 1, 3, 5, or 16 or any combination thereof has been changed to glutamic acid(s) and a human Fc domain with the double mutation H433K/N434F. In still yet another particular embodiment, the binding molecule of the

invention comprise a VH domain of SEQ ID NO. 152 wherein glutamine at position 1 has been changed to glutamic acid and a human Fc domain with the double mutation H433K/N434F.

In other embodiments, binding molecules, for use in the diagnostic and treatment methods described herein have a constant region, e.g., an IgG1 or IgG4 heavy chain constant region, which is altered to reduce or eliminate glycosylation. For example, binding molecules (e.g., antibodies or antigen binding fragments thereof) of the invention may also comprise an Fc variant comprising an amino acid substitution which alters the glycosylation of the antibody Fc. For example, said Fc variant may have reduced glycosylation (e.g., N- or O-linked glycosylation). In exemplary embodiments, the Fc variant comprises reduced glycosylation of the N-linked glycan normally found at amino acid position 297 (EU numbering). In another embodiment, the antibody has an amino acid substitution near or within a glycosylation motif, for example, an N-linked glycosylation motif that contains the amino acid sequence NXT or NXS. In a particular embodiment, the antibody comprises an Fc variant with an amino acid substitution at amino acid position 228 or 299 (EU numbering). In more particular embodiments, the antibody comprises an IgG1 or IgG4 constant region comprising an S228P and a T299A mutation (EU numbering).

Exemplary amino acid substitutions which confer reduce or altered glycosylation are disclosed in International PCT Publication No. WO05/018572, which is incorporated by reference herein. In preferred embodiments, the antibodies, or fragments thereof, of the invention are modified to eliminate glycosylation. Such antibodies, or fragments thereof, may be referred to as "agly" antibodies, or fragments thereof, (e.g. "agly" antibodies). While not being bound by theory, it is believed that "agly" antibodies, or fragments thereof, may have an improved safety and stability profile in vivo. Agly antibodies can be of any isotype or subclass thereof, e.g., IgG1, IgG2, IgG3, or IgG4. In certain embodiments, agly antibodies, or fragments thereof, comprise an aglycosylated Fc region of an IgG4 antibody which is devoid of Fc-effector function thereby eliminating the potential for Fc mediated toxicity to the normal vital organs that express IL-6. In yet other embodiments, antibodies, or fragments thereof, of the invention comprise an altered glycan. For example, the antibody may have a reduced number of fucose residues on an N-glycan at Asn297 of the Fc region, i.e., is afucosylated. Afucosylation increases FcRgII binding on the NK cells and potently increase ADCC. It has been shown that a diabody comprising an anti-IL-6 scFv and an anti-CD3 scFv induces killing of IL-6 expressing cells by ADCC. Accordingly, in one embodiment, the

afucosylated an anti-IL-6 antibody is be used to target and kill IL-6-expressing cells. In another embodiment, the antibody may have an altered number of sialic acid residues on the N-glycan at Asn297 of the Fc region. Numerous art-recognized methods are available for making "agly" antibodies or antibodies with altered glycans. For examples, genetically engineered host cells (e.g., modified yeast, e.g., *Picchia*, or CHO cells) with modified glycosylation pathways (e.g., glycosyltransferase deletions) can be used to produce such antibodies.

iii) Covalent Attachment

Binding molecules of the invention may be modified, e.g., by the covalent attachment of a molecule to the binding polypeptide such that covalent attachment does not prevent the binding polypeptide from specifically binding to its cognate epitope. For example, but not by way of limitation, the antibodies, or fragments thereof, of the invention may be modified by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, etc. Additionally, the derivative may contain one or more non-classical amino acids.

Binding polypeptide (e.g., antibodies, or fragments thereof) of the invention may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, anti-IL-6 antibodies may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

Binding molecules may be fused to heterologous polypeptides to increase the in vivo half life or for use in immunoassays using methods known in the art. For example, in one embodiment, PEG can be conjugated to the binding molecules of the invention to increase their half-life in vivo. Leong, S. R., *et al.*, Cytokine 16:106 (2001); Adv. in Drug Deliv. Rev. 54:531 (2002); or Weir *et al.*, Biochem. Soc. Transactions 30:512 (2002).

Moreover, binding molecules of the invention can be fused to marker sequences, such as a peptide to facilitate their purification or detection. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector

(QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37:767 (1984)) and the "flag" tag.

Binding molecules of the invention may be used in non-conjugated form or may be conjugated to at least one of a variety of molecules, e.g., to improve the therapeutic properties of the molecule, to facilitate target detection, or for imaging or therapy of the patient. Binding molecules of the invention can be labeled or conjugated either before or after purification, when purification is performed. In particular, binding molecules of the invention may be conjugated to therapeutic agents, prodrugs, peptides, proteins, enzymes, viruses, lipids, biological response modifiers, pharmaceutical agents, or PEG.

The present invention further encompasses binding molecules of the invention conjugated to a diagnostic or therapeutic agent. The binding molecules can be used diagnostically to, for example, monitor the development or progression of a immune cell disorder (e.g., CLL) as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment and/or prevention regimen. Detection can be facilitated by coupling the binding molecules to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. See, for example, U.S. Pat. No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, .beta.-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; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

Binding molecules for use in the diagnostic and treatment methods disclosed herein may be conjugated to cytotoxins (such as radioisotopes, cytotoxic drugs, or toxins)

therapeutic agents, cytostatic agents, biological toxins, prodrugs, peptides, proteins, enzymes, viruses, lipids, biological response modifiers, pharmaceutical agents, immunologically active ligands (e.g., lymphokines or other antibodies wherein the resulting molecule binds to both the neoplastic cell and an effector cell such as a T cell), or PEG.

In another embodiment, an anti-IL-6 antibody for use in the diagnostic and treatment methods disclosed herein can be conjugated to a molecule that decreases tumor cell growth. In other embodiments, the disclosed compositions may comprise antibodies, or fragments thereof, coupled to drugs or prodrugs. Still other embodiments of the present invention comprise the use of antibodies, or fragments thereof, conjugated to specific biotoxins or their cytotoxic fragments such as ricin, gelonin, Pseudomonas exotoxin or diphtheria toxin. The selection of which conjugated or unconjugated antibody to use will depend on the type and stage of cancer, use of adjunct treatment (e.g., chemotherapy or external radiation) and patient condition. It will be appreciated that one skilled in the art could readily make such a selection in view of the teachings herein.

It will be appreciated that, in previous studies, anti-tumor antibodies labeled with isotopes have been used successfully to destroy tumor cells in animal models, and in some cases in humans. Exemplary radioisotopes include: 90Y, 125I, 131I, 123I, 111In, 105Rh, 153Sm, 67Cu, 67Ga, 166Ho, 177Lu, 186Re and 188Re. The radionuclides act by producing ionizing radiation which causes multiple strand breaks in nuclear DNA, leading to cell death. The isotopes used to produce therapeutic conjugates typically produce high energy alpha- or beta-particles which have a short path length. Such radionuclides kill cells to which they are in close proximity, for example neoplastic cells to which the conjugate has attached or has entered. They have little or no effect on non-localized cells. Radionuclides are essentially non-immunogenic.

V. Expression of Binding molecules

Following manipulation of the isolated genetic material to provide binding molecules of the invention as set forth above, the genes are typically inserted in an expression vector for introduction into host cells that may be used to produce the desired quantity of the claimed antibodies, or fragments thereof.

The term "vector" or "expression vector" is used herein for the purposes of the specification and claims, to mean vectors used in accordance with the present invention as a vehicle for introducing into and expressing a desired gene in a cell. As known to those skilled

in the art, such vectors may easily be selected from the group consisting of plasmids, phages, viruses and retroviruses. In general, vectors compatible with the instant invention will comprise a selection marker, appropriate restriction sites to facilitate cloning of the desired gene and the ability to enter and/or replicate in eukaryotic or prokaryotic cells.

Numerous expression vector systems may be employed for the purposes of this invention. For example, one class of vector utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV) or SV40 virus. Others involve the use of polycistronic systems with internal ribosome binding sites. Additionally, cells which have integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells. The marker may provide for prototrophy to an auxotrophic host, biocide resistance (e.g., antibiotics) or resistance to heavy metals such as copper. The selectable marker gene can either be directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include signal sequences, splice signals, as well as transcriptional promoters, enhancers, and termination signals. In particularly preferred embodiments the cloned variable region genes are inserted into an expression vector along with the heavy and light chain constant region genes (preferably human) synthetic as discussed above.

In other preferred embodiments the binding molecules, or fragments thereof, of the invention may be expressed using polycistronic constructs. In such expression systems, multiple gene products of interest such as heavy and light chains of antibodies may be produced from a single polycistronic construct. These systems advantageously use an internal ribosome entry site (IRES) to provide relatively high levels of polypeptides of the invention in eukaryotic host cells. Compatible IRES sequences are disclosed in U.S. Pat. No. 6,193,980 which is incorporated by reference herein. Those skilled in the art will appreciate that such expression systems may be used to effectively produce the full range of polypeptides disclosed in the instant application.

More generally, once a vector or DNA sequence encoding an antibody, or fragment thereof, has been prepared, the expression vector may be introduced into an appropriate host cell. That is, the host cells may be transformed. Introduction of the plasmid into the host cell can be accomplished by various techniques well known to those of skill in the art. These include, but are not limited to, transfection (including electrophoresis and electroporation),

protoplast fusion, calcium phosphate precipitation, cell fusion with enveloped DNA, microinjection, and infection with intact virus. See, Ridgway, A. A. G. "Mammalian Expression Vectors" Chapter 24.2, pp. 470-472 Vectors, Rodriguez and Denhardt, Eds. (Butterworths, Boston, Mass. 1988). Most preferably, plasmid introduction into the host is via electroporation. The transformed cells are grown under conditions appropriate to the production of the light chains and heavy chains, and assayed for heavy and/or light chain protein synthesis. Exemplary assay techniques include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or flourescence-activated cell sorter analysis (FACS), immunohistochemistry and the like.

As used herein, the term "transformation" shall be used in a broad sense to refer to the introduction of DNA into a recipient host cell that changes the genotype and consequently results in a change in the recipient cell.

Along those same lines, "host cells" refers to cells that have been transformed with vectors constructed using recombinant DNA techniques and encoding at least one heterologous gene. In descriptions of processes for isolation of polypeptides from recombinant hosts, the terms "cell" and "cell culture" are used interchangeably to denote the source of antibody unless it is clearly specified otherwise. In other words, recovery of polypeptide from the "cells" may mean either from spun down whole cells, or from the cell culture containing both the medium and the suspended cells.

In one embodiment, the host cell line used for antibody expression is of mammalian origin; those skilled in the art can determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, DG44 and DUXB11 (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CVI (monkey kidney line), COS (a derivative of CVI with SV40 T antigen), R1610 (Chinese hamster fibroblast) BALBC/3T3 (mouse fibroblast), HAK (hamster kidney line), SP2/O (mouse myeloma), BFA-1c1BPT (bovine endothelial cells), RAJI (human lymphocyte), 293 (human kidney). In one embodiment, the cell line provides for altered glycosylation, e.g., afucosylation, of the antibody expressed therefrom (e.g., PER.C6.RTM. (Crucell) or FUT8-knock-out CHO cell lines (Potelligent.RTM. Cells) (Biowa, Princeton, N.J.)). In one embodiment NS0 cells may be used. CHO cells are particularly preferred. Host cell lines are typically available from commercial services, the American Tissue Culture Collection or from published literature.

In vitro production allows scale-up to give large amounts of the desired polypeptides. Techniques for mammalian cell cultivation under tissue culture conditions are known in the art and include homogeneous suspension culture, e.g. in an airlift reactor or in a continuous stirrer reactor, or immobilized or entrapped cell culture, e.g. in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges. If necessary and/or desired, the solutions of polypeptides can be purified by the customary chromatography methods, for example gel filtration, ion-exchange chromatography, chromatography over DEAE-cellulose and/or (immuno-)affinity chromatography.

Genes encoding the binding molecules, or fragments thereof, of the invention can also be expressed non-mammalian cells such as bacteria or yeast or plant cells. In this regard it will be appreciated that various unicellular non-mammalian microorganisms such as bacteria can also be transformed; i.e. those capable of being grown in cultures or fermentation. Bacteria, which are susceptible to transformation, include members of the enterobacteriaceae, such as strains of Escherichia coli or Salmonella; Bacillaceae, such as Bacillus subtilis; Pneumococcus; Streptococcus, and Haemophilus influenzae. It will further be appreciated that, when expressed in bacteria, the polypeptides can become part of inclusion bodies. The polypeptides must be isolated, purified and then assembled into functional molecules.

In addition to prokaryotes, eukaryotic microbes may also be used. Saccharomyces cerevisiae, or common baker's yeast, is the most commonly used among eukaryotic microorganisms although a number of other strains are commonly available. For expression in Saccharomyces, the plasmid YRp7, for example, (Stinchcomb *et al.*, Nature, 282:39 (1979); Kingsman *et al.*, Gene, 7:141 (1979); Tschemper *et al.*, Gene, 10:157 (1980)) is commonly used. This plasmid already contains the TRP1 gene which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC No. 44076 or PEP4-1 (Jones, Genetics, 85:12 (1977)). The presence of the trpl lesion as a characteristic of the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

VI. Pharmaceutical Formulations and Methods of Administration of Binding Molecules.

In another aspect, the invention provides pharmaceutical compositions comprising a binding molecule (e.g., an antibody, or antigen binding fragment thereof).

Methods for preparing and administering binding molecules of the invention to a subject are well known to or are readily determined by those skilled in the art. The route of

administration of the antibodies, or fragments thereof, of the invention may be oral, parenteral, by inhalation or topical. The term parenteral as used herein includes intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration. The intravenous, intraarterial, subcutaneous and intramuscular forms of parenteral administration are generally preferred. While all these forms of administration are clearly contemplated as being within the scope of the invention, an exemplary form for administration would be a solution for injection, in particular for intravenous or intraarterial injection or drip. Usually, a suitable pharmaceutical composition for injection may comprise a buffer (e.g. acetate, phosphate or citrate buffer), a surfactant (e.g. polysorbate), optionally a stabilizer agent (e.g. human albumin), etc. In other methods compatible with the teachings herein, the polypeptides can be delivered directly to the site of the adverse cellular population thereby increasing the exposure of the diseased tissue to the therapeutic agent. For example, the high thermal stability and solubility properties of the binding molecules of invention make them ideal agents for local administration, e.g., via subcutaneous (Sub-Q) injections. In addition, the extremely high affinity and potency of the antibodies of the invention allow the use of a lower effective dose, thereby simplifying subcutaneous injection. Accordingly, the binding molecules are particularly well-suited for the treatment or prevention of inflammatory-related disorders (e.g., rheumatoid arthritis), cancers or associated symptoms (e.g., cachexia or anorexia) for which localized delivery of the binding molecule may be desirable.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. In the subject invention, pharmaceutically acceptable carriers include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Other common parenteral vehicles include sodium phosphate solutions, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like. More particularly, pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the

extemporaneous preparation of sterile injectable solutions or dispersions. In such cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and will preferably be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity 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. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols, such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

In any case, sterile injectable solutions can be prepared by incorporating an active compound (e.g., an antibody by itself or in combination with other active agents) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated herein, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying, which yields a powder of an active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparations for injections are processed, filled into containers such as ampoules, bags, bottles, syringes or vials, and sealed under aseptic conditions according to methods known in the art. Further, the preparations may be packaged and sold in the form of a kit such as those described in co-pending U.S. Ser. No. 09/259,337 and U.S. Ser. No. 09/259,338 each of which is incorporated herein by reference. Such articles of manufacture will preferably have labels or package inserts indicating that the associated compositions are useful for treating a subject suffering from, or predisposed to autoimmune or neoplastic disorders.

The binding molecules of the invention can be formulated to a wide range of concentrations for pharmaceutical use. For example, the binding molecule may be formulated to a concentration of between 5 mg/ml and 50 mg/ml (e.g., 5, 10, 20, 50mg/ml). Alternatively, the binding molecules of the invention may be adapted to higher concentration formulations for local (e.g., subcutaneous) administration. For example, the binding molecule may be formulated to a concentration of between 50 mg/ml and 200 mg/ml, e.g, about 50, about 75, about 100, about 150, about 175 or about 200 mg/ml).

Effective doses of the binding molecules of the present invention, for the treatment of the above described conditions, vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but non-human mammals including transgenic mammals can also be treated. Treatment dosages may be titrated using routine methods known to those of skill in the art to optimize safety and efficacy.

For passive immunization with an antibody of the invention, the dosage may range, e.g., from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg (e.g., 0.02 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2 mg/kg, etc.), of the host body weight. For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg. Doses intermediate in the above ranges are also intended to be within the scope of the invention.

Subjects can be administered such doses daily, on alternative days, weekly or according to any other schedule determined by empirical analysis. An exemplary treatment entails administration in multiple dosages over a prolonged period, for example, of at least six months. Additional exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1-10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly. In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered may fall within the ranges indicated.

Binding molecules of the invention can be administered on multiple occasions. Intervals between single dosages can be, e.g., daily, weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of polypeptide or target molecule in the patient. In some methods, dosage is adjusted to achieve a certain plasma antibody or toxin

concentration, e.g., 1-1000 μg/ml or 25-300 μg/ml. Alternatively, antibodies, or fragments thereof, can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, germlined or humanized antibodies show the longest half-life, followed by chimeric antibodies and nonhuman antibodies. In one embodiment, the antibodies, or fragments thereof, of the invention can be administered in unconjugated form. In another embodiment, the antibodies of the invention can be administered multiple times in conjugated form. In still another embodiment, the antibodies, or fragments thereof, of the invention can be administered in unconjugated form, then in conjugated form, or vise versa.

The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, compositions containing the present antibodies or a cocktail thereof are administered to a patient not already in the disease state to enhance the patient's resistance. Such an amount is defined to be a "prophylactic effective dose." In this use, the precise amounts again depend upon the patient's state of health and general immunity, but generally range from 0.1 to 25 mg per dose, especially 0.5 to 2.5 mg per dose. A relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives.

In therapeutic applications, a relatively high dosage (e.g., from about 1 to 400 mg/kg of antibody per dose, with dosages of from 5 to 25 mg being more commonly used for radioimmunoconjugates and higher doses for cytotoxin-drug conjugated molecules) at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

In one embodiment, a subject can be treated with a nucleic acid molecule encoding a polypeptide of the invention (e.g., in a vector). Doses for nucleic acids encoding polypeptides range from about 10 ng to 1 g, 100 ng to 100 mg, 1 μg to 10 mg, or 30-300 μg DNA per patient. Doses for infectious viral vectors vary from 10-100, or more, virions per dose.

Therapeutic agents can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intracranial, intraperitoneal, intranasal or intramuscular means for prophylactic and/or therapeutic treatment. Intramuscular injection or intravenous infusion are preferred for administration of an antibody of the invention. In some methods, therapeutic antibodies, or fragments thereof, are injected directly into the cranium. In some methods,

antibodies, or fragments thereof, are administered as a sustained release composition or device, such as a Medipad™ device.

Agents of the invention can optionally be administered in combination with other agents that are effective in treating the disorder or condition in need of treatment (e.g., prophylactic or therapeutic). Preferred additional agents are those which are art recognized and are standardly administered for a particular disorder.

Effective single treatment dosages (i.e., therapeutically effective amounts) of ^{90}Y-labeled antibodies of the invention range from between about 5 and about 75 mCi, more preferably between about 10 and about 40 mCi. Effective single treatment non-marrow ablative dosages of ^{131}I-labeled antibodies range from between about 5 and about 70 mCi, more preferably between about 5 and about 40 mCi. Effective single treatment ablative dosages (i.e., may require autologous bone marrow transplantation) of ^{131}I-labeled antibodies range from between about 30 and about 600 mCi, more preferably between about 50 and less than about 500 mCi.

While a great deal of clinical experience has been gained with ^{131}I and ^{90}Y, other radiolabels are known in the art and have been used for similar purposes. Still other radioisotopes are used for imaging. For example, additional radioisotopes which are compatible with the scope of the instant invention include, but are not limited to, ^{123}I, ^{125}I, ^{32}P, ^{57}Co, ^{64}Cu, ^{67}Cu, ^{77}Br, ^{81}Rb, ^{81}Kr, ^{87}Sr, ^{113}In, ^{127}Cs, ^{129}Cs, ^{132}I, ^{197}Hg, ^{203}Pb, ^{206}Bi, ^{177}Lu, ^{186}Re, ^{212}Pb, ^{212}Bi, ^{47}Sc, ^{105}Rh, ^{109}Pd, ^{153}Sm, ^{188}Re, ^{199}Au, ^{225}Ac, ^{211}At, ^{213}Bi. In this respect alpha, gamma and beta emitters are all compatible with the instant invention. Further, in view of the instant disclosure it is submitted that one skilled in the art could readily determine which radionuclides are compatible with a selected course of treatment without undue experimentation. To this end, additional radionuclides which have already been used in clinical diagnosis include ^{125}I, ^{123}I, 99Tc, ^{43}K, ^{52}Fe, ^{67}Ga, ^{68}Ga, as well as ^{111}In. Antibodies have also been labeled with a variety of radionuclides for potential use in targeted immunotherapy (Peirersz *et al.* Immunol. Cell Biol. 65: 111-125 (1987)). These radionuclides include ^{188}Re and ^{186}Re as well as ^{199}Au and ^{67}Cu to a lesser extent. U.S. Pat. No. 5,460,785 provides additional data regarding such radioisotopes and is incorporated herein by reference.

As previously discussed, the binding molecules of the invention can be administered in a pharmaceutically effective amount for the in vivo treatment of mammalian disorders. In this regard, it will be appreciated that the disclosed antibodies, or fragments thereof, will be formulated so as to facilitate administration and promote stability of the active agent.

Preferably, pharmaceutical compositions in accordance with the present invention comprise a pharmaceutically acceptable, non-toxic, sterile carrier such as physiological saline, non-toxic buffers, preservatives and the like. For the purposes of the instant application, a pharmaceutically effective amount of a antibody of the invention, conjugated or unconjugated to a therapeutic agent, shall be held to mean an amount sufficient to achieve effective binding to a target and to achieve a benefit, e.g., to ameliorate symptoms of a disease or disorder or to detect a substance or a cell. In the case of tumor cells, the polypeptide will be preferably be capable of interacting with selected immunoreactive antigens on neoplastic or immunoreactive cells and provide for an increase in the death of those cells. Of course, the pharmaceutical compositions of the present invention may be administered in single or multiple doses to provide for a pharmaceutically effective amount of the polypeptide.

In keeping with the scope of the present disclosure, the binding molecules of the invention may be administered to a human or other animal in accordance with the aforementioned methods of treatment in an amount sufficient to produce a therapeutic or prophylactic effect. The polypeptides of the invention can be administered to such human or other animal in a conventional dosage form prepared by combining the antibody of the invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. Those skilled in the art will further appreciate that a cocktail comprising one or more species of polypeptides according to the present invention may prove to be particularly effective.

VII. Methods of Treating IL-6-Associated Disease or Disorders

The binding molecules of the invention are useful for antagonizing IL-6 activity. Accordingly, in another aspect, the invention provides methods for treating IL-6-associated diseases or disorders by administering to a subject in need of thereof a pharmaceutical composition comprising one or more binding molecules of the invention.

IL-6-associated diseases or disorders amenable to treatment include, without limitation, inflammatory diseases and cancer.

One skilled in the art would be able, by routine experimentation, to determine what an effective, non-toxic amount of antibody (or additional therapeutic agent) would be for the

purpose of treating an IL-6-associated disease or disorder. For example, a therapeutically active amount of a polypeptide may vary according to factors such as the disease stage (e.g., stage I versus stage IV), age, sex, medical complications (e.g., immunosuppressed conditions or diseases) and weight of the subject, and the ability of the antibody to elicit a desired response in the subject. The dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. Generally, however, an effective dosage is expected to be in the range of about 0.05 to 100 milligrams per kilogram body weight per day and more preferably from about 0.5 to 10, milligrams per kilogram body weight per day.

VIII. Exemplification

Example 1 Generation and Selection of IL-6-Specific Antagonistic Fabs

Llamas were immunized with human IL-6 (either produced in E.coli purchased from MACS Miltenyi Biotec (Cat. No.130-093-934) or produced in Human Embryonic kidney cells purchased from Humanzyme (Cat. No.HZ-1044)). Immunization of llamas and harvesting of peripheral blood lymphocytes (PBLs), as well as the subsequent extraction of RNA and amplification of antibody fragments, were performed as described by De Haard and colleagues (De Haard H, et al., JBC. 274:18218-30, 1999). After the last immunization, blood was collected and total RNA extracted from PBLs prepared using a Ficoll-Paque gradient and the method described by Chomczynski P *et al.* (Anal. Biochem. 162: 156-159, 1987). The extracted RNA was then used for random cDNA synthesis and PCR amplification of the V-regions of the heavy and the light chains (Vλ and Vκ) in order to construct Fab-containing phagemid libraries as described by De Haard H, *et al.* (Biol. Chem. 274, 1999).

Phage expressing Fabs were produced according to standard protocols and further selected on immobilized human IL-6 either biotinylated and captured by neutravidine or directly coated on maxisorp plates. Total or competitive elution of the IL-6 binding phage with trypsin was performed according to standard phage display protocols.

IL-6-specific Fabs were next screened for cross-competition with the IL-6 neutralizing antibody, B-E8 and IL-6 receptor using an ELISA-based competition assay. The

VH and VL amino acid sequences of exemplary antagonistic IL-6-specific Fabs identified using this assay are set forth in **Table 13** below.

The binding kinetics of IL-6-specific Fabs that were able to cross-compete with the B-E8 antibody was assessed using surface plasmon resonance (Biacore). Specifically, biotinylated (prokaryotic) IL-6 was captured on a streptavidin biacore sensor chip (CM5-SA) and different concentrations of purified Fabs were injected during 3 minutes following by a 5 minute wash with buffer. From the washing phase the off-rate (kd) was determined, while from the injection phase the on-rate (ka) was calculated using the concentration and off-rate as parameters. The measured off-rates and on-rates and calculated affinities of antagonistic Fabs are shown in **Table 2**. Fabs 24C9 and 24D10 have off-rates in the 10^{-5} s^{-1} range and have affinities of 660 and 270 pM, respectively. The binding kinetics of antagonistic purified Fabs (**Table 3**) and periplasmic fractions of Fab-expressing bacteria (**Table 4**) were also evaluated by surface plasmon resonance (Biacore) using both bacterially and eukaryotically produced human IL-6 directly coated on a CM5 chip. The Fabs tested had off-rates between $6x10^{-4}$ and $2x10^{-5}$ s^{-1}.

Table 2 Binding Kinetics of Selected Purified Antagonistic Fab Clones

Fab	ka (1/Ms)	kd (1/s)	Rmax (RU)	KA (1/M)	KD (M)	Chi2
17B3	3.02E+04	2.92E-03	35.7	1.04E+07	9.65E-08	2.67
18C7	1.05E+05	1.85E-03	43.9	5.70E+07	1.75E-08	6.98
18F8	4.84E+04	7.84E-04	51.5	6.18E+07	1.62E-08	8.43
18C9	5.56E+04	1.19E-03	49.9	4.67E+07	2.14E-08	9.51
18C11	5.52E+04	7.84E-04	22.1	7.05E+07	1.42E-08	0.2
28C6	1.01E+05	2.50E-03	22.6	4.04E+07	2.48E-08	1.2
20A4	2.88E+05	1.68E-03	48.2	1.72E+08	5.82E-09	2.56
29B11	1.30E+05	2.98E-03	23.3	4.36E+07	2.29E-08	1.02
24C9	1.33E+05	8.77E-05	38.1	1.51E+09	6.61E-10	2.21
24D10	6.27E+04	1.69E-05	40.6	3.70E+09	2.70E-10	3.48
24E9	1.17E+05	1.39E-04	41	8.38E+08	1.19E-09	3.87

Table 3 Binding Kinetics of Selected Purified Antagonistic Fab Clones

	K_D		k_{off}	
	eukIL-6	**bactIL-6**	**eukIL-6**	**bactIL-6**
17F10	6.0E-09	4.3E-08	7.2E-04	1.2E-03
18C7	7.7E-09	9.1E-09	1.0E-03	1.1E-03
18C9	2.4E-09	4.9E-09	2.1E-04	3.6E-04
20A4	8.1E-10	2.0E-09	3.0E-04	6.2E-04
24D10	8.5E-10	1.2E-09	1.7E-04	1.9E-04
24E9	7.1E-10	9.3E-10	2.4E-04	2.9E-04
24C9	1.7E-09	2.6E-09	3.0E-04	3.7E-04
24A3	5.9E-10	2.2E-10	1.1E-04	4.8E-05
29B11	5.1E-10	9.3E-10	1.0E-04	2.2E-04
29E7	6.6E-10	1.0E-09	1.5E-04	2.4E-04

Table 4 Binding Kinetics of Fab-Containing Periplasmic Fractions

run		ratio bact/euk	bact	euk	average binding	neg comp
55	28d4	1,02	1,79E-05	2,10E-05	43	
64	28e5	2,80	1,84E-05	-1,15E-03	1	
62	28c5	-2,93	1,86E-05	6,66E-04	1	
16	28e8	0,97	2,07E-05	9,02E-06	52	
45	28B3	1,00	2,93E-05	1,02E-04	46	
1	pur61H7	1,13	4,22E-05	3,68E-05	176	
17	28f8	0,98	5,16E-05	7,48E-05	72	
3	purGL18fab	1,08	6,44E-05	3,57E-05	169	
56	28e4	1,01	6,87E-05	6,74E-05	28	
49	28f3(28B6)	1,00	7,71E-05	3,50E-05	43	
18	28g8	0,97	8,13E-05	1,14E-04	59	
30	28c10	1,00	8,16E-05	5,91E-05	86	
12	28A8	1,01	8,19E-05	6,78E-05	96	
33	28f10(24A3)	1,20	8,42E-05	7,60E-05	286	
48	28e3	0,99	8,44E-05	3,56E-05	27	
5	28B7	1,04	8,62E-05	7,55E-05	115	
20	28A9	0,95	8,73E-05	7,10E-05	74	
63	28d5	-3,50	9,29E-05	2,19E-03	1	
2	purBE8fab	1,05	9,41E-05	8,79E-05	207	
28	28A10	1,01	9,50E-05	7,47E-05	99	
31	28d10	0,99	9,64E-05	7,41E-05	81	
42	28g12(24G3)	0,96	1,12E-04	7,52E-05	46	
44	28A3	0,94	1,29E-04	1,12E-04	34	
68	pur24d10	1,14	1,43E-04	1,25E-04	301	
57	28f4	1,09	1,67E-04	3,69E-05	43	
66	28g5	1,96	1,71E-04	8,71E-04	2	
58	28g4	0,95	1,73E-04	1,60E-04	39	
6	28c7	1,09	1,77E-04	1,52E-04	159	
52	28A4	0,87	1,81E-04	1,18E-04	19	
41	28f12(24D10)	1,09	1,83E-04	1,44E-04	167	
26	28g9	1,08	1,84E-04	1,58E-04	196	

Example 2. VH /VL Shuffling for Improved Affinity.

VL chain shuffling was used to improve the affinity of the Fabs 17F10, 18C7, 18C9, 18C11, 20A4, 29B11, 16D2 and 28A6. In this method, the heavy chain of these clones (as a VHCH1 fragment) was reintroduced into the primary phagemid-light chain library (see Example 1). Affinity selections were performed to select for chain shuffled Fabs with an improved affinity for IL-6. The binding kinetics of chain shuffled Fabs were evaluated by surface plasmon resonance (Biacore) using both bacterially and eukaryotically produced human IL-6, and cynomolgus monkey IL-6 (**Tables 5-7**). The VH and VL amino acid sequences of exemplary IL-6-specific Fabs selected by the VL chain shuffling method are set forth in Table 14 below.

VH chain shuffling was also used to improve the affinity of the Fab 24D10. In this method, the light chain of 24D10 was reintroduced into the primary phagemid-heavy chain

library (see Example 1) and selected using an off-rate assay. In this type of selection, the phage were allowed to bind to antigen on a substrate for 1.5 to 2 hours. At round 2, after 15 washes with PBS-Tween, an additional wash was performed with the presence of excess soluble IL-6. The principle is that phage antibodies with inferior off-rates and therefore dissociating more rapidly are captured by the excess of soluble target and are removed during washing. This procedure avoids re-binding of such phage to the coated target. The time of the additional wash step was increased with the number of rounds performed and the temperature was also increased to 37˚C, to select for more stable Fab variants. The binding kinetics of chain shuffled Fabs and the benchmark antibodies, BE8 and GL18, were evaluated by surface plasmon resonance (Biacore) using both bacterially and eukaryotically produced human IL-6 (**Tables 8 and 9**). The VH and VL amino acid sequences of exemplary IL-6-specific Fabs selected by the VH chain shuffling method are set forth in **Table 14** below.

Table 5 Binding Kinetics of Purifed 17F10, 18C11, 18C7 and 20A4 Chain-Shuffled Fabs

		K_D (M)			k_{off} (1/s)		
parental	Light Chain shuffled	**eukIL-6**	**HIS-huIL-6**	**HIS-cyIL-6**	**eukIL-6**	**HIS-huIL-6**	**HIS-cyIL-6**
17F10		6.0E-09	4.3E-08	6.2E-10	7.2E-04	1.2E-03	7.0E-04
	41E10/35B1	4.6E-10	5.4E-10	3.4E-10	1.6E-04	1.6E-04	1.2E-04
	41B5/35C1	4.1E-10	4.7E-10	2.8E-10	1.2E-04	1.1E-04	8.1E-05
	41B5	9.2E-10		7.2E-10	2.0E-04		1.7E-04
17F10	**pur Fab 68nM**	1.4E-08	1.9E-08	1.4E-08	7.7E-04	8.8E-04	7.8E-04
18C11		2.9E-09	Nt	3.4E-09	7.6E-04		8.5E-04
	42H1/36A1	3.4E-10	7.5E-10	6.9E-10	1.1E-04	1.5E-04	1.5E-04
18C7	**(090423)**	7.7E-09	9.1E-09	5.3E-09	1.0E-03	1.1E-03	6.3E-04
	(090429)	5.2E-09		4.9E-09	8.2E-04		6.9E-04
	44C3	2.9E-09	3.9E-09	3.4E-09	4.5E-04	6.4E-04	4.9E-04
	44E3	3.1E-09	3.6E-09	3.6E-09	6.6E-04	7.6E-04	7.6E-04
	44D3	2.5E-09	3.1E-09	3.2E-09	5.2E-04	6.4E-04	6.0E-04
20A4		8.1E-10	2.0E-09	1.7E-09	3.0E-04	6.2E-04	7.5E-04
	68F2				3.3E-05	8.0E-05	

Table 6 Binding Kinetics of Periplasmic Fractions Containing 29B11 Chain Shuffled Fabs

29B11	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	
bact	2.51E+05	**1.31E-04**	1.91E+09	**5.24E-10**	35	
euk	1.87E+05	**1.02E-04**	1.83E+09	**5.46E-10**	48.4	
cy	1.13E+05	**7.46E-04**	1.51E+08	**6.61E-09**	59.5	FOLD IMPROVEMENT

55C1a	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	5.61E+05	**7.38E-05**	7.60E+09	**1.32E-10**	21	2.24	1.78	3.97
euk	4.40E+05	**7.93E-05**	5.55E+09	**1.80E-10**	37.7	2.35	1.29	3.03
cyno	4.75E+05	**3.81E-04**	1.25E+09	**8.01E-10**	32.4	4.20	1.96	8.25
55E2b	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	4.89E+05	**6.72E-05**	7.28E+09	**1.37E-10**	15.6	1.95	1.95	3.82
euk	4.14E+05	**6.53E-05**	6.34E+09	**1.58E-10**	29.2	2.21	1.56	3.46
cy	4.68E+05	**3.36E-04**	1.39E+09	**7.17E-10**	24.1	4.14	2.22	9.22
55H1c	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	**1.28E+06**	**1.27E-04**	1.00E+10	**9.97E-11**	17.2	5.10	1.03	5.26
euk	**1.13E+06**	**1.11E-04**	1.02E+10	**9.77E-11**	11.7	6.04	0.92	5.59
cy	**1.16E+06**	**6.15E-04**	1.89E+09	**5.29E-10**	29.9	10.27	1.21	12.50
47C2 (R4)	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	1.12E+06	**3.15E-04**	3.56E+09	**2.81E-10**	18.3	4.46	0.42	1.86
euk	8.49E+05	**2.40E-04**	3.54E+09	**2.82E-10**	16.6	4.54	0.43	1.94
cy	8.51E+05	**1.31E-03**	6.48E+08	**1.54E-09**	18.7	7.53	0.57	4.29
48C10	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	2.62E+05	**1.84E-04**	1.43E+09	**7.01E-10**	29	1.04	0.71	0.75
euk	bad fit…							
cy	1.80E+05	**4.40E-04**	4.10E+08	**2.44E-09**	5.11	1.59	1.70	2.71

Table 7 Binding Kinetics of Periplasmic Fractions Containing 28A6 Chain-Shuffled Fabs

28A6 (parental)	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2			
bact	2.38E+05	**1.78E-04**	1.34E+09	**7.49E-10**	40.7			
euk	1.82E+05	**1.05E-04**	1.73E+09	**5.80E-10**	63.1			
cyno	1.28E+05	**6.73E-04**	1.91E+08	**5.25E-09**	74.5	FOLD IMPROVEMENT		
55A11d	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
BACT	1.88E+05	**6.76E-05**	2.78E+09	**3.59E-10**	14.5	0.79	2.63	2.09
euk	1.01E+05	**6.36E-05**	1.59E+09	**6.31E-10**	9.18	0.55	1.65	0.92
cyno	1.44E+05	**8.17E-05**	1.77E+09	**5.66E-10**	5.69	1.13	8.24	9.28
55C10e	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	1.71E+05	**6.99E-05**	2.44E+09	**4.09E-10**	7.83	0.72	2.55	1.83
euk	1.39E+05	**6.14E-05**	2.26E+09	**4.43E-10**	15.2	0.76	1.71	1.31
cy	1.36E+05	**8.67E-05**	1.56E+09	**6.39E-10**	6.97	1.06	7.76	8.22
55C11f	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	2.28E+05	**6.94E-05**	3.29E+09	**3.04E-10**	6.56	0.96	2.56	2.46
euk	2.01E+05	**6.47E-05**	3.10E+09	**3.23E-10**	13.4	1.10	1.62	1.80
cy	2.85E+05	**8.90E-05**	3.20E+09	**3.13E-10**	26.7	2.23	7.56	16.77
55E10g1	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	1.93E+05	**6.09E-05**	3.18E+09	**3.15E-10**	10.4	0.81	2.92	2.38
euk	1.46E+05	**5.59E-05**	2.62E+09	**3.82E-10**	8.45	0.80	1.88	1.52
cyno	1.45E+05	**6.88E-05**	2.10E+09	**4.76E-10**	9.6	1.13	9.78	11.03
55E11g3	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**
bact	1.68E+05	**7.05E-05**	2.38E+09	**4.21E-10**	4.98	0.71	2.52	1.78
euk	1.38E+05	**5.14E-05**	2.68E+09	**3.73E-10**	8.62	0.76	2.04	1.55
cy	1.39E+05	**7.46E-05**	1.86E+09	**5.38E-10**	7.34	1.09	9.02	9.76
48H1g2,R4	ka (1/Ms)	**kd (1/s)**	KA (1/M)	**KD (M)**	Chi2	ka (1/Ms)	**kd (1/s)**	**KD (M)**

bact	2.06E+05	**7.04E-05**	2.93E+09	**3.41E-10**	8.93	0.87	2.53	2.20
euk	1.06E+05	**6.80E-05**	1.56E+09	**6.40E-10**	19.9	0.58	1.54	0.91
cy	1.12E+05	**9.46E-05**	1.18E+09	**8.45E-10**	15.7	0.88	7.11	6.21

Table 8 Binding Kinetics of Periplasmic Fractions Containing 24D10 Chain-Shuffled Fabs

	Bact	RANKED euk	cyno	Average binding (RU)
62B6	9.07E-05	5.58E-05	7.49E-05	214
62c6	1.20E-04	6.11E-05	1.05E-04	150
62f6	1.13E-04	7.19E-05	1.01E-04	154
CAT-GL18Fab	9.41E-05	7.30E-05	1.20E-04	547
62g6	1.78E-04	7.67E-05	8.58E-05	132
62f5	1.63E-04	7.96E-05	1.15E-04	139
62h5	1.57E-04	8.28E-05	1.28E-04	139
BE8-Fab	9.70E-05	8.39E-05	1.18E-04	338
62h6	1.53E-04	8.46E-05	9.76E-05	196
BE8-Fab	1.03E-04	8.72E-05	1.28E-04	340
BE8-Fab	9.29E-05	8.96E-05	1.04E-04	347
61h7	7.54E-05	9.32E-05	9.45E-05	635
CAT-GL18Fab	9.98E-05	9.33E-05	1.40E-04	486
62d6	1.30E-04	9.53E-05	1.02E-04	134
62g5	1.68E-04	9.78E-05	1.31E-04	150
61B7	9.07E-05	9.79E-05	1.16E-04	597
55H1c	1.35E-04	1.01E-04	4.17E-04	773
62A6	1.62E-04	1.01E-04	1.39E-04	138
62A5	1.48E-04	1.05E-04	1.29E-04	138
62f3	1.75E-04	1.05E-04	1.16E-04	109
55H1c	1.40E-04	1.06E-04	4.30E-04	770
62c5	9.95E-05	1.09E-04	1.17E-04	131
61g7	1.19E-04	1.10E-04	3.18E-04	139
62B5	1.30E-04	1.11E-04	1.46E-04	170
61f6	1.12E-04	1.13E-04	1.25E-04	606
55H1c	1.26E-04	1.13E-04	3.90E-04	873
61g3	1.39E-04	1.15E-04	5.28E-04	687
61A3	1.34E-04	1.18E-04	5.19E-04	694
62d5	1.63E-04	1.18E-04	1.47E-04	129
62c2	1.37E-04	1.20E-04	5.44E-04	619
62g1	1.38E-04	1.21E-04	5.38E-04	629
61e1	1.39E-04	1.21E-04	5.36E-04	690
61B4	1.55E-04	1.21E-04	5.68E-04	561
62h1	1.41E-04	1.24E-04	5.40E-04	647
61g12	1.42E-04	1.27E-04	4.30E-04	138
62g4	1.51E-04	1.27E-04	5.51E-04	605
61g10	1.45E-04	1.30E-04	3.99E-04	159
61h9	1.31E-04	1.31E-04	4.12E-04	152
62e5	1.48E-04	1.32E-04	1.88E-04	148
62A1	1.73E-04	1.32E-04	6.41E-04	597
61g5	1.30E-04	1.39E-04	3.69E-04	229
61c12	1.43E-04	1.39E-04	4.44E-04	267

Table 9 Binding Kinetics of Purified 24D10 Chain-Shuffled Fabs

clone		ka (1/Ms)	kd (1/s)	KD (M)	Chi2
24D10	Bact	2.1E+05	1.0E-04	5.0E-10	5.4
	Euk IL-6	2.5E+05	1.0E-04	4.1E-10	5.04
61B7	Bact	3.5E+05	5.7E-05	1.6E-10	2.04
	euk	3.3E+05	6.6E-05	2.0E-10	3.84
61H7	Bact	1.2E+05	2.0E-06	1.7E-11	1.3
	Euk IL-6	1.2E+05	5.5E-05	4.5E-10	0.711
BE8-Fab(D)	Bact	2.8E+05	7.7E-05	2.8E-10	18.7
	Euk IL-6	3.6E+05	7.7E-05	2.2E-10	12.3

Example 3 Crystal Structure of Fab 61H7 in complex with IL-6

i) IL-6/Fab 61H7 Complex Characterization

Size exclusion chromatography was performed on an Alliance 2695 HPLC system (Waters) using a Silica Gel KW803 column (Shodex) eluted with 50 mM Tris-HCl pH 7.5, 150 mM NaCl at a flow rate of 0.5 ml/min. Detection was performed using a triple-angle light scattering detector (Mini-DAWN^{TM} TREOS, Wyatt technology, Sanata Barbara, USA). Molecular weight determination was performed by ASTRA V software (Wyatt technology).

ii) Crystallization

Initial crystallization screening of the IL-6/Fab 61H7 complex was performed with commercial kits Structure screen 1 and 2, Proplex screen and Stura Footprint screen (Molecular Dimensions Ltd). Drops were set-up with a 1:1(v:v) ratio of protein (8.45 mg/ml) to mother liquor in a total volume of 200 nl on Greiner 96-well plates using a Cartesian MicroSys SQ robot. Diffraction-quality crystals of complex were obtained by sitting-drop vapor diffusion at 277 K after optimization in 27.14% PEG MME 2K, 0.1M Na Hepes pH 7.14. Crystals belong to the C2 space group with unit cell dimensions: a= 108.2 Å, b= 47.5 Å, and c=148.3 Å and ß=97°. They contain one ILF/Fab complex per asymmetric unit with a Vm value of 2.36 Å^3/Da which correspond to a solvent content of 48%.

iii) Analysis of the Structure of the IL-6:61H7 Complex

The canonical structures predicted for the CDR loops of 61H7 mAb are 1 and 3 for H1 and H2, respectively, and 7, 1, and 4 for L1, L2, and L3, respectively (www.bioinf.org.uk/abs/chothia.html). The overlay of the 61H7 VH with Protein Data Bank (PDB) entry 1dfb (derived from a patient derived antibody against the HIV-1 protein gp41) shows that H1 and H2 adopt the predicted canonical folds (see **Figure 3A**). The overlay of the 61H7 VL with Protein Data Bank (PDB) entry 1mfa demonstrates that all three light chain CDRs adopt the predicted conformations (see **Figure 3B**). Accordingly, structural analysis confirms that the VH (a VH3 family member) of 61H7 belongs to the human 1-3 combination of canonical H1-H2 structures, while the VL (a VL8 family member) of 61H7 belongs to the human 7λ1-4 combination of human canonical structures.

IL-6 was previously crystallized and classified as a four helix bundle linked by loops and an additional mini-helix (Somers *et al.*, 1997, EMBO Journal 16, 989-997, which is incorporated herein by reference in its entirety). Superposition of the apo IL-6 (pdb 1ALU) with the IL-6 from the IL-6:61H7 complex shows good agreement between both models (rms 0.54 Å). This confirms that the 61H7 Fab recognizes and binds the native conformation of IL-6.

The crystal structure of the IL-6 in complex with its receptor and the signalling receptor gp130 showed a hexameric complex (Boulanger et al., 2003, Science 27, 2101-2104, which is incorporated herein by reference in its entirety). IL-6 forms a non-signalling complex with IL-6R through site I. Site II is a composite epitope formed by the binary complex of IL-6 and IL-6R. Interaction of site III with gp130 forms the signalling complex.

Superposition of the IL-6:IL-6R structure (pdb 1P9M) with the IL-6:61H7 structure shows good agreement (rms 1.2 Å) between both IL-6 structures. Two loops differ in conformation. The first loop covering residues Asn48-Asn61, is a long loop that is unstructured in the apo IL-6 and IL-6:61H7 complex. This loop is stabilized in the IL-6:IL-6R structure by the binding of the IL-6R. The second loop that differs in conformation is the so called BC loop.

The crystallographic asymmetric unit contains a single 1:1 complex. The global architecture of the IL-6:61H7 complex shows that both the VH (60%) and the VL (40%) contribute to the large interaction surface (940 $Å^2$). From the crystal structure the residues important for the interaction with IL-6 were determined. The hydrogen bonds and salt bridges formed between the 61H7 Fab and the cytokine are listed in **Table 10**. The

interactions are limited to the CDR1 and CDR3 of the light chain and the CDR1, CDR2 and CDR3 of the heavy chain.

Table 10. Hydrogen bonds and salt bridges in the 61H7:IL-6 complex

		61H7 residue structure	Kabat numbering	Distance (Å)	IL-6 residue
Hydrogen bonds	Light chain-CDR1	THR 30[OG1]	**THR 28**	3.21	LYS 27[NZ]
		SER 32[OG]	**SER 30**	2.66	ASP 26[OD1]
		ASN 33[ND2]	**ASN 31**	2.99	GLU 23[OE2]
		TYR 34[OH]	**TYR 32**	2.62	ARG 30[NH1]
		TYR 34[OH]	**TYR 32**	2.55	ASP 26[OD2]
	Light chain-CDR3	ASP 93[OD2]	**ASP 91**	2.72	ARG 182[NH1]
		ASP 93[OD2]	**ASP 91**	2.99	ARG 182[NH2]
		GLY 95[O]	**GLY 93**	3.45	SER 22[N]
		GLY 95[N]	**GLY 93**	2.91	GLU 23[OE1]
		GLY 95[O]	**GLY 93**	3.06	GLU 23[N]
		ASP 96[OD1]	**ASP 94**	3.04	SER 22[OG]
		ASP 96[OD1]	**ASP 94**	2.94	SER 22[N]
	Heavy chain-CDR1	THR 28[OG1]	**THR 28**	3.44	GLN 75[NE2]
		SER 31[OG]	**SER 31**	2.96	GLN 75[O]
		ARG 33[N]	**ARG 33**	2.73	GLN 183[OE1]
	Heavy chain-CDR2	ALA 53[N]	**ALA 52a**	2.76	GLN 183[O]
		ALA 53[N]	**ALA 52a**	3.66	GLU 80[OE1]
		GLY 54[N]	**GLY 53**	3.23	GLU 80[OE1]
		GLY 56[N]	**GLY 55**	2.78	GLU 80[OE2]
		TYR 59[OH]	**TYR 58**	3.54	MET 184[O]
	Heavy chain-CDR3	ARG 99[NH1]	**ARG 95**	2.71	ARG 182[O]
		ALA 100[O]	**ALA 96**	2.94	GLN 183[NE2]
Salt bridges	Light chain-CDR3	ASP 93[OD2]	**ASP 91**	2.72	ARG 182[NH1]
		ASP 93[OD2]	**ASP 91**	2.99	ARG 182[NH2]

Overlay of the IL-6:61H7 complex and the IL-6:IL-6R complex shows that there is sterical hindrance between the 61H7 Fab and the IL-6R. It is mainly the VL that gives a sterical clash with the IL-6R. Epitopes of IL-6R and 61H7 will be very close to each other. To verify if there is overlap between both epitopes, residues within 4.0 Å of the IL-6R and residues within 4.0 Å of the 61H7 Fab were mapped and searched for overlap between both epitopes. The overlap between both epitopes is rather small and is mainly formed by the VH paratope. The overlap concentrates around a cavity occupied by both the HCDR3 loop of the 61H7 and the IL-6R molecule. This binding site of IL-6R on IL-6 has been referred to as site

I (Boulanger *et al.*, 2003, Science 27, 2101-2104, which is incorporated herein by reference in its entirety). The cavity forming site I is occupied by the hydrophobic side chain of Phe 229 of IL-6R. This amino acid is called the hotspot residue by Boulanger *et al*, because mutagenesis studies have shown its critical role in the interaction between the receptor and the cytokine. Mutation of this residue to valine or serine completely abolished the IL-6R binding to IL-6 (Kalai et al., 1997, Blood, 1319-1333, which are both incorporated herein by reference in their entirety). Trp98 in the center of the heavy chain CDR3 loop of Fab 61H7 occupies the same cavity, suggesting that it hits thus the critical epitope in IL-6 to block its interaction with IL-6R (shown in **Figure 5**). Trp98 is likely a key residue for the ultra high affinity of Fab61H7 for IL-6.

Example 4 Crystal Structures of Fabs 68F2 and 129D3 in complex with IL-6

i) Generation, Data Collection and Structure determination of the IL-6:68F2 Crystal

8 mg of 68F2 mAb (4 mg/ml) in Dulbecco's Phosphate buffered saline (d-PBS) pH 7.2 were buffer-exchanged to digestion buffer containing 20mM cystein-HCl on a Zeba TM Desalt Spin Column (Pierce Fab Preparation Kit Thermo Scientific). Sample was incubated with Immobilized Papain (Pierce Thermo Scientific) and digested for 6 hours at 37°C. The Fc fragments were separated from the Fab fragments using a CaptureSelect human Fc affinity matrix (BAC BV Unilever) equilibrated in d-PBS. Fab fragments were recovered in the flow-through and Fc fragments were eluted using 0.1M glycine pH 2.0. Protein concentration was determined by UV spectrometry from the absorbance at 280 nm. 4.6 mg (>50%) of purified Fab 68F2 was recovered and concentrated to 1.53 mg/ml on an Amicon-Ultra (cut-off 10 kDa).

2.5 mg of rh IL-6 (Immunotools) was incubated with 2.6 mg of Fab 68F2 in Dulbecco's Phosphate buffered saline (d-PBS) pH 7.2 for 1 hour at 4°C before being concentrate to 1 ml on a Amicon-Ultra (cut-off 10kDa). The IL-6:68F2 complex was then separated from excess free IL-6 by gel filtration chromatography on a Superdex75 column in d-PBS and finally concentrated to 8.1 mg/ml on an Amicon-Ultra concentrator (cut-off 10 kDa). Purification of the complex was evaluated on SDS-PAGE.

Size exclusion chromatography was performed on an Alliance 2695 HPLC system (Waters) using a Silica Gel KW803 column (Shodex) eluted with 50 mM Tris-HCl pH 7.5, 150 mM NaCl at a flow rate of 0.5 ml/min. Detection was performed using a triple-angle

light scattering detector (Mini-DAWN^{TM} TREOS, Wyatt technology, Santa Barbara, USA). Molecular weight determination was performed by ASTRA V software (Wyatt technology). Initial crystallization screening of the IL-6:68F2 complex was performed with commercial kits Structure screen 1 and 2, Proplex screen and Stura Footprint screen (Molecular Dimensions Ltd). Drops were set-up with a 1:1 (v/v) ratio of protein (8.1 mg/ml) to mother liquor in a total volume of 200 nl on Greiner 96-well plates using a Cartesian MicroSys SQ robot. A diffraction-quality crystal of complex was obtained by sitting-drop vapor diffusion at 277 K after 9 months in 25% PEG 4K, 0.15M $(NH_4)_2SO_4$, 0.1M MES pH 5.5.

Crystals for data collection were transferred to liquor mother with 7.5% ethylene glycol and flash-frozen in liquid nitrogen. Diffraction data were collected under standard cryogenic conditions on beamline ID14-4, using an ADSC Quantum 4 detector at the ESRF synchrotron (Grenoble, France), processed using XDS and scaled with XSCALE. The crystal structure of IL-6 in complex with Fab 68F2 was determined from single-wavelength native diffraction experiments by molecular replacement with Fab 129D3 and the IL-6 structure using MOLREP (table 4). Refinement was performed with BUSTER. The IL-6:129D3 Crystal was similarly produced.

iii) Analysis of the Structure of the IL-6:68F2 and IL-6:129D3 Complex

The crystal structure of the IL-6:68F2 complex has a resolution of 2.9 Å. The model was refined to an R-factor of 26.7% and an R_{free}-factor of 29.6% with reasonable stereochemistry (meaning that more than 95% of the residues adopt allowed conformations). The crystal structure of the IL-6:129D3 complex has a resolution of 2.8 Å. The model was refined to an R-factor of 28.5% and an R_{free}-factor of 31.3% with reasonable stereochemistry.

An overlay of the crystallized 68F2 and 129D3 Fabs (r.m.s.d. 1.4 Å), VH domain (r.m.s.d. 0.5 Å) and of the VL domain was made (r.m.s.d. 0.4). These superpositions show that there is no significant difference between the parental 68F2 and germlined 129D3 Fab structures.

The canonical structures predicted for the CDR loops of the 68F2 mAb and its germlined variant 129D3 are 3 and 1 for H1 and H2, respectively, and 6λ, 1 and 5 for L1, L2 and L3, respectively. The canonical folds of the heavy chain were predicted by the server at www.bioinf.org.uk/abs/chothia.html, the canonical folds of the light chain were manually determined. The reference Fab (PG16) for comparison of the light chain canonical folds, was found manually by searching the Antibody Structure Summary Page

(www.bioinf.org.uk/abs/sacs/antibody_structure_summary_page.html). The overlay of the 68F2 and 129D3 VL with the VL of PG16 (Protein Data Bank (PDB) entry 3MUG) demonstrates that all three CDR's adopt the predicted conformations (see Figure 4A). The overlay of the 68F2/129D3 VH with the reference PDB entry 1ACY shows that H1 and H2 adopt the predicted canonical folds (see Figure 4B). Accordingly, structural analysis confirms that the VL (a VL2 family member) of 68F2/129D3 belongs to the human 6λ-1-5 combination of canonical L1-L3 structures, while the VH (a VH4 family member) of 68F2/129D3 belongs to the 3-1 combination of human canonical H1-H2 structures.

The crystallographic asymmetric unit contains a single 1:1 complex. The global architecture of the IL-6:68F2 complex shows that the VH (50%) and the VL (50%) contribute equally to the large interaction surface (1156 Å^2). The interaction surface is slightly bigger than the interaction surface of the 61H7 with IL-6 (940 Å^2). Analogous to the 61H7:IL-6 complex, only the L2 loop is not directly involved in the interaction with IL-6.

The interface between the heavy and light chain corresponds to 1764.7 Å^2 for the 68F2 and 1768.5 Å^2 for the 129D3 structure. This interface area was comparable to the areas measured for the 61H7 (1580.6 Å^2) and the 27B3 (1700.3 Å^2) antibodies. All interface areas were calculated with EMBL web service program PISA.

From the crystal structure the residues important for the interaction with IL-6 were determined. The hydrogen bonds and salt bridges formed between the 68F2 Fab and the cytokine are listed in **Table 11**. The interactions are limited to the CDR1 and CDR3 of the light chain and the CDR1, CDR2 and CDR3 of the heavy chain.

The VL shuffling of the 20A4 clone resulted in the 68F2 clone which has a 10x better affinity than the parental 20A4. Both antibodies differ mainly in their L1 and L2 CDRs. The light chain CDR2 loop does not contribute to the binding of IL-6, thus, the improvement in affinity is to be attributed to mutations in the L1 loop. Two out of the three residues that make important interactions with IL-6 are not conserved in the 20A4 clone: Asn26 that makes a hydrogen bond with Ser76 of IL-6 is a Ser in 20A4; and Thr31 that makes two hydrogen bonds with IL-6 is a Gly in the 20A4 parental L1. The addition of three new hydrogen bonds when changing these two residues likely explains some gain in affinity observed after the VL shuffling. Most importantly, the changes in L1 probably stabilize and/or position Y30 (Kabat numbering) properly in the F229 cavity allowing for extra high potency.

Table 11. Hydrogen bonds and salt bridges in the 68F2:IL-6 complex.

		68F2 residue structure	Kabat numbering	Distance (Å)	IL-6 residue
Hydrogen bonds	Light chain-CDR1	ASN 26[O]	**ASN 27**	3.60	SER 76[OG]
		TYR 32[OH]	**TYR 30**	3.43	SER 176[O]
		THR 31[N]	**THR 29**	3.55	SER 76[OG]
		THR 31[O]	**THR 29**	3.42	GLN 75[N]
	Light chain-CDR3	ASN 95[ND2]	**ASN 93**	3.77	MET 67[O]
		ASN 97[OD1]	**ASN 95**	3.73	ARG 179[NH2]
	Heavy chain-CDR1	TYR 33[OH]	**TYR 33**	3.47	ARG 30[O]
		TYR 33[OH]	**TYR 33**	2.16	ASP 34[OD1]
		ARG 32[NE]	**ARG 32**	3.20	ASP 34[OD2]
		ARG 32[NH2]	**ARG 32**	3.28	ASP 34[OD2]
	Heavy chain-CDR2	TYR 60[OH]	**TYR 58**	2.59	GLU 172[OE2]
		ASP 54[OD2]	**ASP 52**	3.37	LYS 171[NZ]
		ASP 56[OD1]	**ASP 54**	2.90	SER 37[OG]
		ASP 58[OD1]	**ASP 56**	3.86	HIS 164[NE2]
		ASP 58[OD2]	**ASP 56**	3.42	LYS 171[NZ]
		THR 59[O]	**THR 57**	2.52	ARG 168[NH2]
		TYR 60[OH]	**TYR 58**	3.69	ARG 168[NE]
		TYR 60[OH]	**TYR 58**	3.15	LYS 171[NZ]
	Heavy chain-CDR3	ASP 102[OD2]	**ASP 97**	2.77	ARG 30[NH2]
		VAL 104[O]	**VAL 99**	3.69	ARG 179[NH1]
Salt bridges	Heavy chain-CDR1	ARG 32[NE]	**ARG 30**	3.20	ASP 34[OD2]
		ARG 32[NH2]	**ARG 30**	3.28	ASP 34[OD2]
	Heavy chain-CDR2	ASP 54[OD2]	**ASP 52**	3.37	LYS 171[NZ]
		ASP 58[OD1]	**ASP 56**	3.86	HIS 164[NE2]
		ASP 58[OD2]	**ASP 56**	3.42	LYS 171[NZ]
	Heavy chain-CDR3	ASP 102[OD1]	**ASP 97**	3.40	ARG 30[NH2]
		ASP 102[OD2]	**ASP 97**	2.77	ARG 30[NH2]

Overlay of the IL-6:68F2 complex and the IL-6:IL-6R complex shows that there is steric hindrance between the 68F2 Fab and the IL-6R, as was observed for the 61H7:IL-6 complex. However, in contrast to the 61H7:IL-6 complex, it is mainly the VH of 68F2 that gives a sterical clash with the IL-6R in the 68F2:IL-6 complex. 68F2 Fab interacts with IL-6 exactly at the same site as IL-6R. Furthermore, 68F2 does not overlap with the gp130 binding sites and therefore competes specifically and only with the IL-6R.

Overlay of the IL-6:IL-6R and the IL-6:68F2 complexes suggests that the epitopes of IL-6R and 68F2 will be very close to each other. The residues belonging to both epitopes were mapped on IL-6 and the overlap determined. The overlap of the 68F2 epitope with the IL-6R is almost complete. The binding site of IL-6R on IL-6 has been called site I (Boulanger *et al.*, 2003, Science 27, 2101-2104). The cavity forming site I is occupied by the hydrophobic side chain of Phe 229 of IL-6R. This amino acid is called the hotspot residue by Boulanger *et al*, since mutagenesis studies have shown its critical role in the interaction

between the receptor and the cytokine. Mutation of this residue to valine or serine completely abolished the IL-6R binding to IL-6 (Kalai *et al.*, 1997, Blood, 1319-1333). Inspection of the cavity described as site I in the IL-6:68F2 structure reveals that is occupied by the CDR1 loop of the light chain of Fab 68F2. In particular, Tyr32 (position 30 in Kabat numbering) in the CDR1 of the light chain plays a crucial role in binding this site (**Figure 5C**).

Another key residue in the interaction between IL-6 and IL-6R is Phe279 of IL-6R. This residue represents 20% (129 Å^2) of the total binding interface (compared to 28% (174 Å^2) for Phe 229) making it the second most important interaction. Like Phe229, Phe279 also binds in a cavity formed on the surface of IL-6. This cavity is also occupied by a 68F2 residue, more particularly by Val104 (position 99 in Kabat numbering) of the CDR3 loop of the heavy chain (**Figure 6**).

IL-6 was previously crystallized and classified as a four helix bundle linked by loops and an additional mini-helix (Somers *et al.*, 1997, EMBO Journal 16, 989-997). The crystal structure of IL-6 in complex with its receptor and the signalling receptor gp130 has also been solved (Boulanger *et al.*, 2003, Science 27, 2101-2104). IL-6 forms a non-signalling complex with IL-6R through site I. Site II is a composite epitope formed by the binary complex of IL-6 and IL-6R. Interaction of site III with gp130 forms the signalling complex.

Comparison of the structure of the IL-6:61H7 complex with the IL-6:68F2 structure shows that although both mAbs compete with IL-6R for binding to site I of IL-6, the two antibodies bind IL-6 at two different epitopes. 68F2 binds on the side of the barrel shaped IL-6 and exclusively competes for IL-6R binding, while 61H7 interacts more at the base of the barrel shaped IL-6, competing with both IL-6R and gp130. Interestingly, the unique overlapping epitope on IL-6 is the cavity that is filled by the hot spot residue Phe229 of IL-6R (**Figure 5**). This suggests that binding to this cavity is key to the high potency observed for 68F2 and 61H7.

Example 5 Structure function Analysis of W98 in HCDR3 of 61H7

A striking feature of the extremely highly potent antibodies disclosed herein is their capacity to occupy the cavity on IL-6 where F229 of the IL-6R binds (herein referred to as the F229 cavity). For 61H7 (and its germlined variants e.g., 111A7), the F229 cavity is occupied by the tryptophan 98 residue (W98) of the HCDR3. To assess the functional importance of W98 to 61H7 binding to IL-6, mutants of 111A7 were generated in which VH

position 98 was mutated towards all the possible amino acids in the background of M100A or M100L. The binding kinetics of periplasmic fractions of bacteria containing the mutant Fabs were tested using surface Plasmon resonance (Biacore) and the off-rate for each mutant was determined. The results of the mutational analysis are set forth in **Table 12**. The data clearly show that the tryptophan (W) at position 98 is the best possible amino acid to achieve the best off-rate. Mutation of W98 was always detrimental to the binding of 111A7 to IL-6.

Table 12. Off-rate of 61H7 Fabs with VH mutations at Positions 98 and 100

M100A/L	W98X	EUK_IL-6 (3-1)		BACT_IL-6 (2-1)		
		Off rate (s-1)	Binding (RU)	Off rate (s-1)	Binding (RU)	
M	WGM	4.67E-05	353	5.00E-05	127	n=3
L	WGL	5.50E-05	130	3.60E-05	51	n=1
L	FGL	2.20E-04	120	2.40E-04	40	n=1
L	YGL	3.10E-04	54	3.50E-04	18	n=1
L	QGL	4.20E-04	110	5.50E-04	36	n=1
L	MGL	5.90E-04	100	8.10E-04	31	n=1
L	VGL	7.17E-04	87	9.90E-04	25	n=3
L	CGL	7.70E-04	14	5.45E-04	2	n=2
L	SGL	7.77E-04	68	1.07E-03	20	n=5
L	LGL	8.35E-04	58	1.08E-03	16	n=6
L	GGL	9.46E-04	74	1.30E-03	21	n=7
L	*GL	9.53E-04	19	1.13E-03	4	n=3
L	RGL	1.00E-03	72	1.35E-03	19	n=2
L	PGL	1.10E-03	33	1.40E-03	10	n=2
A	WGA	8.30E-05	97	3.40E-05	33	n=1
A	FGA	9.20E-05	120	6.10E-05	32	n=1
A	HGA	2.83E-04	43	1.34E-04	8	n=3
A	YGA	3.75E-04	59	3.80E-04	15	n=2
A	MGA	7.35E-04	60	9.75E-04	15	n=2
A	EGA	7.45E-04	81	1.10E-03	18	n=2
A	NGA	9.50E-04	75	1.10E-03	16	n=1
A	IGA	9.63E-04	66	1.40E-03	15	n=3
A	CGA	9.95E-04	39	1.25E-03	6	n=2
A	LGA	1.05E-03	49	1.13E-03	11	n=5
A	*GA	1.05E-03	25	1.25E-03	4	n=2
A	VGA	1.23E-03	70	1.68E-03	14	n=4
A	RGA	1.25E-03	47	1.53E-03	9	n=5
A	KGA	1.45E-03	48	1.95E-03	9	n=2
A	TGA	1.55E-03	53	1.65E-03	10	n=2
A	GGA	1.77E-03	69	2.28E-03	13	n=6
A	AGA	1.85E-03	80	2.50E-03	15	n=2

Example 6 Germlining of the VH and VL of Fab Clones 61H7 and 68F2

The VH and VL sequences of clones 68F2 and 61H7 were aligned against human germline VH and VL sequences to identify the closest related germline sequences. The germlining process was performed as described in WO 2010/001251 and by Baca *et al.* (J. Biol. Chem. (1997) 272: 10678–10684) and Tsurushita *et al.* (J. Immunol. Methods (2004) 295: 9- 19). A library/phage display approach was used, in which the deviating FR residues for both the human and the llama residues were incorporated.

The camelid derived IL-6 antibodies of the invention were remarkably human-like in sequence and structure. As a result, only a minimal number of sequence alterations (via germlining) were incorporated into final germlined variants. For example, of the 87 (VH) and 79 (VL) amino acids in VH and VL framework regions of the parental 68F2 antibody, only 6 (VH) and 7 (VL) amino acid changes were introduced (a total of 13 amino acid changes), resulting in a final germlined lead (129D3) with 93.1% and 91.1% identities in their respective VH and VL frameworks (see alignment of **Figure 10A**). Similarly, of the 87 (VH) and 79 (VL) amino acids in the VH and VL framework regions of the parental 61H7 antibody, only 8 (VH) and 5 (VL) amino acid changes were introduced (a total of 13 amino acid changes), resulting in a final germlined lead (111A7) with 90.8 and 93.7 % identities in their respective VH and VL frameworks (see alignment of **Figure 10B**).

By contrast, art-recognized IL-6 antibodies require an extensive amount of engineering (CDR-grafting) and sequence alterations (backmutations) to generate variant suitable for therapeutic use. For example, the reference mouse IL-6 antibody CNTO-328 required 14 (VH) and 22 (VL) amino acid alterations (a total of 36) to generate the humanized variant CNTO136 with only 84% and 72.5% homology in its VH and VL frameworks (for alignment, see Figure 11A). Another reference rabbit IL-6 antibody, ALD518, required a total of 46 framework changes (26 in VH and 20 in VL) to generate a final humanized variants with only 70.5% and 74% sequence homology to the parental antibody. Therefore, the IL-6 antibodies clearly require only minimal engineering and result in molecules which are much more human in sequence.

Furthermore, the small number of FR residues to be changed makes it possible to incorporate changes in CDR residues into the germlining process. Such CDR mutations can be used to remove amino acid introducing production variability (glycosylation site,

oxidation, isomerisation, etc) or to change CDR residues toward amino acids found in different variant of the antibody to germline.

Phage display, applying stringent selection conditions, was used to select for additional functional Fabs. Individual clones were screened for off-rate and the best hits were sequenced to determine the human sequence identity. The VH and VL amino acid sequences of exemplary germlined IL-6-specific Fabs are set forth in **Tables 15 and 16** below.

CDR region sequences from all identified VH and VL domains that are variant Fabs of 129D3 and 111A7 were compared and CDR amino acid consensus sequences determined. CDR variants of 129D3 and 111A7 and derived CDR consensus sequences are set forth in **Tables 17 and 18** below.

Example 7 *In vitro* Potency Assay

The *in vitro* efficacy of clones 129D3, 68F2, 61H7, 133A9, 133H2, 133E5 and 132E7 were determined using a cell-based neutralizing bioassay using the B9 cell line, essentially as described in Helle *et al.* 1988, Eur. J. Immunol 18;1535-1540. B9 cells are derived from the murine B cell hybridoma cell line B13.29, which require IL-6 for survival and proliferation and respond to very low concentrations of human IL-6. The assay was performed using 10 pg/ml (or 0.5 pM) human IL-6 and a concentration series of purified 129D3, B-E8, CAT6001, CNTO136, 61H7, UCB124.g1. B9 cells were seeded in IL-6-free medium at 5000 cells/200 microl in flat-bottom wells in the presence of IL-6, with and without antibodies. Proliferation was measured by a [3H]thymidine pulse at 64-72 h. The results (shown in **Figure 1 and Table 23**) demonstrate that all clones have high potency, with 129D3 having an IC50 in this assay of less than 0.1pM. Interestingly, as shown in **Figure 1**, the IC50 of clone 129D3 was superior to the benchmark CNTO136, CAT6001, UCB124, and B-E8 antibodies.

The *in* vitro efficacy of clones 133E5, 133A9, 133H2, 111B1, 104C1, 129D3, 68F2, 61H7, were also determined using a cell-based neutralizing bioassay using the 7TD1 cell line, essentially as described in Van Snick et al. PNAS; 83, :9679 (1986), which is hereby incorporated by reference in its entirety. 7TD1 cells are a murine hybridoma cell line formed by fusion of the mouse myeloma cell line Sp2/0-Ag14 with spleen cells from a C57BL/6 mouse immunized with Escherichia coli lipopolysaccharides three days before fusion. The 7TD1 cell line is dependent on IL-6 for its growth and IL-6 withdrawal leads to cell death by

apoptosis. The assay was performed using 75 pg/ml human IL-6 and a concentration series of purified 133E5, 133A9, 133H2, 111B1, 104C1, 129D3, 68F2, 61H7, B-E8, GL18LB, CNTO136 and hu1U.

Briefly, 7TD1 cells (7.10E3) were incubated for 2-4h in RPMI1640 medium +10%FCS before addition of IL-6 (75 pg/ml final concentration) in microtiter plates (200ul final volume). The cells were incubated 3 days at 37C, before washing with PBS and addition of 60ul of substrate solution (p-nitrophenyl-N-acetyl-β-D-glucosaminide (Sigma N-9376); 7.5 mM substrate in 0.05 M NaCitrate pH 5; 0.25 vol% triton X-100) for 4h. The enzymatic reaction was stopped with 90ul of stop solution (100 mM glycine + 10 mM EDTA pH 10.4) and OD at 405nm measured. The results (shown in **Table 24**) demonstrate that all clones have high potency in this assay, with IC50s of less than 1pM.

Example 8 Epithelial Ovarian Cancer Mouse Xenograft Assay

The *in vivo* potency of clone 129D3 was determined using a mouse xenogaft model. IGROV-1 epithelial cells (5×10^6) were injected subcutaneously into nude mice. After three days, mice were administered 129D3 or CNT0328 biweekly, at a dosage of 4 or 20 mg/kg. There were 5 mice per group and 10 mice in the control group. Percentage survival of mice in each study group was determined each week and the results plotted as a survival curve. The results (shown in **Figure 2**) demonstrate that 129D3 exhibits an *in vivo* potency that is superior to the benchmark CNT0328 IL-6 antibody.

Example 9. Immunogenicity Analysis

VH and VL regions of the IL-6 antibodies of the invention were scored for the presence of potential immunogenic sequences (e.g., putative HLA class II restricted epitopes, also known as TH- epitopes) and compared with immunogenicity scores for a variety of commercially-available reference antibodies using the Epibase® profiling method.

Profiling was done at the allotype level for 18 DRB1, 6 DRB3/4/5, 13 DQ and 5 DP, i.e. 42 HLA class II receptors in total. Strong and medium binders of DRB1, DRB3/4/5 were identified, as well as the strong binders of DQ and DP epitopes. Epitope counting was done separately for strong and medium affinity DRB1 binders. Peptides binding to multiple allotypes of the same group were counted as one. An approximate score expressing a worst-case immunogenic risk was calculated as follows: Score = Σ (epitope count x allotype frequency).

In other words, the number of epitopes affecting a particular HLA allotype is multiplied by the allele frequency of the affected allotype. For a given sequence, the products were summed for all DRB1 allotypes used in the study that are present in 2% or more of the Caucasian population.

DRB1 scores for the IL-6 antibodies of the invention and representative reference antibodies are provided in **Figure 9**. Total DRB1 scores were a composite of the VH and VL scores for each antibody and low scores indicate low immunogenicity for the antibody. Accordingly, **Figure 9** demonstrates that IL-6 antibodies of the invention are equal to or less immunogenic than benchmark IL-6 antibodies as well as other commercially-available antibodies (e.g., Humira and Remicade).

Example 10. Manufacturability

The VH and VL of the germlined versions of 68F2 were recloned in pUPE Heavy Chain and Light Chain expression vectors, respectively, for transient expression of full-length IgG1 antibodies. After transient expression in HEK293E cells, IgG1 antibodies were purified with protein A and quantified by measurement of OD280. **Table 19** below summarizes the production levels of the germlined derivatives together with the levels of the 68F2 parental antibody. Potencies (in pM) were also measured in a 7TD1 based proliferation assay for each antibody.

The variants 126A3, 127F1, 129D3 and 129F1, all selected from the germlined libraries under stringent conditions, were found to have similar potencies as the wild type 68F2 (i.e. between 0.5 and 0.7 pM). Moreover, all germlined variants expressed very well, i.e. between 24 and 28 μg/ml. The exception was germlined variant 129F2 that gave a production yield of 9 μg/ml.

Example 11. Stability Analysis

To examine the thermal stability of the germlined and the parental versions of 68F2 in full length human IgG1 format, antibody samples were incubated at a concentration of 100 μg/ml (in PBS) at 4, 50, 55, 60, 65, 70 and 75°C for 1 hour. Following this, the samples were cooled down slowly during a period of 15 minutes to 25°C and kept at this temperature for 2 hours, after which they were stored overnight at 4°C. Following centrifugation to remove precipitates (of denatured antibody), the concentration of functional antibody remaining in

solution was measured using Biacore (1/10 dilution in PBS and 1/10 in HBSEP). The slope of the association curve obtained after injection on the IL-6 immobilized chip is a measure of the concentration of functional antibody.

As shown in **Figure 7A**, the melting curves and the melting temperatures of wild type 68F2 and its germlined derivatives were clearly unaffected by germlining. Quite unexpectedly, the melting temperatures even seemed to be improved. For example, 129D3 has a Tm of around 70˚C, which is 3˚C higher than the parental 68F2 antibody. The melting curves of the germline variant 129D3 and the parental 68F2 together were also compared with the reference antibodies GL18 and CNTO136 (see **Figure 7B**). The favorable thermal stability of the SIMPLE antibody 68F2 and especially of its germlined variant 129D3 (Tm of 70˚C) was striking when compared to Tm of 65˚C for CNTO136 and the Tm of 61˚C for the GL18 antibody. Surprisingly, the extensive antibody engineering (e.g., humanization) and *in vitro* affinity maturation applied to both reference antibodies strongly affected their stability, whereas the *in vivo* generated SIMPLE antibody and the minimal engineering by germlining resulted in extremely good thermal stabilities.

The serum stability of the full length human IgG1 versions of 68F2 and its germline variant (129D3) (and the germlined variant 103A1 derived from SIMPLE™ antibody lead 61H7) were compared to those of the reference antibodies. Following incubation at 37˚C in human serum. functional concentration of antibody was measured at weeks 1, 2, 4, 8, 12, 16, 24, 32 and 56 and compared to a pre-aliquoted standard. As depicted in **Figure 8**, the serum stability for the antibodies of the invention compared favourably to that reference antibodies.

Example 12. CMC Optimization

Several residues or motifs are not recommended for CMC-quality manufacturing of antibodies. Among them is the presence of Methionine in the CDR loops of the antibody. Methionine can be oxidized leading to chemically-altered variant of the antibody with altered properties such as affinity, potency, and stability. Accordingly, the methionine present in CDR3 of 111A7 (and its germlined variant of 61H7) was mutated to Alanine (111A7MA), leucine (111A7ML) or Serine (111A7MS). The resultant CMC-optimized sequences are provided in **Table 20** below. As shown in **Table 21**, the mutation of the methionine residue has a negligible effect on the binding to IL-6.

Example 13. Pharmacokinetic (PK) study in Cynomolgus Monkeys of Clone 129D3 and Fc Mutants Thereof

Pharmacokinetic analysis of antibody clone 129D3 formatted as various IgG1 molecules was performed. The following antibodies were analysed: Wild-type IgG1 129D3 (129D3-WT), IgG1 129D3 with the mutations M252Y/S254T/T256E in the Fc region (129D3-YTE), and IgG1 129D3 with the mutations H433K and N434F in the Fc region (129D3-HN).

Cynomolgus monkeys (3 per antibody tested) were injected intravenously with a single 5 mg/kg dose of 129D3-WT, 129D3-YTE, or 129D3-HN. Samples were taken at different time points and tested for plasma concentration of mAb by the ELISA. Specifically, a microtiterplate (Maxisorb Nunc) was coated with 1 ug/ml IL-6 (Immunotools) in PBS overnight at 4C. The plate was washed 2 times with PBS-Tween and blocked for 2 hours with 300 µl PBS-1%casein. After 2 washes with PBS-Tween, the samples were applied. All dilutions were made in 1% pooled blank plasma (this is a pool from 3 naive cynomolgus monkeys, see chapter 4.2). The samples were allowed to bind for 2 hours at RT. Plates were then washed 5 times with PBS-Tween and goat biotinilated anti-human IgG heavy and light chain monkey adsorbed polyclonal antibodies were applied at a 1000-fold dilution (Bethyl, catno: A80-319B) and allowed to bind for 1 hour at RT. After washing the plates 5 times with PBS-Tween, streptavidin conjugated with HRP (Jackson Immunoresearch 016-030-084) was applied at a 300,000-fold dilution and allowed to bind for 1 hour at RT. Plates were then washed 5 times with PBS-Tween and a 1:1 mixture of TMB (calbiochem CL07)-s(HS)TMB weakener (SDT, #sTMB-W) was added. The staining was allowed to proceed for 10 minutes and then stopped with 0.5 M H_2SO_4, after which the Optical Density was measured at 450nm. The samples were analysed four times and 129D3-WT (from the same batch that was injected into the animals) was used for a standard curve.

The relevant PK parameters for the non-compartmental analysis are shown in **Table 22** below. The pharmacokinetic profiles for the different 129D3 IgG1 antibodies are shown graphically in **Figure 12** (the results are shown are the average result of the group of monkeys). This data clearly shows that 129D3-YTE and 129D3-HN have a longer mean residency time (MRT) than the parental 129D3-WT antibody. Moreover, 129D3-YTE and 129D3-HN have a slower elimination rate and thus a substantially prolonged half-life as compared to 129D3-WT.

Interestingly, although both antibodies contain a wild-type IgG1 Fc region, the half-life of 129D3-WT is significantly longer than the half-life of the MedImmune anti-IL-6 IgG1 antibody (GL18) described in US201200344212. Specifically, 129D3-WT has a half-life of about 15.6 days as compared to about 8.5 days for antibody GL18. Thus, the extended half-life of the antibodies of the invention appears to be due to the properties of their respective Fab regions.

Example 14. Serum Amyloid A (SAA) Mouse Model

The *in vivo* efficacy of clones 68F2 and 61H7 was further investigated by measuring the ability of these antibodies to block serum amyloid A (SAA) induction in response to injected IL-6. General methods for performing this assay are set forth in WO2006/119115A2, which is hereby incorporated by reference in its entirety. Specifically, Balb/c mice were injected intravenously with 68F2, 61H7, the benchmark antibodies GL18, or CNTO136, or salt solution (control). Four hours after administration of the antibody, the mice were injected with 0.1 ug of IL-6. After a further 16 hours, blood was taken from the mice and the concentration of Serum Amyloid A was determined by ELISA. The experimental groups, dosages and results are set forth in **Table 26**, herein. The dose responses are also graphically depicted in **Figure 13**. The results show that antibody clones 68F2 and 61H7 have *in vivo* efficacy at least equal to the high potency benchmark controls GL18 and CNTO136.

Example 15. Humanized Mouse Psoriasis Xenograft Model

A mouse xenograft model was employed to evaluate the prophylactic efficacy of clone 68F2 on the development of induced psoriatic lesions. Specifically, BNX mice were transplanted with 5mm diameter full-thickness skin biopsies from non-involved skin from psoriasis patients (1 per mouse). After 3 weeks, the transplants were injected with $0.5x10^6$ activated PBMCs. Treatment of mice with clone 68F2, anti-TNF antibody (Remicade), or betamethasone dipropionate (positive control) was begun 1 day before the activated cells were injected into the transplants. Details of the treatment groups and regimes are shown in **Table 25**.

Treatment efficacy was determined by epidermal ridge thickness, as measured by light microscopy. Significance between groups was analyzed statistically using analysis of variance (ANOVA) followed by post-hoc Least Square Difference (LSD) tests to establish

statistical significance differences between treatment groups. A value of $p<0.05$ denoted a significant difference between groups.

The results of these experiments are set forth in **Figure 14**, herein. The epidermal ridge thickness of the control group (group 2) was 156μm ± 4 (mean ± s.e.m.). Treatment with betamethasone (group 1, n=3) significantly reduced epidermal ridge thickness to 83μm ± 13 ($p< 0.05$) (Figures 12 and 13). The average epidermal ridge thicknesses of the Remicade treatment group (group 3) was 125μm ± 12 and the 68F2 treatment group (group 4) was 125μm ± 12. These data show that clone 68F2 is as efficacious as the anti-TNF antibody Remicade in a humanized mouse psoriasis model.

Example 16. Renal Cell Cancer Mouse Xenograft Model

The *in vivo* efficacy of clones 68F2 was investigated in a renal cell cancer mouse xenograft model. General methods for performing this assay are set forth in WO2008/144763, which is hereby incorporated by reference in its entirety. Briefly, RXF393 cells (2×10^6) were injected subcutaneously at both lateral sides of a nude mouse. Tumors were allowed to grow to a volume between of 50 en 300 mm^3, prior to antibody administration. 90% of the injected mice developed a tumor. 40 mice were split into 5 groups of 8 mice. Each group was received intraperatoneal injection of either PBS (control) or a specific dose of clone 68F2 (1, 3, 10, or 30 mg/kg). Tumor size and survival was monitored twice per week.

The survival data, set forth in **Figure 15** herein, show that 68F2 is effective at delaying death of mice relative to control. Specifically, the observed median survival times were 15.5 days for the PBS group, 21 days for the 1 mg/kg, 3 mg/kg and 30 mg/kg 68F2 group, and 27.5 days for the 10 mg/kg 68F2 group. The survival data, set forth in **Figure 18** herein, show that 129D3 and 111A7 dosed at 3 mg/kg are effective at delaying death of mice relative to control. The tumor growth rate data, set forth in **Figure 16** herein, shows that clone 68F2 is effective at inhibiting tumor outgrowth in a dose-dependent manner with saturating effects at 10mg/kg dose. The tumor growth rate data, set forth in **Figure 17** herein, shows that clone 129D3 and 111A7SDMA>A are effective at inhibiting tumor outgrowth when dosed at 3 mg/kg.

Additional Tables.

Table 13. VH and VL Amino Acid Sequences of Exemplary Anti-IL-6 Neutralizing Fabs.

FAB CLONE	VH SEQUENCE	SEQ ID NO	VL SEQUENCE	SEQ ID NO
17F10	EVQLQESGPGLVKPSQTLSLTCTVSGGSI ATSYYAWSWIRQPPGKGLEWMGVIDYDGD TYYKPSLKSRTSISRDTSKNQFSLQLSSV TPEDTAVYYCARAGLGDSYYLGTYYAMDY WGKGTLVTVSS	1.	QAGLTQPPSVSGSPGKTVTISCAGTTSDVG TGNFVSWYQQLPGMAPKLLIYDVNKRASGI ADRFSGSKSGNTASLTISGLQSEDEADYYC ASYRSLNNVVFGGGTHLTVLG	233.
18C11	EVQLVESGGGLVQPGGSLRLSCAASGFTF SSYAMSWVRQAPGKGLEWVSAINSGGGST SYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCAKEGDTGWKDPMYDYWGQGT QVTVSS	2.	QSVVTQPSALSVTLGQTAKITCQGGGLRSS YAHWYQQKPGQAPVLVIYDDDSRPSGIPER FSGSSSGGRATLTISGAQAEDEGDYYCQSA DSSGNAAVFGGGTHLTVLG	234.
18C7	EVQLVESGPGLVKPSQTLSLTCTVSGGSI TASFDAWSWIRQPPGKGLEWMGVIAYDGS TYYSPSLKSRTSISRDTSKNQFSLQLSSV TPEDTAVYYCARKSSWLIGYGMDYWGKGT LVTVSS	3.	QAGLTQPSALSVTLGQTAKITCQGGSLGSS YAHWYQQKPGQAPVLVIYDDDSRPSGIPER FSGSSSGGRATLTISGAQAEDEGDYYCQSA DSSGNAAVFGGGTHLTVLG	235.
18C9	EVQLVESGGGLVQPGGSLRLSCAASGFTF SRNAMSWVRQAPGKGLEWVSAINSGGGST SYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCAKEGYTGWKDPMYDYWGQGT QVTVSS	4.	LNFMLTQPSALSVTLGQTAKITCQGGSLGS RYAHWYQQKPGQAPVLVIYDDDSRPSGIPE RFSGSSSGGRATLTISGAQAEDDGDYYCQS ADSSGNASVFGGGTHLTVLG	236.
18F8	EVQLVESGGGLVQPGGSLRLSCAASGFTF SRNAMSWVRQAPGKGLEWVSAINSGGGST SYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCAKEGYTGWKDPMYDYWGQGT QVTVSS	5.	QSALTQPSALSVTLGQTAKITCQGGSLGSR YAHWYQQKPGQAPVLVIYDDDSRPSGIPER FSGSSSGGRATLTISGAQAEDEGDYYCQSA DTSEHIVFGGGTHLTVLG	237.
20G2	EVQLVESGGGLVQPGGSLRLSCAASGFTF SRNAMSWVRQAPGKGLEWVSAINSGGGST SYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCAKEGYTGWKDPMYDYWGQGT QVTVSS	6.	ALNFMLTQPSALSVTLGQTAKITCQGGSLG SSYAHWYQQKPGQAPVLVIYDDDSRPSGIP ERFSGSSSGGRATLTISGAQAEDEGDYYCQ SADSSGNAVFGGGTHLTVLGQ	238.
18E12	EVQLQESGPGLVKPSQTLSLTCTVSGGSI TTRYYAWSWIRQPPGKGLEWMGVIDYDGD TYYSPSLKSRTSISWDTSKNQFSLQLSSV TPEDTAVYYCARDPDVVTGFHYDYWGQGT QVTVSS	7.	QSALTQPPSMSGTLGKTLTISCAGTSSDIG YGDYVSWYQQLPGTAPKLLIYKVSTRASGI PDRFSGSKSGNTASLTISGLQSEDEADYYC ASYRHYNNAVFGGGTHLTVLG	239.
20A4	EVQLQESGPGLVKPSQTLSLTCTVSGGSI TTRYYAWSWIRQPPGKGLEWMGVIDYDGD TYYSPSLKSRTSISWDTSKNQFSLQLSSV TPEDTAVYYCARDPDVVTGFHYDYWGQGT QVTVSS	8.	ALNFMLTQPPSVSGTLGKTVTISCAGTSSD IGGYNYVSWYQQLPGTAPKLLIHRVSTRAS GIPDRFSGSKSGNTASLTISGLRSEDEANY YCASYRNFNNAVFGGGTQLTVLG	240.
22C10	QVQLQESGPGLVKPSQTLSLTCTVSGGSI TTSYYAWSWIRQPPGKGLEWMGVIGYDGS TYYSPSLKSRTSISRDTSKNQFSLQLSSV TPEDTAVYYCARDAGWYVGYEYDYWGQGT QVTVSS	9.	ALPVLTQPPSVSGSPGQKFTISCTGSSSNI GENYVNWYQQLPGMAPKLLIYSNTNRASGV PDRFSGSKSGSSASLTITGLQVEDEADYYC SSWDDSLSGLVFGGGTKLTVLG	241.
22D11	QLQLVESGGGLVQPGGSLRLSCAASGFTF DDYAMSWVRQAPGKGLEWVSDISWNGGNT YYAESMKGRFTISRDNAKNTLYLQMNSLK SEDTAVYYCAKEGGAVVAGTVGYYGMDYW GKGTLVTVSS	10.	ALNFMLTQPPSLSASPGSSVRLTCTLSSGN SVGSYDISWYQQKAGSPPRYLLYYYSDSYK HQGSGVPSRFSGSKDASANAGLLLISGLQP EDEAAYYCSAYKSGSYVFGGGTKLTVLG	242.

24A3	QVQVQESGGGLVQPGGSLRLSCAASGFTF SNYAMSWVRQAPGKGLEWVSGISFRGGMI SYVDSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCAKNSGSSRSNALDAWGQGTL VTVSS	11.	ALNFMLTQPPSVSGSPGQKFTIRCTGSFRS DSYVNWYQQLPGTAPKLLINYDDRRVSGVP SRFSGSKSGNSASLTIDGLQAEDEAEYYCS FWDHTFGGHVFGGGTKLTVLG	243.
24B9	QVQLQESGGGLVQPGESLRLSCVASGFTF SSHRMYWVRQPPGKGLEWVSAISSSGVST YYTDSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKRRTWYAGEYDYWGQGTQVT VSS	12.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	244.
24C9	QVQLVESGGGLVQPGGSLRLSCAASGFTF SSYRMYWVRQPPGKGLEWVSAISAGGGST YYGDSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKKSTWADGESDYWGQGTQVT VSS	13.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	245.
24D10	QLQVVESGGGLVQPGGSLRLSCAASGFTF SSYAMSWVRQAPGKGPEWVSRISSGGGST SYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCANRAGWGMGDYWGQGTQVTV SS	14.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	246.
24D9	EVQVQESGGGLVQPGESLRLSCAASGFTF SSHRMYWVRQPPGKGLEWVSAISSSGVST YYADSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKRRTWYGGEYDYWGQGTQVT VSS	15.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	247.
24E9	EVQLVESGGGLVQPGGSLRLSCAASGFTF STYAMSWVRQAPGKGPEWVSRISSGGGST NYADSVKGRFTISRDNAKKTLYLQMKSLK PEDTAVYYCANRAGWGMGDYWGQGTQVTV SS	16.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	248.
24F4	EVQLVESGGGLVQPGESLRLSCAASGFTF SSHRMYWVRQPPGKGLEWVSAISSSGVST YYADSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKRRTWYGGEYDYWGQGTQLT VAS	17.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	249.
24G3	QLQVVESGGGLVQPGSSLRLSCGASGFTF SSHRMYWVRQPPGKGLEWVSAISSSGVST YYADSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKRRTWYGGEYDYWGQGTQVT VSS	18.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	250.
24B3	EVQLVESGGGLPXPGESLRLSCAASGFTF SSHRMYWVRQPPGKGLEWVSAISSSGVST YYADSVKGRFTISRDNAKNTVYLQMNSLK PEDTALYYCKRRTWYGGEYDYWGQGTQLT VAS	19.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVT ASNYPGWFQQTPGQAPRALIYSTNDRHSGV PSRFSGSISGNKAALTITGAQPEDEADYYC ALDIGDITEFGGGTHLTVLG	251.
29B11	EVQLVESGGGLVQPGGSLRLSCAASGFTF SSYAMSWVRQAPGKGLEWVSRISSGGIST YYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCVRYAWGVQWAFDFWGQGTQV TVSS	20.	QSVLTQPPSVSGSPGQTVTISCAGTSEDVG YGNYVSWYQQLPGMAPKLLIYDVNKRASGI ADRFSGSKSGNTASLTISGLQSEDEADYYC ASYRRTIDNIFGGGTHLTVLG	252.
28C6	QVQLVESGGGLVQPGGSLRLSCAASGFTF SNYYMTWVRQAPGKGLEWVSSIYSFSGDT AYADSVKGRFTISRDNAKNTLYLQMNKLK SEDTAVYYCTRDLGGVVVTANGYDYWGQG TQVTVSS	21.	DIVMTQTPSSLSASLGDRVTITCQASQSIS TELSWYQQKPGQTPKLLIYGASRLQTGVPA RFSGSGSGTSFTLTISGLEAEDLATYYCLQ DYSWPYSFGSGTRL	253.
28B6	QVQLVESGGGLVQPGGSLRLSCAASGFTF SNYYMTWVRQAPGKGLEWVSSIYSFSGDT AYADSVKGRFTISRDNAKNTLYLQMNSLK SEDTAVYYCTRNLGGVVVTTNGYDYWGQG	22.	DIQLTQSPSSLSASLGDRVTITCQASQSIS TELSWYQQKPGQTPKLLIYGASRLQTGVPA RFSGSGSGTSFTLTISGLEAEDLATYYCLQ DYSWPYSFGSGTRL	254.

	TQVTVSS			
28E6	QVQLVESGGGLVQPGGSLRLSCAASGFTF SNYYMTWVRQAPGKGLEWVSSIYSFSGDT AYADSVKGRFTISRDNAKNTLYLQMNSLK SEDTAVYYCTRNLGGVVVTTNGYDYWGQG TQVTVSS	23.	DIQMTQSPSSLSTSLGDRVTITCQASQAIT TELSWYQQKPGQPPKLLIYGTSRLQTGVPS RFSGTGSGTSFTLTISDLEAEDLATYYCLQ DYGWPFTFGQGTKV	255.
28F6	QVQLVESGGGLVQPGGSLRLSCAASGFTF SNYYMTWVRQAPGKGLEWVSSIYSFSGDT AYADSVKGRFTISRDNAKNTLYLQMNSLK SEDTAVYYCTRNLGGVVVTTNGYDYWGQG TQVTVSS	24.	DIVMTQSPSSLSASLGDRVTITCQTSQTIS TELSWYQQKPGQAPKLLIYGASRLQTGVPS RFSGSGSGTSFTLTISGLEAEDLATYYCLQ DYSWPFTFGQGTKV	256.
16A2	ELQLVESGGGLVQPGGSLRLSCAASGYTF DDYAMGWVRQAPGKGLEWVSSIYSYSSDT YYADSVKGRFTISRDNAQNTVYLQMTSLK PEDTALYYCARCARDIGSAWCGGVDYWGK GTLVTVSS	25.	DIVMTQSPFSLSASLGDRVTITCQASESIL TEVSWYQQKPGQTPKLLIYGASGLQTGVPN RFSGSGSGTSFTLTISGLEAEDLATYYCLQ DYRWPLTFGQGTKVELKR	257.
16B1	ELQLVESGGGLVQPGGSLRLSCAASGYTF DDYAMGWVRQAPGKGLEWVSSIYSYSSDT YYADSVKGRFTISRDNAQNTVYLQMTSLK PEDTALYYCARCARDIGSAWCGGVDYWGK GTLVTVSS	26.	DIVMTQSPSSLTASLGDRVTITCQASQSIR TDISWYQQKPGQTPKLLIYAASRLQTGVPS RFSGSGSGTSFTLTISGLEAEDLGTYYCLQ DYSWPLTFGQGTKVELKR	258.
16D2	ELQLVESGGGLVQPGGSLRLSCAASGYTF DDYAMGWVRQAPGKGLEWVSSIYSYSSDT YYADSVKGRFTISRDNAQNTVYLQMTSLK PEDTALYYCARCARDIGSAWCGGVDYWGK GTLVTVSS	27.	DIVMTQSPSSLSASLGDRVTITCQASQSIS TELSWYQQKPGQTPKLLIYGASRLQTGVPS SFSGSGSGTSFTLTISGLEAEDLATYYCLQ DYNWPFTFGQGTKVELKR	259.
29G3	ELQLVESGGGLVQPGGSLRLSCAASGFTF SSYAMSWVRQAPGKGLEWVSRISSGGIST YYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTAVYYCARYAWGVQWAFDFWGQGTQV TVSS	28.	DIQMTQSPSSVTASVGEKVTLNCKSSQSVV VRSDQKSYLNWYQQRPGQSPRLLIYYASTQ ESGIPDRFSGSGSTTDFTLTINSVQPEDAA VYYCQQASSAPYNFGSGTRL	260.

Table 14. VH and VL Amino Acid Sequences of Exemplary Anti-IL-6 Neutralizing Fabs Generated by VH or VL Shuffling

FAB CLONE	VH SEQUENCE (clone name given in place of sequence if sequence identical to VH in another clone)	SEQ ID NO	VH SEQUENCE (clone name given in place of sequence if sequence identical to VL in another clone)	SEQ ID NO
35C1	VH_17F10	1.	QSALTQPPSMSGTLGKTLTISCNGTSSDIGSGDYVSWYQ QLPGTTPKLLIEGVTTRASGIPDRFSASKSDNTASLTIS GLQSEDEATYYCASYRETNNVVFGGGTHLTVLS	261.
35B1	VH_17F10	1.	QAVLTQPPSMSGTLGKTLTISCNGTSSDIGSGNYVSWYQ QLPGTTPKLLIEGVTTRVSGIPDRFSGSKSDNTASLTIS GLQSEDEATYYCASYRETNNVVFGGGTHLTVLG	262.
35F5	VH_17F10	1.	QAGLTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSWYQ QLPGMAPKLLIYDVNKRASGIADRFSGSKSGNTASLTIS RLQSEDEADYYCASYKTYNNVVFGGGTHLTVLG	263.
35D1	VH_17F10	2.	QSVVTQPPSVSGTLGKTVTISCAGTTSDIGGYNYVSWYQ QLPGTAPKFLIYEVSKRAAGIPDRFSGSKSGSTASLTIS GLQSEDEADYYCASYRDTANVVFGGGTHLTVLG	264.
37A1	VH_18C11	2.	ALNFMLTQPSALSVTLGQTAKITCQGGSLGNNYAHWYQQ KPGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISG AQAEDEGDYYCQSADSSGNAVFGGGTHLTVLG	265.
36A1	VH_18C11	2.	AQSALTQPSALSVTLGQTAKITCQGGSLGTRYAHWYQQK PGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISGA QAEDEGDYYCQSADSSGNASVFGGGTHLTVLG	266.
36F8	VH_18C11	2.	ALNFMLTQPSALSVTLGQTAKITCQGGSLGSRYAHWYQQ KPGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISG AQAEDEGDYYCQSADSSGNAAVFGGGTHLTVLG	267.
37D1	VH_18C11	2.	AQAGLTQPSALSVTLGQTAKITCQGGSLGSSYAHWYQQK PGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISGA QAEDEGDYYCQSADSSGNAIVFGGGTHLTVLG	268.
37G1	VH_18C11	2.	AQAVLTQPSALSVTLGQTAKITCQGGSLRSSYAHWYQQK PGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISGA QAEDEGDYYCQSADSSGNASVFGGGTHLTVLG	269.
20G2	VH_18C11	2.	ALNFMLTQPSALSVTLGQTAKITCQGGSLGSSYAHWYQQ KPGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISG AQAEDEGDYYCQSADSSGNAVFGGGTHLTVLG	270.
44C6	VH_18C7	3.	AQSALTQPSALSVTLGQTAKITCQGGSLGSSYAHWYQQK PGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLTISGA	271.

			QAEDEGDYYCQSADSSGNASVFGGGTHLTVLG	
44E7	VH_18C7	3.	ALNFMLTQPSALSVTLGQTAKITCQGGSLGSSYAHWYQQ KPGQAPVLVIYDDDSRPSGIPERFSGSSSGGRATLSISG AQAEDEGDYYCQSGDSSGNAAVFGGGTKLTVLG	272.
68F2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWIR QPPGKGLEWMGVIDYDGDTYYSPSLKSRTSISWDTSKNQF SLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQVTV SS (Identical to VH_20A4)	8.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQ QLPGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTIS GLQSEDEADYYCASYRNFNNAVFGRGTHLTVLG	273.
71C8	VH_20A4	8.	QSALTQPPSVSGTLGKTLTISCAGTSSDVGYGNYVSWYQ QLPGTAPKLLIYRVSTRASGIPDRFSGSKSGNTASLTIS GLQSEDEADYYCASYRSSNNAVFGGGTHLTVLG	274.
70H2	VH_20A4	8.	QSVLTQPPSVSGTLGKTVTISCAGTSSDVGYGNYVSWYQ QLPGTAPKLLIYAVSYRVSGIPDRFSGSKSGNTASLTIS GLQSEDEADYYCASYRNRNNAVFGGGTHLTVLG	275.
71D12	VH_20A4	8.	QAVLTQPPSVSGTLGKTVTISCAGTSSDVGYGNYVSWYQ QLPGTAPKLVIYAVNYRASGIPDRFSGSKSGNTASLFIS GLQSEDEADYYCASYRDFNNAVFGGGTHLTVLG	276.
70B2	VH_20A4	8.	QAVLTQPPSVSGSPGKTVTISCAGTSSDVGFGNYVSWYQ QLPGMAPKLLIYEVNKRTSGIPDRFSGSKSGNTASLTIS GLQSEDEADYHCASYRNFNNAVFGGGTHLTVLG	277.
71C3	VH_20A4	8.	QSALTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSWYQ QLPGMAPKLLIYDVNKRASGIADRFSGSKSGNTASLTIS RLQSEDEADYYCASYKTYNNVVFGGGTHLTVLG	278.
69H4	VH_20A4	8.	QSALTQPPSVSGTLGKTVTISCAGTSSDVGYGNYVSWYQ QLPGTAPKLLIYAVSYRASGIPDRFSGSKSGNTASLTIS GLQSEDEADYYCASYRYFNNAVFGGGTHLTVLG	279.
68G8	VH_16D2	27.	LDIVMTQTPSSLSASLGDRVTITCQATQNINTELSWYQQ KPGQTPKLLIYDTSRLQTGVPSRFSGSGSRTTFTLTISG LEAEDLATYYCMQDYNWPLTFGQGTKVELKR	280.
68E10	VH_16D2	27.	LDIVMTQTPSSLSASLGDRVTITCQASQSISTELSWYQQ KPGQSPKLLIYGASRLQIGVPSRFSGSGSGTSFTLTISG LEADDLATYYCLQDYNWPLSFGSGTRLEIK	281.
69H7	VH_16D2	27.	LDIQMTQSPSSLSASLGDRVTITCQASQSISTELAWYQQ KPGQTPKLLIYGASKLQTGVPSRFSGSGSGTSFTLTISG LEAEDLATYYCLQDYNWPFTFGQGTKVELKR	282.
70B5	VH_16D2	27.	LDIVMTQTPSSLSASLGDRVAITCQASQSINVDVSWYQQ KPGQTPKLLIYAASRLQTGVPSRFSGSGSGTSFALTISG LEAEDLASYYCLQDYSWPLTFGQGTKVELKR	283.

70C5	VH_16D2	27.	LDIQMTQSPSSLSVFLGDRVTITCQASQRISTELSWYQQ KPGQTPKLLIWGASRLQTRVPSRFSGSGSGTSFTLTISG LEAEDLATYYCLQDYSWPLTFGQGTKVELKR	284.
70C6	VH_16D2	27.	LDIVMTQSPSSLSASLGDRVTITCQASQNIITELSWYQQ KPGQTPKLLIYGASRLQTGVPSRFSGSGSGTSFTLTISG LEAEDLATYYCLQDYNWPLTFGQGTKVELKR	285.
70H4	VH_16D2	27.	LDIVMTQTPSSLSASLGDRVTITCQASQNINTDLSWYQQ KPGQTPKLLFYGASGLQTGIPSRFSGSGSGTSFTLAISG LEAEDLATYYCLQDYNWPLTFGQGTKVELKR	286.
72A4	VH_16D2	27.	LEIVMTQSPSSLSASVGDRVTITCQASQSISTELSWYQQ KPGQTPKLLIYDASRLQTGVPSRFSGSRSGTTFTLTISG LEAEDLATYYCLQDYNWPLTFGQGTKVELK	287.
72B6	VH_16D2	27.	LDIVMTQSPSSLSASLGDRVTITCQATQSISTELSWYQQ KPGQAPKLLIYDASKLQTGVPSRFSGSGSGRSFTLTISG LEAEDSATYYCLQDYNWPLSFGSGTRLEIK	288.
72D2	VH_16D2	27.	LDIQLTQSPSSLSASLGDRVTITCQASQSINIDLSWYQQ KPGQTPKLLFYGASGLQAGVPSRFSGSGSGTSFTLTING LEAEDLATYYCLQDYNWPLTFGQGTKVELKR	289.
72G1	VH_16D2	27.	LETTLTQSPSSLSVSLGDRVTITCQASQRISTELSWYQQ KPGQAPKLLIYDASTLQTGVPFRFGGSGSGTSFTLTISG LEAEDLATYYCLQDYSWPLTFGQGTKVELNR	290.
47C2	VH_29B11	20.	ALSYDLTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSW YQQLPGMAPKILIYDVNKRASGIADRFSGSKSGNTASLT ISGLQSEDEADYYCASYRRGETIVFGGGTHLTVLG	291.
47C3	VH_29B11	20.	ALSYELTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSW YQQLPGMAPKLLIYDVNKRASGIADRFSGSKSGNTASLT ISGLQSEDEADYYCASYRLGNKYVFGGGTKLTVLG	292.
48C10	VH_29B11	20.	AQSVLTQPPSVSGSPGQTVTISCAGTSEDVGYGNYVSWY QQLPGMAPKLLIYDVNKRASGIADRFSGSKSGNTASLTI SGLQSEDEADYYCASYRRTIDNIFGGGTHLTVLG	293.
47B2	VH_29B11	20.	AQSALTQPPSVSGSPGKTVTISCAGTSSDIGYGNYVSWY QQFPGMAPKFLIYDVHRRASGIADRFSGSKSGNTASLTI SGLQPEDEAVYYCASYRRGSNAVFGGGTHLTVLG	294.
55C1	VH_29B11	20.	ALNFMLTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSW YQQLPGTAPKLLIYNVNKRASGITDRFSGSKSGNTASLT ISGLQSEDEADYYCASYRTGDNAAFGGGTKLTVLG	295.
55E2	VH_29B11	20.	AQSVLTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSWY QQLPGMAPKLLIYDVNKRASGIADRFSGSKFANTASLTI SGLQSEDEADYYCASYKRGDNAVFGGGTKLTVLG	296.

55H1	VH_29B11	20.	AQSVVTQPPSVSGSPGKTVTISCAGTSSDVGYGNYVSWY QQLPGMAPKLLIYDVSKRASGIADRFSGSKSGNTASLTI SGLQSEDEADYVCASYRRGGTAVFGGGTHLTVLG	297.
65B7	QVQVQESGGGLVHPGESLRLSCAASGFTFSSHRMYWVRQP PGKGLEWVSAISSSGVSTYYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTALYYCKRRTWYGGEYDYWGQGTQVTVSP	29.	VL_24B9	12.
65B12	EVQLVESGGALVHPGGSLRLSCAASGFTFSSHRMYWVRQP PGKGLEWVSAISSSGVSTYYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTALYYCKRRTWYGGEYDYWGQGTQVTVSS	30.	VL_24B9	12.
65H8	QVQLVESGGGLVHPGESLRLSCAASGFTFSSHRMYWVRQP PGKGLEWVSAISSSGVSTYYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTALYYCKRRTWYGGEYDYWGQGTQVTVSS	31.	VL_24B9	12
77D1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSRISSGGISTYYADSVKGRFTISRDNAKNTLY LQMNSLKPEDTAVYYCVRYAWGVQWAFDFWGQGTQVTVSS	32.	VL_24B9	12
77D6	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSRISSGGISTYYADSVKGRFTISRDNAKNTLY LQMNSLKPEDTAVYYCVRYAWGVQWAFDFWGQGTQVTVSS	33.	VL_24B9	12
61A7	QVQLVESGGGLVQPGGSLRLSCVASGFTFSSYAMSWVRQA PGKGPEWVSRISSGGGSTSYADSVKGRFTISRDNAKNTLY LQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	34.	VL_24B9	12
61B7	ELQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGPEWVSRISSGGGSAYYADSVKGRFTISRDNAKNTLY LQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	35.	VL_24B9	12
65F9	QVQLVESGGGLVHPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGPEWVSRISSGGGSAYYADSVKGRFTISRDNAKNTLY LQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	36.	VL_24B9	12
61H7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQP PGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNTVY LQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	37.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQ QTPGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTIT GAQPEDEADYYCALDIGDITEFGGGTHLTVLG (IDENTICAL TO VL_24B9)	12
65D7	EVQLVESGGGLVQPGESLRLSCVASGFTFSSHRMYWVRQP PGKGLEWVSAISSSGVSTYYTDSVKGRFTISRDNAKNTVY LQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	38.	VL_24B9	12
48H1	VH_28B6	22.	DVVMTQSPSSLPTSLGDSVTITCQASQSISDELSWYQQK PGQTPKLLIYGASKLQTGVPSRFSGSGSGTSFTLTISGL EAEDLATYYCLQGYSWPFMFGQGTKVELK	298.
55E10	VH_28B6	22.	DIQMTQSPSSLPTSLGDSVTITCQASQSISDELSWYQQK PGQTPKLLIYGASKLQTGVPSRFSGSGSGTSFTLTISGL	299.

			EAEDLATYYCLQGYSWPFMFGQGTKVELK	
55A11	VH_28B6	22.	DIQMTQSPSSLPTSLGDSVTITCQASQSISDELSWYQQK PGQTPKLLIYGASRLQTGVPSRFSGRGSGTSFTLTISGL EAEDLATYYCLQGYSWPFMFGQGTKVELK	300.
55C11	VH_28B6	22.	DIQLTQSPSSLSASLGDSVTITCQASQSISDELSWYQQK PGQTPKLLIYGASKLQTGVPSRFSGSGSGTSFTLTISGL EAEDLATYYCLQGYRWPFMFGQGTKVELK	301.
55C10	VH_28B6	22.	DIQMTQSPSSLSTSLGDRVTITCQASQSISTELSWYQQK PGQTPKLLIYGASRLQTGVPSRFSGXGSGTSFTLTISGM EAEDLATYYCLQDYSWPYXFGXGTRVEIK	302.

Table 15. VH and VL Amino Acid Sequences of Exemplary Germlined Variants of Fab Clone 61H7.

FAB CLONE	VH SEQUENCE	SEQ ID NO	VL SEQUENCE	SEQ ID NO
100A8	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	39.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPSRFSGSISGNKAALTITGAQP DDEADYYCALDIGDITEFGGGTHLTVLG	303.
100E8	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ PPGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	40.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTHLTVLG	304.
100F2	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKTENTAVYYCANRAGWGMGDYWGQGTLVTVS S	41.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQP EDESDYYCALDIGDITEFGGGTHLTVLG	305.
100G8	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	42.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTHLTVLG	306.
101B2	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNTLKTEDTAVYYCANRAGWGMGDYWGQGTLVTVS I	43.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPSRFSGSILGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTQLTVLG	307.
101B8	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLRAENTAVYYCANRAGWGMGDYWGQGTQVTVS	44.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTHLTVLG	308.

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101D8	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	45.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLLGGKAALTILGAQA DDEAEYYCALDIGDITEFGGGTQLTVLG	309.
101G8	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTENTAVYYCANRAGWGMGDYWGQGTQVTVS S	46.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGTPSRFSGSLSGGKAALTILGAQP EDEAEYYCALDIGDITEFGGGTKLTVLG	310.
104A5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGLEWVSPISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	47.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQP DDEADYYCALDIGDITEFGGGTQLTVLG	311.
104C1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	48.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTKLTVLG	312.
104C5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	49.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPSRFSGSISGNKAALTITGAQP EDEADYYCALDIGDITEFGGGTHLTVLG	313.
104C7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	50.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTKLTVLG	314.
104D1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	51.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPSRFSGSISGNKAALTITGAQP EDEADYYCALDIGDITEFGGGTHLTVLG	315.
104D5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	52.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQA EDESDYYCALDIGDITEFGGGTHLTVLG	316.
104F11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	53.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDESDYYCALDIGDITEFGGGTQLTVLG	317.
104F7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT	54.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA	318.

	VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S		EDESDYYCALDIGDITEFGGGTHLTVLG	
104G7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	55.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTQLTVLG	319.
105A1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	56.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTQLTVLG	320.
105A5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	57.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRTLIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTHLTVLG	321.
105A7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	58.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGTPSRFSGSLSGNKAALTILGAQP EDEADYYCALDIGDITEFGGGTHLTVLG	322.
105B11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	59.	QAVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP EDEAEYYCALDIGDITEFGGGTHLTVLG	323.
105B5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	60.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSISGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTHLTVLG	324.
105B7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	61.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLLGGKAALTILGAQA DDEAEYYCALDIGDITEFGGGTQLTVLG	325.
105C1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	62.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSLSGGKAALTITGAQA EDEAEYYCALDIGDITEFGGGTQLTVLG	326.
105C7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	63.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPARFSGSLSGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTHLTVLG	327.
105D1	ELQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ	64.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK	328.

	APGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S		PGQAPRALIYSTNDRHSWVPARFSGSLSGNKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTHLTVLG	
105E5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	65.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSISGGKAALTLTGAQP DDEAEYYCALDIGDITEFGGGTKLTVLG	329.
105G1	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	66.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPSRFSGSLSGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTQLTVLG	330.
105H11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	67.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSISGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTQLTVLG	331.
105H5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	68.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSILGGKAALTILGAQP NDEAEYYCALDIGDITEFGGGTHLTVLG	332.
98C10	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	69.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLLGGKAALTILGAQA DDEAEYYCALDIGDITEFGGGTQLTVLG	333.
98E10	ELQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	70.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLSGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTQLTVLG	334.
98F2	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	71.	QAVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGTPARFSGSLSGNKAALTITGAQP EDEADYYCALDIGDITEFGGGTKLTVLG	335.
99C10	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS T	72.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPARFSGSISGGKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTQLTVLG	336.
104G5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	73.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTHLTVLG	337.

108A1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	74.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTKLTVL	338.
108A3	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	75.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTHLTVL	339.
108A5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	76.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRTLIYSTNDRHSGVPSRFSGSILGNKAALTITGAQP EDESDYYCALDIGDITEFGGGTHLTVL	340.
108A9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCAKRAGWGMGDYWGQGTQVTVS S	77.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGTPARFSGSLSGNKAALTILGAQP EDEADYYCALDIGDITEFGGGTQLTVL	341.
108B1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	78.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA EDESDYYCALDIGDITEFGGGTHLTVL	342.
108B3	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	79.	QTVVTQEPRLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTQLTVL	343.
108B7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	80.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSWVPARFSGSLSGGKAALTILGAQP EDEAEYYCALDIGDITEFGGGTHLTVL	344.
108B9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	81.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLSGNKAALTILGAQP EDEADYYCALDIGDITEFGGGTQLTVL	345.
108C5	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	82.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRTLIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA EDESDYYCALDIGDITEFGGGTHLTVL	346.
108C9	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS	83.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPSRFSGSLSGNKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	347.

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111A11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	84.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTHLTVL	348.
111A5	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCAKRAGWGMGDYWGQGTQVTVS S	85.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTKLTVL	349.
111A7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	86.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTQLTVL	350.
111B1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	87.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTQLTVL	351.
111B11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	88.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDESDYYCALDIGDITEFGGGTKLTVL	352.
111B5	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISSGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	89.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTQLTVL	353.
111B7	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	90.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQP EDESDYYCALDIGDITEFGGGTHLTVL	354.
111C11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	91.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQP EDESDYYCALDIGDITEFGGGTQLTVL	355.
111C5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ APGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	92.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDEADYYCALDIGDITEFGGGTHLTVL	356.
111C9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT	93.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP	357.

	VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S		DDEADYYCALDIGDITEFGGGTKLTVL	
111D7	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGLEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	94.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTHLTVL	358.
111D9	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	95.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTKLTVL	359.
111E11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	96.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQP EDESDYYCALDIGDITEFGGGTQLTVL	360.
111E7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	97.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDEADYYCALDIGDITEFGGGTHLTVL	361.
111E9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	98.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSISGNKAALTITGAQA EDEADYYCALDIGDITEFGGGTKLTVL	362.
111F11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	99.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRTLIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDESDYYCALDIGDITEFGGGTQLTVL	363.
111F7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	100.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTKLTVL	364.
111F9	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	101.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSILGNKAALTITGAQP EDEADYYCALDIGDITEFGGGTKLTVL	365.
111G1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	102.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTHLTVL	366.
111G11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ	103.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT	367.

	APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S		PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDESDYYCALDIGDITEFGGGTHLTVL	
111G7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	104.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQP DDESDYYCALDIGDITEFGGGTHLTVL	368.
111G9	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ APGKGLEWVSAISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	105.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQP EDEADYYCALDIGDITEFGGGTHLTVL	369.
111H7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	106.	QTVVTQEPSFSVSPGGTVTLTCGLSSGSVTASNYPGWYQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGNKAALTITGAQP DDEADYYCALDIGDITEFGGGTHLTVL	370.
111H9	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	107.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPDRFSGSISGNKAALTITGAQA DDEADYYCALDIGDITEFGGGTHLTVL	371.
112A11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	108.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLLGGKAALTILGAQA DDEAEYYCALDIGDITEFGGGTQLTVL	372.
112A4	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	109.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPARFSGSISGGKAALTILGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	373.
112A7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	110.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLSGGKAALTILGAQP EDEADYYCALDIGDITEFGGGTHLTVL	374.
112B1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGLEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	111.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPARFSGSLLGGKAALTITGAQP EDEAEYYCALDIGDITEFGGGTHLTVL	375.
112B11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	112.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPARFSGSLSGGKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTHLTVL	376.

112C11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRLYWVRQ PPGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	113.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSWVPSRFSGSLSGGKAALTITGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	377.
112C7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	114.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSLSGGKAALTITGAQP EDEADYYCALDIGDITEFGGGTHLTVL	378.
112C9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	115.	QAVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSLSGNKAALTITGAQA EDEAEYYCALDIGDITEFGGGTHLTVL	379.
112D11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ PPGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	116.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPARFSGSLLGGKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	380.
112D7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMSWVRQ APGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVS S	117.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSWVPSRFSGSLLGGKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	381.
112D9	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ PPGKGLEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	118.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQK PGQAPRALIYSTNDRHSGVPSRFSGSLLGGKAALTLLGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	382.
112E11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNT LYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	119.	QTVVTQEPSLTVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSWVPARFSGSLSGGKAALTLTGAQP EDEADYYCALDIGDITEFGGGTKLTVL	383.
112E4	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQ PPGKGPEWVSAISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	120.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSWVPARFSGSLLGGKAALTITGAQP EDEAEYYCALDIGDITEFGGGTHLTVL	384.
112E7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQ APGKGLEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNT LYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVS S	121.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPARFSGSILGGKAALTILGAQP EDEAEYYCALDIGDITEFGGGTHLTVL	385.
112F11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNAKNT VYLQMNSLKTEDTAVYYCANRAGWGMGDYWGQGTLVTVS	122.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQT PGQAPRALIYSTNDRHSGVPSRFSGSILGGKAALTLTGAQP EDEAEYYCALDIGDITEFGGGTQLTVL	386.

	S			
112G11	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNSKNTVYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	123.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQTPGQAPRALIYSTNDRHSGVPARFSGSISGGKAALTLLGAQPEDEAEYYCALDIGDITEFGGGTQLTVL	387.
112G4	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQPPGKGLEWVSRISAGGGSTYYGDSVKGRFTISRDNAKNTVYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTLVTVSS	124.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQKPGQAPRALIYSTNDRHSGVPARFSGSISGGKAALTLLGAQAEDEAEYYCALDIGDITEFGGGTQLTVL	388.
112G7	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMYWVRQAPGKGPEWVSRISSGGGSTYYGDSVKGRFTISRDNSKNTLYLQMNSLKPEDTAVYYCANRAGWGMGDYWGQGTLVTVSS	125.	QTVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQTPGQAPRALIYSTNDRHSGVPARFSGSLSGNKAALTITGAQPEDEAEYYCALDIGDITEFGGGTQLTVL	389.
112H7	ELQLLESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQPPGKGPEWVSAISAGGGSTYYGDSVKGRFTISRDNAKNTVYLQMNSLRAEDTAVYYCANRAGWGMGDYWGQGTQVTVSS	126.	QAVVTQEPSLSVSPGGTVTLTCGLSSGSVTASNYPGWFQQKPGQAPRALIYSTNDRHSGVPARFSGSILGGKAALTLTGAQPEDEADYYCALDIGDITEFGGGTHLTVL	390.

Table 16. VH and VL Amino Acid Sequences of Exemplary Germlined Variants of Fab Clone 68F2.

FAB CLONE	VH SEQUENCE	SEQ ID NO	VL SEQUENCE	SEQ ID NO
128B7	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWIRQPPGKGLEWMGVIDYEGDTYYSPSLKSRVSISWDTSKNQFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQVTVSS	127.	QSALTQPPSVSGTPGQRVTISCAGANNDIGTYAYVSWYQQLPGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTITGLQSEDEADYYCASYRNFNNAVFGRGTKLTVL	391.
128B8	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWIRQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSNNQFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTLVTVSS	128.	QSVLTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQLPGTAPKLLIYKVTTRASGIPDRFSGSKSGATASLTITGLQAEDEADYYCASYRNFNNAVFGRGTHLTVL	392.
128C2	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWIRQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKNQFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTMVTVSS	129.	QSALTQPPLVSGTPGQRVTISCAGANNDIGTYAYVSWYQQLPGTAPRLLIYKVTTRASGVPDRFSGSKSGNTASLTITGLQSEDEADYYCASYRNFNNAVFGGGTKLTVL	393.
128D3	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWIRQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKNQFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTMVTVSS	130.	QSALTHPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQLPGTAPKLLIYKVTTRASGVPDRFSGSKSANTASLTITGLQAEDEADYYCASYRNFNNAVFGRGTKLTVL	394.

128D7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGKGTL VTVSS	131.	QSALTQPPLVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISELQS EDEADYYCASYRNFNNAVFGGGTHLTVL	395.
128E10	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	132.	QSVLTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	396.
128E2	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	133.	QSALTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	397.
128E3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	134.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLAITGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	398.
128E7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISVDTSKN QFSLHLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	135.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGATASLTITGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	399.
128F3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISVDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	136.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNSASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	400.
128F7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	137.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	401.
128F8	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	138.	QSVLTQPPLVSGTPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGRGTHLTVL	402.
128G3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISVDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	139.	QSALTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLAISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	403.
128H7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ	140.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	404.

	VTVSS			
129A10	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	141.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	405.
129A3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGPGTQ VTVSS	142.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	406.
129A5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISVDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	143.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	407.
129A9	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	144.	QSALTQPPLVSGIPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	408.
129B3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	145.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	409.
129B7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	146.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	410.
129B8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	147.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTKLTVL	411.
129C10	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	148.	QSAMTQPPSVSGSPGQSVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	412.
129C11	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QISLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	149.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL AGTAPKLMIYKVTTRASGIPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGTGTHLTVL	413.
129D11	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN	150.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS	414.

	QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS		EDEADYYCASYRNFNNAVFGTGTHLTVL	
129D2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITPRYYVWTWI RHPPGKGLDWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARYPDVVTGFHYDYWGQGTQ VTVSS	151.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSISGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	415.
129D3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	152.	QSALTQPPSVSGTPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGTGTKLTVL	416.
129D5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	153.	QSALTQPPSVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNGVFGTGTKLTVL	417.
129D8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	154.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTHLTVL	418.
129E11	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	155.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	419.
129E3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	156.	QSALTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRYFNNAVFGTGTKLTVL	420.
129F10	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSSYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	157.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCSSYRNFNNAVFGTGTKLTVL	421.
129F11	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	158.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTSRASGVPSRFSGSKSGNTASLSISGLQA EDEADYYCASYRNFNNAVFGSGTKLTVL	422.
129F2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	159.	QSALTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	423.
129F3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI	160.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL	424.

	RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS		PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTHLTVL	
129F5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	161.	QSALTQPPLVSGTPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	425.
129G7	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISVDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	162.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	426.
129G9	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	163.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGSGTHLTVL	427.
129H5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	164.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYRVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	428.
129H6	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	165.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	429.
129H7	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	166.	QSAMTQPPSVSGSPGQSVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	430.
129H8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	167.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGNGTQLTVL	431.
129H9	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLESRTTISWDTSKN QFSLNLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	168.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLMIYKVTTRASGVPSRFSGSISGNTASLTISGLQA EDEADYYCASYRNFNNAVFGTGTHLTVL	432.
126F4	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	169.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	433.

127D11	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTK VTVSS	170.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	434.
127H10	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	171.	QSVLTQPPLVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNSASLTITGLQA EDEADYYCASYRNFNNGVFGGGTHLTVL	435.
127H1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	172.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	436.
127G1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISVDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	173.	QSVLTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLAISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	437.
126H5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISVDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	174.	QSALTQPPSVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGTGTHLTVL	438.
127B12	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTK VTVSS	175.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	439.
127F1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	176.	QSVLTQPPSVSGTPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	440.
127D7	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	177.	QSALTQPPLVSGTPGQPVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLISKVTTRASGVPDRFSGSKSGTTASLTITGLQS EDEADYYCASYRNFNNGVFGGGTHLTVL	441.
127F5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	178.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRTFNNAVFGSGTHLTVL	442.
127C6	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ	179.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGIPDRFSGSISGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	443.

	VTVSS			
127F3	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISVDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	180.	QSVLTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTITGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	444.
127G5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	181.	QSALTQPPSVSGTPGQSVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGSGTHLTVL	445.
126H2	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	182.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	446.
127D5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	183.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	447.
127B5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	184.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGSGTKLTVL	448.
126E1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	185.	QSALTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	449.
126B5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDNWGQGTL VTVSS	186.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGSGTHLTVL	450.
127B8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	187.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTSRASGVPSRFSGSKSGNTASLSISGLQA EDEADYYCASYRNFNNAVFGSGTKLTVL	451.
127E1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	188.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	452.
126G2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN	189.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA	453.

	QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS		EDEADYYCASYRNFNNAVFGTGTHLTVL	
126D2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	190.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	454.
126G3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QISLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	191.	QSALTQPPSVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	455.
126D4	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	192.	QFALTQPPLVSGTPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTHLTVL	456.
127F2	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	193.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGSGTKLTVL	457.
127H2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	194.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	458.
127G2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLHLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	195.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	459.
126E5	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVSISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	196.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNGVFGTGTKLTVL	460.
127E9	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	197.	QSVLTQPPSVSGTPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	461.
127E8	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	198.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	462.
127E3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI	199.	QSVLTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL	463.

	RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS		PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLAITGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	
126F3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDADTYYSPSLKSRTSISWDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	200.	QSALTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	464.
126A4	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	201.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	465.
127B4	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QISLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	202.	QSALTQPPSVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	466.
126A3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	203.	QSALTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTITGLQS EDEADYYCASYRNFNNAVFGRGTKLTVL	467.
127D6	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	204.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	468.
126D5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVTISVDTSKN HFSLKLSSVTAEDTAVYYCATDPDVVTGFHYDYWGQGTT VTVSS	205.	QSALTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	469.
127D8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVSISVDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDNWGQGTL VTVSS	206.	QSALTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPVRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	470.
126E4	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWMGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	207.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGTGTHLTVL	471.
126F2	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	208.	QFALTQPPLVSGTPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTHLTVL	472.

132A7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	209.	QSVLTQPPLVSGTPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	473.
132B1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISVDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	210.	QSVLTQPPLVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	474.
132B2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	211.	QSALTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSSNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	475.
132B7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	212.	QSVLTQPPSVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGATASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	476.
132D3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYEGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	213.	QSALTQPPSVSGAPGQTVTISCAGANNDVGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNSASLTITGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	477.
132E7	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	214.	QSVLTQPPRVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSKSGNSASLTITGLQA EDEADYYCASYRNFNNAVFGGGTKLTVL	478.
132F1	EVQLEESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	215.	QSVLTQPPLVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGRGTHLTVL	479.
132F2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	216.	QSVLTQPPSVSGAPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTITGLQS EDEADYYCASYRNFNNAVFGRGTHLTVL	480.
132G1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	217.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPNRFSGSKSGNTASLTITGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	481.
132G2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL	218.	QSVLTQPPLVSGTPGQRVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	482.

	VTVSS			
132G3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	219.	QSVLTQPPLVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTKLTVL	483.
132G7	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	220.	QSALTQPPSVSGAPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	484.
133A3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	221.	QSALTQPPLVSGTPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPDRFSGSISGNTASLTISGLQS EDEADYYCASYRNFNNGVFGTGTHLTVL	485.
133A7	EVHLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIYYEGDTYYSPSLKSRTSISWDTSKN QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	222.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPSRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTKLTVL	486.
133A9	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYEGDTYYSPSLKSRVTISVDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTM VTVSS	223.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLMIYKVTTRASGIPDRFSGSISGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTKLTVL	487.
133D1	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVINYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTPEDTAVYYCARYPDVVTGFHYDYWGQGTQ VTVSS	224.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGRGTKLTVL	488.
133D8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS	225.	QSALTQPPLVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGVPSRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	489.
133E3	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLHLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	226.	QSALTQPPSVSGSPGQSVTLSCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGSGTKLTVL	490.
133E5	QVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLKLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	227.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQL PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGRGTKLTVL	491.
133F2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN	228.	QSALTQPPSVSGSPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPQLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS	492.

	QFSLQLSSVTPEDTAVYYCARDPDVVTGFHYDYWGQGTL VTVSS		EDEADYYCASYRNFNNAVFGGGTKLTVL	
133G8	EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISWDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	229.	QSALTQPPSVSGTPGQSVTISCAGANNDIGTYAYVSWYQQL PGTAPKLLIYKVTTRASGIPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGGGTHLTVL	493.
133H2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTTISWDTSKN QFSLKLSSVTPADTAVYYCARDPDVVTGFHYDYWGQGTT VTVSS	230.	QSALTQPPLVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLMIYKVTTRASGIPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGSGTKLTVL	494.
133H9	QVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRTSISWDTSKN QFSLKLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	231.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQS EDEADYYCASYRNFNNAVFGTGTHLTVL	495.
127E2	EVQLQESGPGLVKPSQTLSLTCTVSGGSITTRYYAWSWI RQPPGKGLEWIGVIDYDGDTYYSPSLKSRVTISVDTSKN QFSLQLSSVTAEDTAVYYCARDPDVVTGFHYDYWGQGTQ VTVSS	232.	QSALTQPPSVSGSPGQTVTISCAGANNDIGTYAYVSWYQQP PGTAPKLLIYKVTTRASGVPDRFSGSKSGNTASLTISGLQA EDEADYYCASYRNFNNAVFGGGTHLTVL	496.

Table 17 Sequence Variants of Fab 129D3 CDR Amino Acid Sequences and CDR Consensus Sequences Thereof

CDR	SEQUENCE	SEQ ID NO
HCDR3	DPDVVTGFHYDY	497.
	YPDVVTGFHYDY	498.
	DPDVVTGFHYDN	499.
	X_1PDVVTGFHYDX_2 Where: X1= D or Y X2= Y or N	500.
HCDR2	VIDYDGDTYYSPSLKS	501.
	VIDYDGDTYYSPSLES	502.
	VIDYDADTYYSPSLKS	503.
	VIDYEGDTYYSPSLKS	504.
	VIYYEGDTYYSPSLKS	505.
	VINYDGDTYYSPSLKS	506.
	VIX_1YX_2X_3DTYYSPSLX_4S Where: X1= D, Y or N X2= D or E X3= A or G X4= E or K	507.
HCDR1	SRYYAWS	508.
	TRYYAWS	509.
	PRYYVWT	510.
	SSYYAWS	511.
	X_1X_2YYX_3WX_4 Where: X1= T, S or P X2= R or S X3= A or V X4= S or T	512.
LCDR3	ASYRNFNNAV	513.
	ASYRHYNNAV	514.
	ASYRRTIDNI	515.
	ASYRSSNNAV	516.
	ASYRNRNNAV	517.
	ASYRDFNNAV	518.
	ASYKTYNNVV	519.
	ASYRYFNNAV	520.
	ASYRNFNNGV	521.
	SSYRNFNNAV	522.
	ASYRTFNNAV	523.
	ASY$X_1X_2X_3X_4X_5X_6X_7$ Where: X1= R or K X2= N, H, R, S, D, T or Y X3= F, Y, T, S or R X4= N or I X5= N or D X6= V, N, G or A X7= V or I	524.

LCDR2	KVTTRAS	525.
	KVSTRAS	526.
	DVNKRAS	527.
	RVSTRAS	528.
	AVSYRVS	529.
	AVNYRAS	530.
	EVNKRTS	531.
	AVSYRAS	532.
	KVTSRAS	533.
	RVTTRAS	534.
	$X_1VX_2X_3RX_4S$ Where: X1= R, K, D, A OR E X2= S, N or T X3= T, K or Y X4= A, T or V	535.
LCDR1	AGANNDIGTYAYVS	536.
	AGTSSDIGGYNYVS	537.
	AGTSSDIGYGDYVS	538.
	AGTSEDVGYGNYVS	539.
	AGTSSDVGYGNYVS	540.
	AGTSSDVGFGNYVS	541.
	$AGX_1X_2X_3DX_4GX_5X_6X_7YVS$ Where: X1= A or T X2= S or N X3= S, E or N X4= V or I X5= G, Y, T or F X6= G or Y X7= N, D or A	542.

Table 18 Sequence Variants of Fab 111A7 CDR Amino Acid Sequences and CDR Consensus Sequences Thereof

CDR	SEQUENCE	SEQ ID NO
HCDR3	RAGWGMGDY	543.
	$RAGX_1GX_2G$ Where: X1 = any amino acid or no amino acid X2 = any amino acid	544.
HCDR2	RISAGGGSTYYGDSVKG	545.
	AISAGGGSTYYGDSVKG	546.
	RISSGGGSTSYADSVKG	547.
	RISSGGGSTNYADSVKG	548.
	RISSGGGSAYYADSVKG	549.
	AISSSGVSTYYTDSVKG	550.
	AISSGGGSTYYGDSVKG	551.
	RISSGGGSTYYGDSVKG	552.
	PISAGGGSTYYGDSVKG	553.
	$X_1ISX_2X_3GX_4SX_5X_6YX_7DSVKG$ Where: X1= A, P or R X2= A or S X3= S or G X4= G or V X5= A or T X6= Y, N or S X7= G, A or T	554.
HCDR1	SYAMS	555.
	TYAMS	556.
	SYRMY	557.
	SHRMY	558.
	SYAMY	559.
	SYRMS	560.
	SYRLY	561.
	$X_1X_2X_3X_4X_5$ Where: X1= S or T X2= H or Y X3= A or R X4= M or L X5= S or Y	562.
LCDR3	ALDIGDITE	563.
LCDR2	STNDRHS	564.
LCDR1	GLSSGSVTASNYPG	565.

Table 19. Production levels and potencies (pM) of germlined 68F2 variants

Exp:	22.06 (7TD1)		29.06 (7TD1)		7.07 (7TD1)			HEK (ug/ml)	
Clone and batch date	IC50	Rel. Potency	IC50	Rel. Potency	IC50	Rel. Potency	Total Identity (%)	#1	#2
129F2 (17.06.)	0.703	1.14	0.517	1.08			95.1	9.2	
126A3 (24.06.)			0.564	0.99	0.63	2.16	94.4		28
129D3 (17.06.)	0.791	1.02	0.574	0.98			95.2	24	
127F1 (24.06.)			0.637	0.88	1.49	0.91	95.1		24
129E11 (24.06.)			0.857	0.65	1.55	0.88	94.5		26
128G3 (17.06.)	1.344	0.60	1.073	0.52			94.5	6	
128G3(24.06)			1.464	0.38					34
127E2 (24.06.)	1.381	0.58	1.245	0.45			95.8		15
127E2 (17.06.)			1.507	0.37				0.8	
68F2 (#12 9)	0.8026	1	0.521	1.08	1.46	0.93	88.5	48	
68F2 (24.06.)			0.560	1.00	1.36	1.00			48
68F2 (Dec. batch)			0.645	0.87					
68F2 (large batch)			1.311	0.43					

Table 20 CMC Optimized Sequence Variants of Fab 111A7

CMC Variant	CDRH3 SEQUENCE	SEQ ID NO	VH SEQUENCE	SEQ ID NO
111A7M_A	RAGWGAG	566.	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGPEWVSRISAGGGSTYY GDSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCANRAGWGAGDYWGQGTLVTVSS	569.
111A7 M_L	RAGWGLG	567.	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGPEWVSRISAGGGSTYY GDSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCANRAGWGLGDYWGQGTLVTVSS	570.
111A7 M_S	RAGWGSG	568.	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGPEWVSRISAGGGSTYY GDSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCANRAGWGSGDYWGQGTLVTVSS	571.

Table 21 IL-6 Binding Kinetics of CMC Optimized Sequence Variants of Fab 111A7

	Off rate (s^{-1})				
M98X:	bact-hIL-6	euk-hIL-6	bact-cy IL-6	average binding	
C	8.69E-05	3.72E-05	9.46E-05	42	n=1
R	8.05E-05	4.08E-05	1.21E-04	64	n=1
A	8.50E-05	4.77E-05	1.31E-04	102	n=3
M	9.11E-05	5.45E-05	1.38E-04	191	n=4
S	9.81E-05	5.46E-05	1.46E-04	118	n=5
T	1.03E-04	5.90E-05	1.44E-04	130	n=2
Y	1.06E-04	6.01E-05	1.58E-04	104	n=3
W	1.12E-04	6.12E-05	1.77E-04	26	n=1
L	1.17E-04	6.78E-05	1.84E-04	141	n=1
N	1.36E-04	7.74E-05	2.07E-04	137	n=1
H	1.39E-04	7.76E-05	2.22E-04	109	n=4
F	1.40E-04	8.17E-05	2.03E-04	144	n=1
D	1.54E-04	8.78E-05	2.34E-04	112	n=3
G	1.43E-04	8.80E-05	2.05E-04	109	n=3
V	1.16E-04	9.03E-05	2.42E-04	163	n=2
P	7.72E-04	5.20E-04	8.99E-04	66	n=5
K	4.61E-03	1.39E-03	4.17E-03	81	n=1

Table 22 Non-Compartmental PK Analysis of anti-IL-6 mAbs after Single Intravenous Administration Into Cynomolgus Monkey.

Antibody	MRT [days]	Cl [ml/day]	k [day-1]	T1/2 [days]
129D3-WT	22.4	6.96	0.0468	15.6
129D3-YTE	34.6	4.54	0.0303	24.0
129D3-HN	35.9	3.34	0.0281	24.9

MRT = Mean Residence Time; k = mean elimination rate constant; t1/2 = elimination half-life; Cl = elimination clearance

Table 23 *In Vitro* IL-6 Neutralization Assay Using B9 Cells

Clone and batch	IC 50 (pM)	R^2	Rel. potency	
133A9 (A3.1)	?			R4
133H2 (A1.8)	0.37	0.9712	2.2	germl
133E5 (A2.1)	0.19	0.9465	4.3	68F2
132E7 (A1.9)	0.38	0.9849	2.1	
68F2 (12.9)	0.98	0.9388	0.8	(average IC50
68F2 (A8.10)	0.62	0.9731	1.3	= 0.8pM)
61H7 (12.8)	1.83	0.8923	0.4	
61H7 (A8.11)	1.57	0.9574	0.5	
B-E8 P70822D1	5.106	0.9574	0.2	

Table 24 *In Vitro* IL-6 Neutralization Assay Using 7TD1 Cells

	IC50 (pM)	Potency relative to 68F2
VH_133E5#A2.1	0.10	6.69
VH_133A9(QSV)#A3.3	0.17	4.00
VH_133A9#A3.1	0.18	3.66
CNTO136LB	0.19	3.49
129D3U#15.1	0.23	2.91
129D3#A1.1	0.25	2.65
Alder_hu1U#12.5	0.29	2.31
VH_133H2#A1.8	0.35	1.94
VH_132E7#A1.9	0.37	1.85
111B1_SDM #A6.7	0.38	1.79
VH_133H2#A9.11	0.47	1.44
111B1_1 SDM M/L#A6.9	0.51	1.32
104C1_1 SDM M/L#A6.6	0.59	1.14
111B1_SDM2_M100L#A9.5	0.67	1.01
68F2#A8.10	0.67	1.00
104C1_SDM2_M100A#A9.2	0.73	0.93
GL18LB	0.76	0.89
104C1_SDM2_M100L#A9.3	0.98	0.69
111A7_SDM2_M100A#A9.7	1.57	0.43
61H7#A8.11	3.48	0.19

Table 25. Groups and Treatment Regimes Employed in Psoriasis Xenograft Model.

Group	Treatment	group size	Dose –route	Treatment frequency
1	Betamethasone dipropionate	3	Topical	2 x day, three weeks
2	PBS	4	i.p.	200µl, 2 x weeks, 3 weeks
3	Remicade (10mg/kg)	7	i.p	200µl, 2 x weeks, 3 weeks
4	68F2 (10mg/kg)	5	i.p.	200µl, 2 x weeks, 3 weeks

Table 26. *In Vivo* IL-6 Neutralization in an SAA Mouse Model

Group			Ab dose/ mouse	Mouse1	Mouse2	Mouse3	Mouse4	Mouse5	Mouse6	**Mean**	**SD**
1	NaCl	NaCl	0	61	52	64	73	77	72	**66.5**	**9.3**
2	0.1 µg IL-6	hIgG	5µg	168	186	178	206	197	161	**182.7**	**17.1**
3		68F2	0.31µg	83	129	116	132	145	136	**123.5**	**22.0**
4			1.25µg	69	67	81	73	47	83	**70.0**	**12.9**
5			5µg	76	38	46	63	43	40	**51.0**	**15.2**
6		GL18	0.31µg	122	114	61	100	107	94	**99.7**	**21.4**
7			1.25µg	59	51	40	44	44	59	**49.5**	**8.2**
8			5µg	53	49	36	58	51	56	**50.5**	**7.8**
9		61H7	0.31µg	184	148	124	140	133	76	**134.2**	**35.2**
10			1.25µg	66	29	33	30	24	35	**36.2**	**15.1**
11			5µg	47	62	47	40	46	47	**48.2**	**7.3**
12		CNTO 136	0.31µg	158	175	161	134	183	171	**163.7**	**17.2**
13			1.25µg	107	54	67	56	62	71	**69.5**	**19.5**
14			5µg	80	80	45	55	70	84	**69.0**	**15.7**

CLAIMS

We claim:

1. A binding molecule that specifically binds to IL-6, the binding molecule comprising at least one antibody CDR, wherein the CDR comprises at least one amino acid residue that is buried in the F229 cavity or the F279 cavity on IL-6 when the binding molecule is bound to IL-6.

2. The binding molecule of claim 1 comprising a VL domain, the VL domain having an amino acid at position 30, according to Kabat, that is buried in the F229 cavity on IL-6 when the binding molecule is bound to IL-6.

3. The binding molecule of claim 2, wherein the amino acid at position 30 is a tyrosine.

4. The binding molecule of any one of the preceding claims comprising a VH domain, the VH domain having an amino acid at position 99, according to Kabat, that is buried in the F279 cavity on IL-6 when the binding molecule is bound to IL-6.

5. The binding molecule of claim 4, wherein the amino acid at position 99 is a valine.

6. The binding molecule of any one of the preceding claims which is an antibody or antigen binding fragment thereof.

7. The binding molecule of any one of the preceding claims comprising a VH domain, the VH domain comprising an HCDR3 amino acid sequence selected from the group consisting of SEQ ID NO: 497-500, 543, 544, 566, 567 and 568.

8. The binding molecule of claim 7, wherein the VH further comprises an HCDR2 amino acid sequence selected from the group consisting of SEQ ID NO: 501-507, and 545-554.

9. The binding molecule of claim 7 or 8, wherein the VH further comprises an HCDR1 amino acid sequence selected from the group consisting of SEQ ID NO: 508-512, and 555-562.

10. The binding molecule of any one of claims 7-9 further comprising a VL domain, wherein the VL domain comprises an LCDR3 amino acid sequence selected from the group consisting of SEQ ID NO: 513-524 and 563.

11. The binding molecule of claim 10, wherein the VL domain further comprises an LCDR2 amino acid sequence selected from the group consisting of SEQ ID NO: 525-535 and 564.

12. The binding molecule of claim 10 or 11, wherein the VL domain further comprises an LCDR1 amino acid sequence selected from the group consisting of SEQ ID NO: 536-542 and 565.

13. The binding molecule of claim 6 comprising a VH domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 1-232 and 569-571.

14. The binding molecule of claim 6 comprising a VL domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 233-496.

15. The binding molecule of claim 6 comprising: a VH domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 1-232 and 569-571; and a VL domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 233-496.

16. The binding molecule of any one of the preceding claims comprising a VH domain and a VL domain, said VH domain comprising hypervariable loops H1, H2 and H3, wherein said VH domain polypeptide is paired with a VL domain comprising hypervariable loops L1, L2 and L3 wherein at least one of hypervariable loops H1-H3 and L1-L3 are obtained from a conventional antibody of a *Lama* species by active immunization of the *Lama* species with the IL-6 antigen

17. The binding molecule of claim 16, wherein:

a) at least one of the hypervariable loops H1, H2, L1, L2 and L3 exhibits a predicted or actual canonical fold structure which is identical or substantially identical to a corresponding canonical fold structure of a H1, H2, L1, L2 or L3 hypervariable loop which occurs in a human antibody;

b) hypervariable loops H1 and H2 each exhibit a predicted or actual canonical fold structure which is identical or substantially identical to the corresponding human canonical fold structure;

c) hypervariable loops L1, L2 and L3 each exhibit a predicted or actual canonical fold structure which is identical or substantially identical to the corresponding human canonical fold structure;

d) hypervariable loops H1 and H2 form a combination of predicted or actual canonical fold structures which is identical or substantially identical to a corresponding combination of canonical fold structures known to occur in a human germline VH domain;

e) hypervariable loops H1 and H2 form a combination of canonical fold structures corresponding to a combination of human canonical fold structures selected from the group consisting of 1-1, 1-2, 1-3, 1-4, 1-6, 2-1, 3-1 and 3-5;

f) hypervariable loops L1 and L2 form a combination of predicted or actual canonical fold structures which is identical or substantially identical to a corresponding combination of canonical fold structures known to occur in human germline VL domains;

g) hypervariable loops L1 and L2 form a combination of canonical fold structures corresponding to a combination of human canonical fold structures selected from the group consisting of 11-7, 13-7(A,B,C), 14-7 (A,B), 12-11, 14-11, 12-12, 2-1, 3-1, 4-1 and 6-1;

h) hypervariable loops H1 and H2 form a combination of canonical fold structures corresponding to the 3-1 combination of human canonical fold structures as found in a human 1ACY antibody structure;

i) hypervariable loops L1 and L2 form a combination of canonical fold structures corresponding to the 6λ-1 combination of human canonical fold structures as found in a human 3MUG antibody structure; and/or

j) hypervariable loops L1, L2 and L3 form a combination of canonical fold structures corresponding to the 6λ-1-5 combination of human canonical fold structures as found in the human 3MUG antibody structure.

18. The binding molecule of any one of the preceding claims that:

a) inhibits binding of IL-6 to an IL-6 receptor;
b) inhibits binding of gp130 to an IL-6 receptor;
c) binds specifically to human and cynomolgus monkey IL-6;
d) comprising at least one CDR from a camelid antibody that specifically binds to IL-6;
e) is characterized by an EpiBase® score of less than about 10.0;
f) is expressed at at least 20 mg/ml by transient expression in a HEK293 cell;
g) exhibits a melting temperature (Tm) of greater than 65 °C;
h) inhibits IL-6-induced proliferation of B9 hybridoma cells with an IC50 of less than 0.1 pM;
i) binds to human IL-6 with an off-rate (k_{off} measured by surface Plasmon resonance) of less than 2×10^{-5} s^{-1};
j) is a germlined variant of a parental camelid antibody, said germlined variant having a higher melting temperature than the parental camelid antibody;
k) comprises at least one CDR from the conventional antibody of the Lama without subsequent affinity maturation;

l) has a serum half-life of at least 9 days, preferably at least 15 days, when administered intravenously into a cynomolgus monkey in a native IgG1 Fc format; or

m) is a germlined variant of a parental binding molecule, wherein the binding molecule comprises a VH and VL domain, and wherein one or both of the VH and VL domains of the binding molecule comprise a total of between 1 and 10 amino acid substitutions across the framework regions as compared to the corresponding VH and VL domains of the parental non-human antibody; and/or comprises a VH and VL domain, wherein one or both of the VH domain or VL domain of the binding molecule exhibit a sequence identity of 90% or greater with one or more corresponding human VH or VL domains across framework regions FR1, FR2, FR3 and FR4.

19. The binding molecule of any one of the preceding claims comprising a VH domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 1-232 and 569-571 wherein at least one glutamine is changed to glutamic acid.

20. The binding molecule of any one of the preceding claims comprising a human Fc domain with a double mutation H433K/N434F.

21. A pharmaceutical composition comprising the binding molecule of any of the preceding claims and one or more pharmaceutically acceptable carrier.

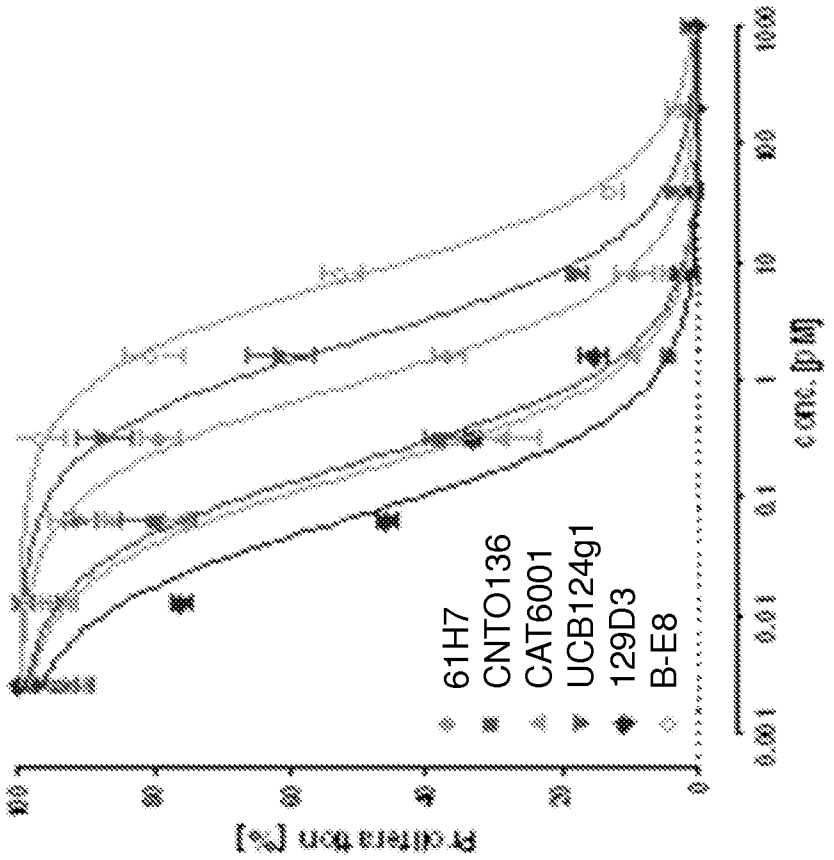
22. A method of treating an IL-6-associated disease or disorder, comprising administering to a subject in need of treatment thereof an effective amount of the pharmaceutical composition of claim 21.

23. An isolated nucleic acid encoding the binding molecule of any one of the preceding claims.

24. A recombinant expression vector comprising the nucleic acid of claim 23.

25. A host cell comprising the recombinant expression vector of claim 24.

Figure 1


B9 cells and 4 pg/ml IL-6
Fraction Bon [%]
61H7
CNTO136
CAT6001
UCB124g1
129D3
B-E8
Conc. [µg/ml]

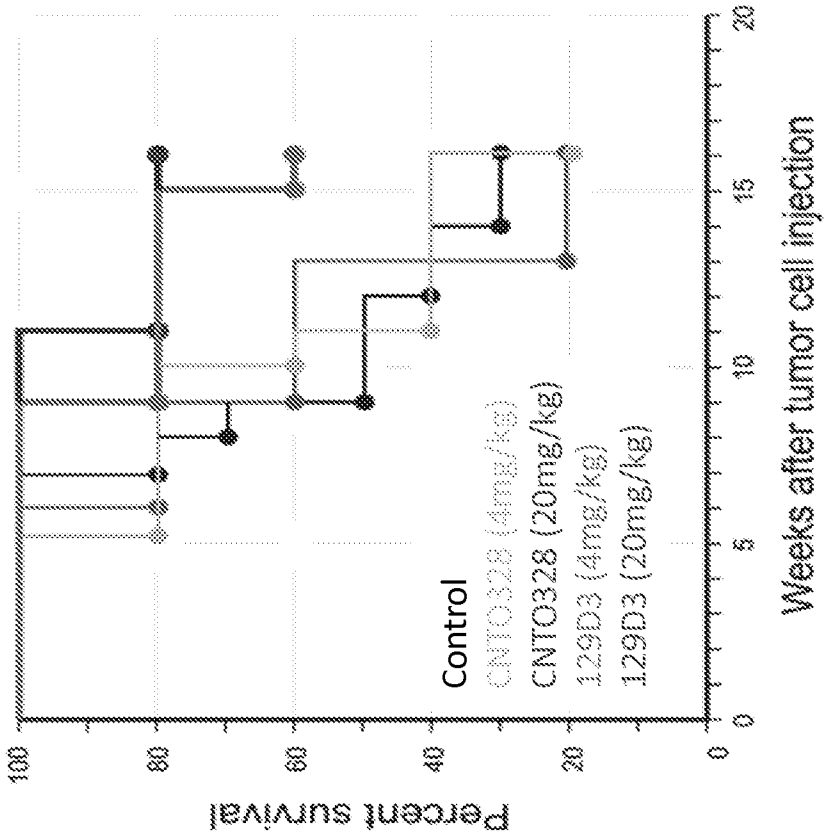

Percent survival
100
80
60
40
20
0
0
5
10
15
20
Weeks after tumor cell injection
Control
CNTO328 (4mg/kg)
CNTO328 (20mg/kg)
129D3 (4mg/kg)
129D3 (20mg/kg)

Figure 2

Figure 3

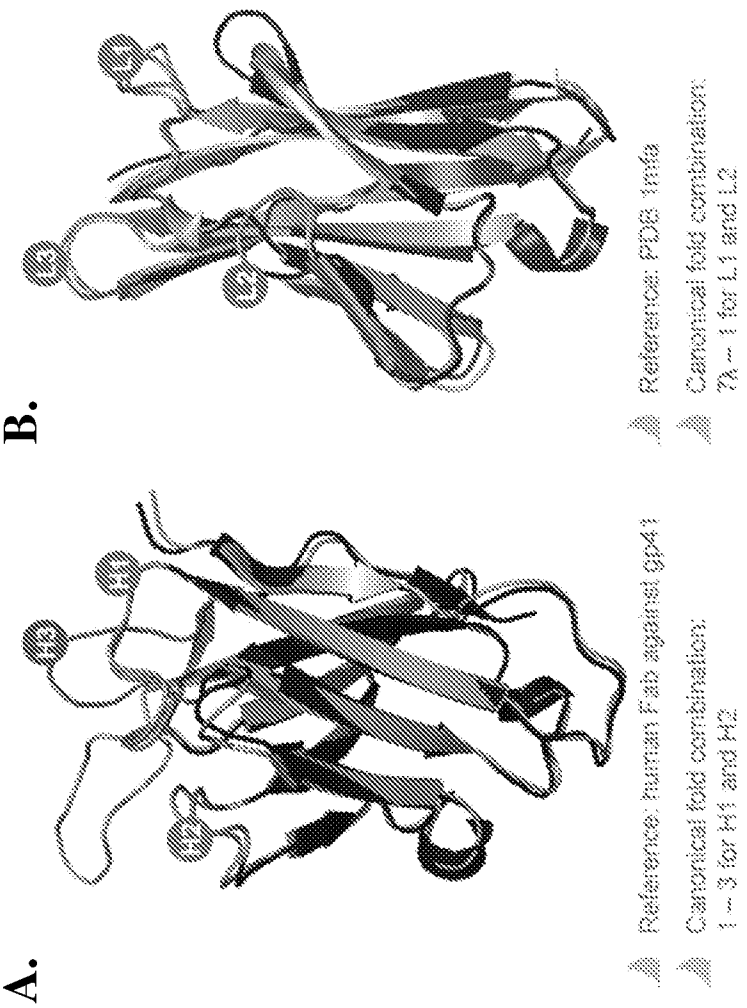

A.
B.
Reference: human Fab against gp41
Canonical fold combination:
1 – 3 for H1 and H2
Reference: PDB 1mfa
Canonical fold combination:
7A – 1 for L1 and L2

Figure 4

A.
The VL (VL2) belongs to the human 6λ-1-5 canonical structure class
L3
L1
L2
129D3/63F2
Reference: 3MUG
B.
H1
CDR3
H2
Reference: 1ACY
129D3/63F2
The VH (VH4) belongs to the human 3-1 canonical structure class

Figure 5

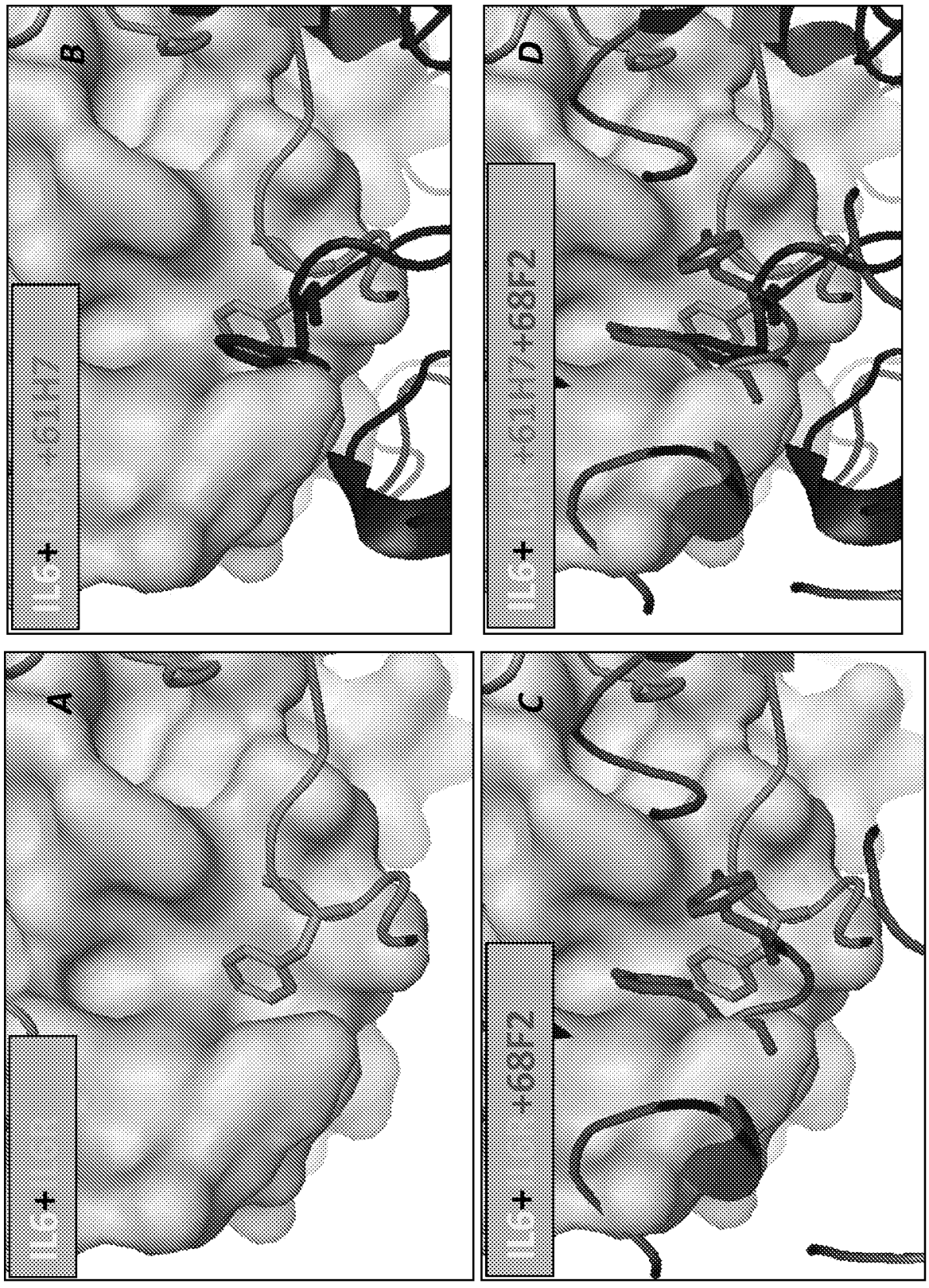


Figure 6

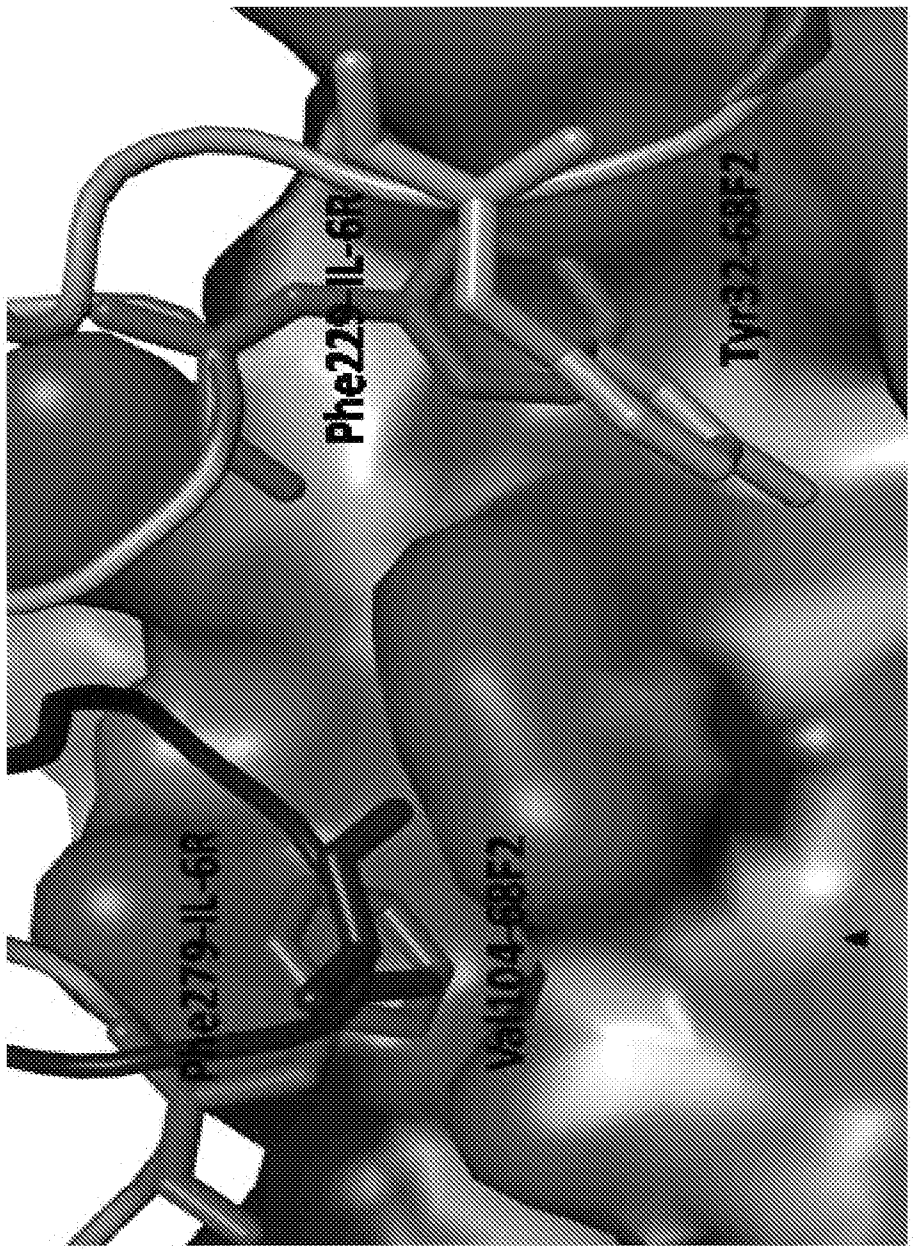
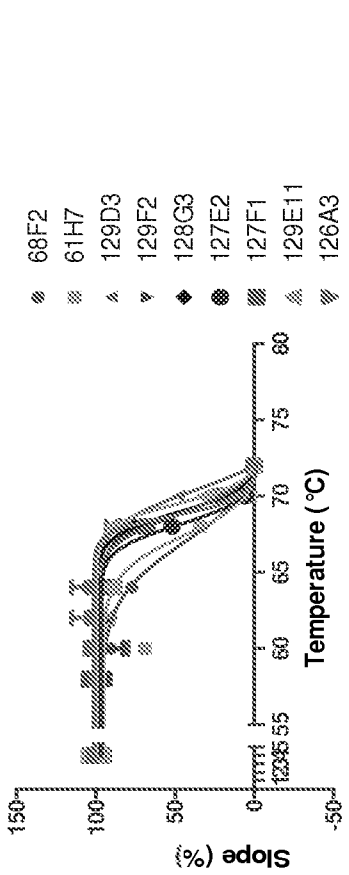


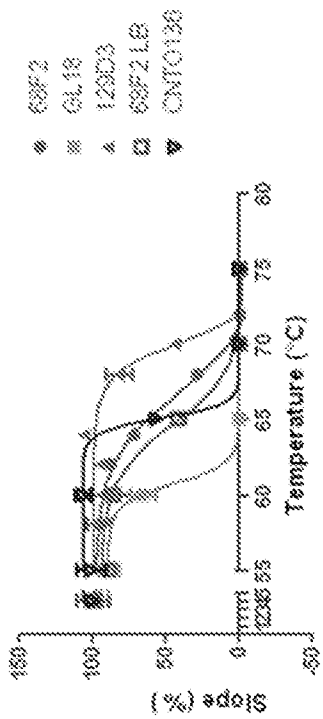
Figure 7

A.



	68F2	61H7	129D3	129F2	128G3	127E2	127F1	129E11	126A3
LogIC50	67.06	67.36	70.36	68.93	68.92	68.12	68.81	69.50	68.72

B.



	68F2	129D3	GL18	68F2 LB	CNTO136
LogIC50	66.69	70.19	69.71	64.64	> 65.07

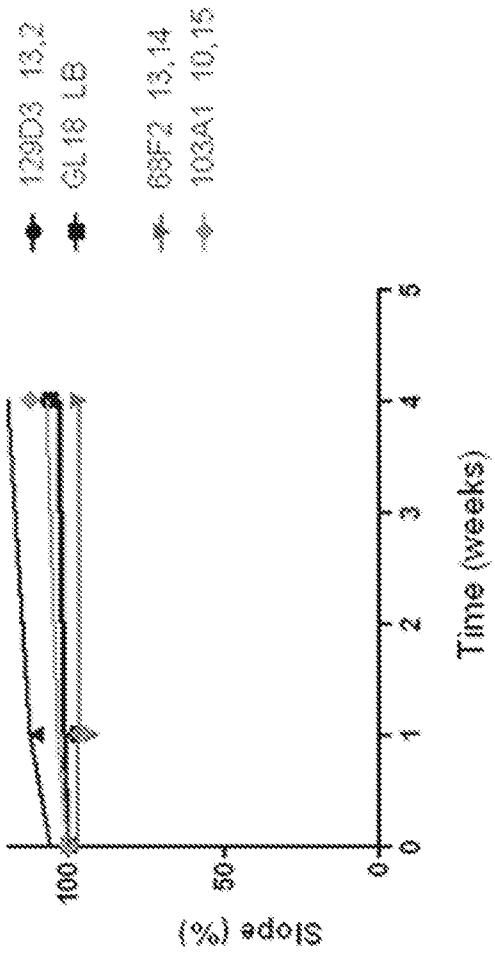

120D3 13,2
GL18 L8
66F2 13,14
103A1 10,15
Slope (%)
100
50
0
0
1
2
3
4
5
Time (weeks)

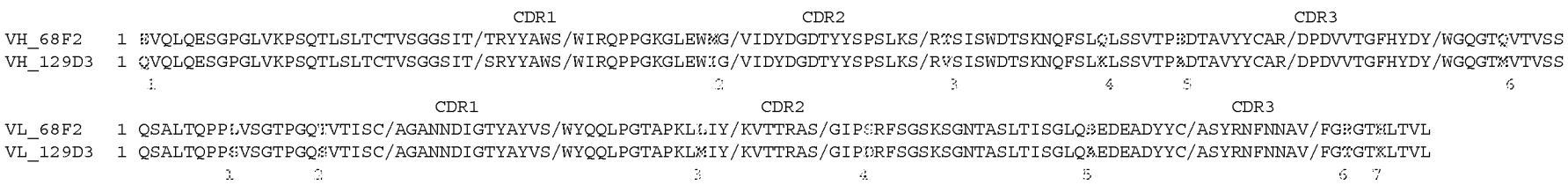
Figure 8

Figure 9

		VL	VH	TOTAL DRB1 SCORE
1	111A7	2.77	2.35	5.12
2	**Humira**	**2.47**	**5.04**	**7.51**
3	104G5ML	2.14	5.58	7.72
4	129E11	5.58	3.72	9.30
5	**CAT18**	**2.50**	**7.34**	**9.84**
6	**ALDER**	**6.08**	**4.25**	**10.33**
7	127F1	6.08	4.25	10.34
8	104C1	2.73	7.98	10.71
9	104C1COMBA	2.73	8.03	10.76
10	129D3	4.91	6.69	11.60
11	61H7	4.54	7.12	11.66
12	133E5	6.54	5.29	11.83
13	**Herceptin**	**6.22**	**5.89**	**12.11**
14	**CNTO136**	**5.70**	**6.56**	**12.26**
15	68F2	6.54	5.85	12.39
16	**Synagis**	**5.29**	**7.40**	**12.69**
17	103A1ML	4.54	8.22	12.76
18	**Campath**	**4.84**	**9.42**	**14.26**
19	**HuA33**	**6.41**	**9.07**	**15.48**
20	**Remicade**	**7.57**	**9.72**	**17.28**
21	**CNTO328**	**9.71**	**10.69**	**20.40**
22	**Rituxan**	**8.71**	**11.71**	**20.42**
23	**OKT3**	**14.17**	**34.39**	**48.56**

Figure 10

A.


CDR1
CDR2
CDR3
VH_68F2 1 EVQLQESGPGLVKPSQTLSLTCTVSGGSIT/TRYYAWS/WIRQPPGKGLEWIG/VIDYDGDTYYSPSLKS/RVTISWDTSKNQFSLQLSSVTPEDTAVYYCAR/DPDVVTGFHYDY/WGQGTQVTVSS
VH_129D3 1 QVQLQESGPGLVKPSQTLSLTCTVSGGSIT/SRYYAWS/WIRQPPGKGLEWIG/VIDYDGDTYYSPSLKS/RVSISWDTSKNQFSLKLSSVTPADTAVYYCAR/DPDVVTGFHYDY/WGQGTMVTVSS
1 2 3 4 5 6
CDR1
CDR2
CDR3
VL_68F2 1 QSALTQPPLVSGTPGQTVTISC/AGANNDIGTYAYVS/WYQQLPGTAPKLLIY/KVTTRAS/GIPSRFSGSKSGNTASLTISGLQSEDEADYYC/ASYRNFNNAV/FGSGTKLTVL
VL_129D3 1 QSALTQPPSVSGTPGQSVTISC/AGANNDIGTYAYVS/WYQQLPGTAPKLMIY/KVTTRAS/GIPDRFSGSKSGNTASLTISGLQAEDEADYYC/ASYRNFNNAV/FGTGTKLTVL
1 2 3 4 5 6 7

B.

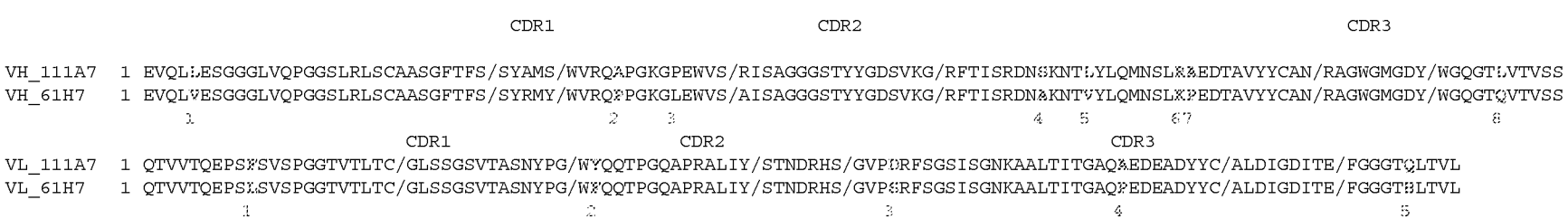

CDR1
CDR2
CDR3
VH_111A7 1 EVQLLESGGGLVQPGGSLRLSCAASGFTFS/SYAMS/WVRQAPGKGPEWVS/RISAGGGSTYYGDSVKG/RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAN/RAGWGMGDY/WGQGTLVTVSS
VH_61H7 1 EVQLVESGGGLVQPGGSLRLSCAASGFTFS/SYRMY/WVRQPPGKGLEWVS/AISAGGGSTYYGDSVKG/RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAN/RAGWGMGDY/WGQGTQVTVSS
1 2 3 4 5 6 7 8
CDR1
CDR2
CDR3
VL_111A7 1 QTVVTQEPSFSVSPGGTVTLTC/GLSSGSVTASNYPG/WYQQTPGQAPRALIY/STNDRHS/GVPDRFSGSISGNKAALTITGAQAEDEADYYC/ALDIGDITE/FGGGTQLTVL
VL_61H7 1 QTVVTQEPSLSVSPGGTVTLTC/GLSSGSVTASNYPG/WPQQTPGQAPRALIY/STNDRHS/GVPERFSGSISGNKAALTITGAQPEDEADYYC/ALDIGDITE/FGGGTELTVL
1 2 3 4 5

Figure 11

A.

```
                              CDR1                    CDR2                                                CDR3
VH_CNTO136 1 EVQLVESGGGLVQPGGSLRLSCAASGFTFS/PFAMS/WVRQAPGKGLEWVA/KISPGGSWTYYSDTVTG/RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR/QLWGYYALDI/WGQGTTVTVSS
VH_CNTO328 1 EVQLVESGGKLLKPGGSLKLSCAASGFTFS/SFAMS/WFRQSPEKRLEWVA/EISSGGSYTYYPDTVTG/RFTISRDNAKNTLYLEMSSLRSEDTAMYYCAR/GLWGYYALDY/WGQGTSVTVSS
                        1 23     4                  5  6 7 8                                  9   0 1   2    3                      4
                                                CDR1                    CDR2                                                CDR3
VK_CNTO328 QIVLIQSPAIMSASPGEKVTMTC/SASSSVSYMY/WYQQKPGSSPRLLIY/DTSNLAS/GVPVRFSGSGSGTSYSLTISRMEAEDAATYYC/QQWSGYPYT/FGGGTKLEIK
VK_CNTO136 EIVLTQSPATLSLSPGERATLSC/SASISVSYMY/WYQQKPGQAPRLLIY/DMSNLAS/GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC/MQWSGYPYT/FGGGTKVEIK
         1   2    34 5    67 89                   01               2 3         456    78 9  0 1                   2
```

B.

```
                                          CDR1                    CDR2                                                CDR3
VH_rabbit  1 -QSLEESGGRLVTPGTPLTLTCTASGFSLS/NYYVT/WVRQAPGKGLEWIG/IIYGSDETAYATWAIG/RFTISKTST--TVDLKMTSLTAADTATYFCAR/DDSSDWDAKFNL/WGQGTLVTVSS
VH_human   1 EVQLVESGGGLVQPGGSLRLSCAASGFSLS/NYYVT/WVRQAPGKGLEWVG/IIYGSDETAYATWAIG/RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR/DDSSDWDAKFNL/----
             123 4    5  6  78 9 0 1                          2                       345678 90 1 2  3 4   5 6

                                       CDR1                    CDR2                                          CDR3
VK_rabbit  1 AYDMTQTPASVSAAVGGTVTIKC/QASQSINNELS/WYQQKPGQRPKLLIY/RASTLAS/GVSSRFKGSGSGTEFTLTISDLECADAATYYC/QQGYSLRNIDNAFGGGTEVVVK
VH_human   1 -IQMTQSPSSLSASVGDRVTITC/QASQSINNELS/WYQQKPGKAPKLLIY/RASTLAS/GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC/QQGYSLRNIDNA----------
             123   4 5 6  7  89   0                    12                3   4      5      6 789 0
```

Figure 12

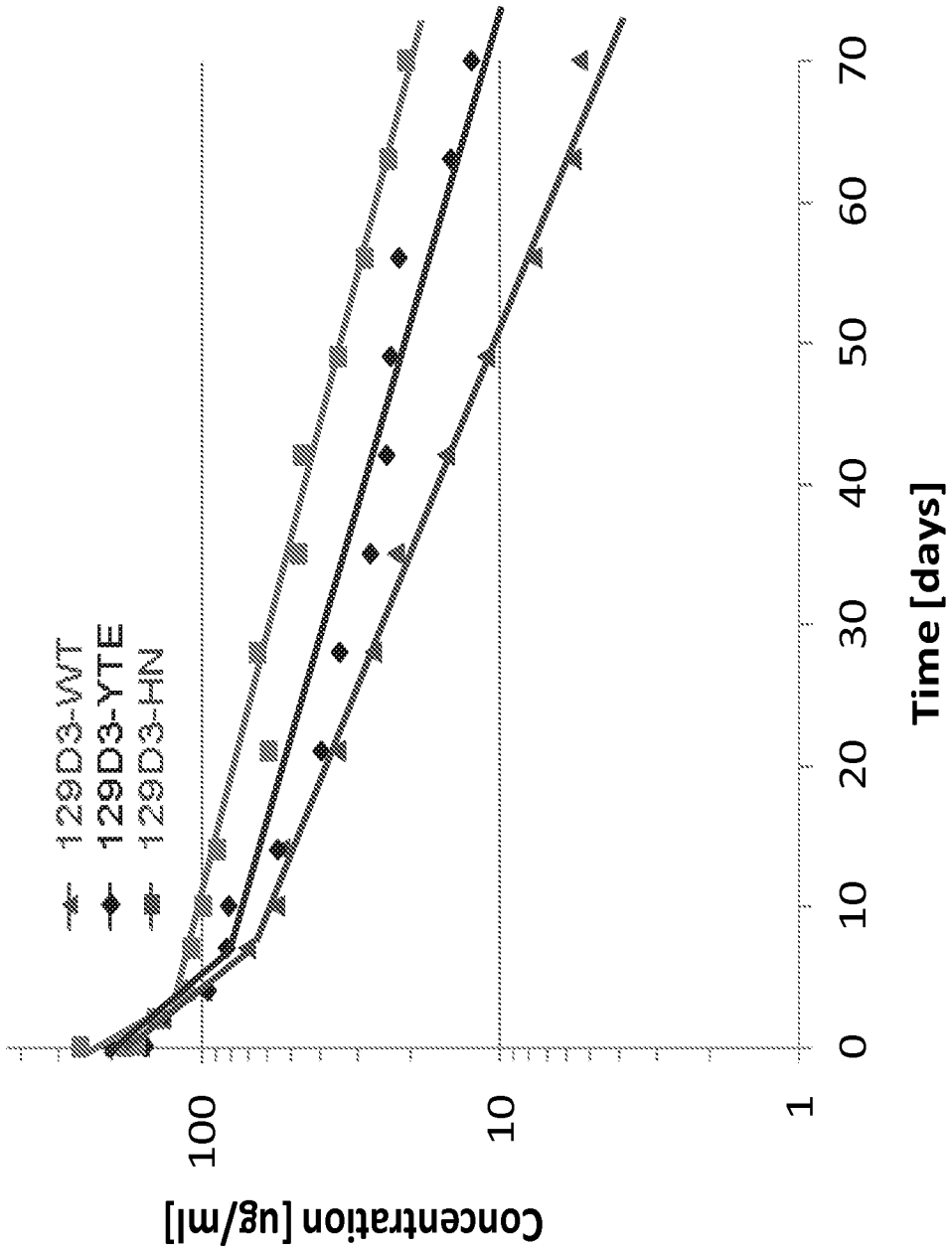
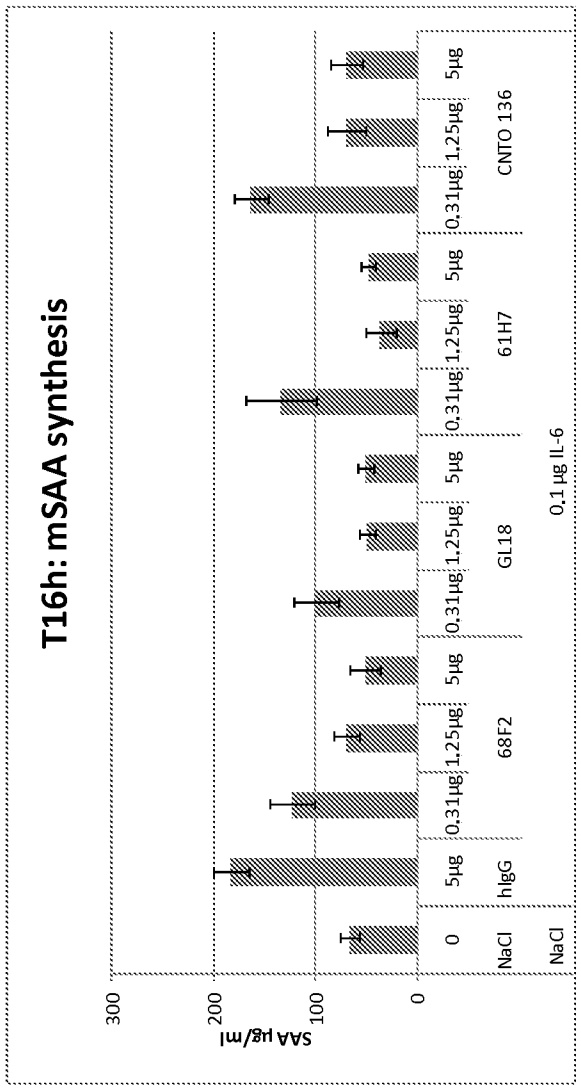

129D3-WT
129D3-YTE
129D3-HN
Concentration [ug/ml]
100
10
1
0
10
20
30
40
50
60
70
Time [days]

Figure 13


T16h: mSAA synthesis
SAA µg/ml
300
200
100
0
0
NaCl
5µg
hIgG
0,31µg
1,25µg
5µg
68F2
0,31µg
1,25µg
5µg
GL18
0,31µg
1,25µg
5µg
61H7
0,31µg
1,25µg
5µg
CNTO 136
NaCl
0,1 µg IL-6

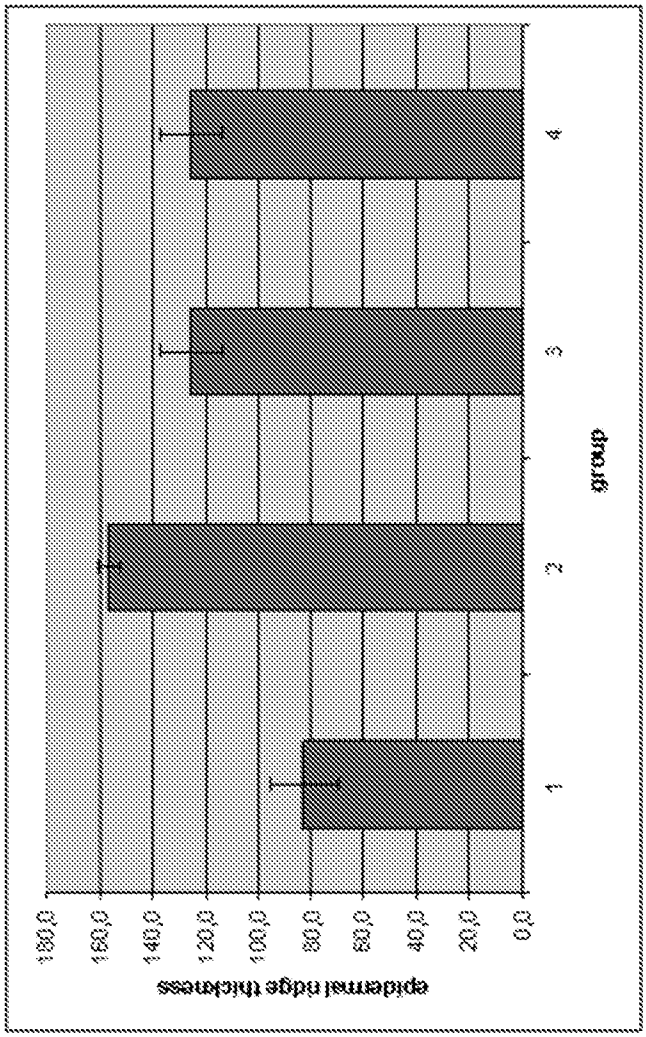
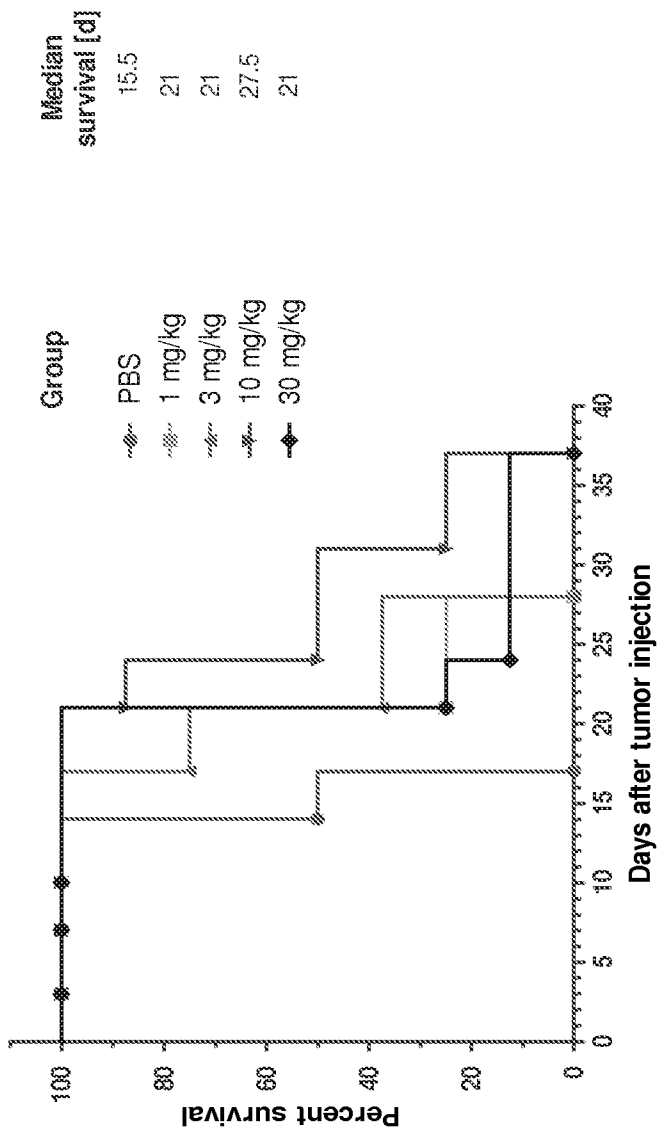

epidermal ridge thickness
180,0
160,0
140,0
120,0
100,0
80,0
60,0
40,0
20,0
0,0
1
2
3
4
group

Figure 14

Figure 15


Median survival [d]
15.5
21
21
27.5
21
Group
PBS
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
Percent survival
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
Days after tumor injection

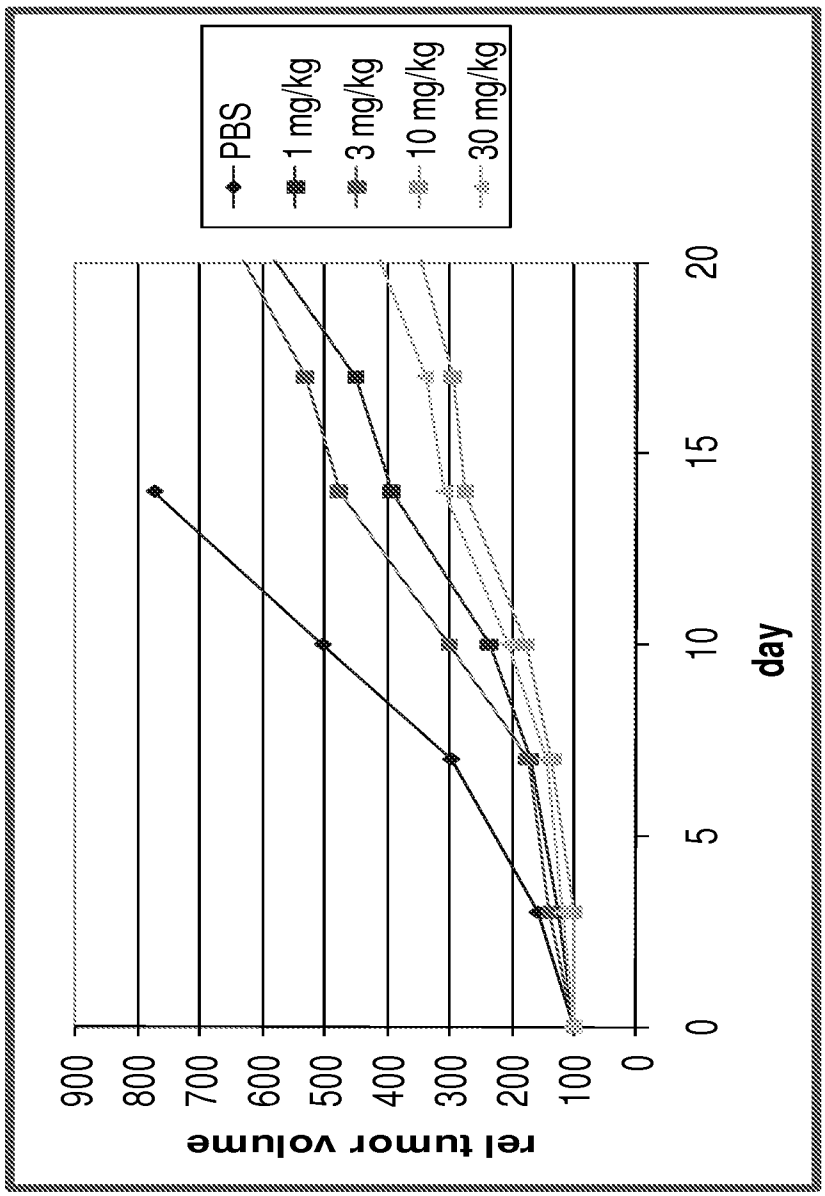

PBS
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
rel tumor volume
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
day

Figure 16

Figure 17

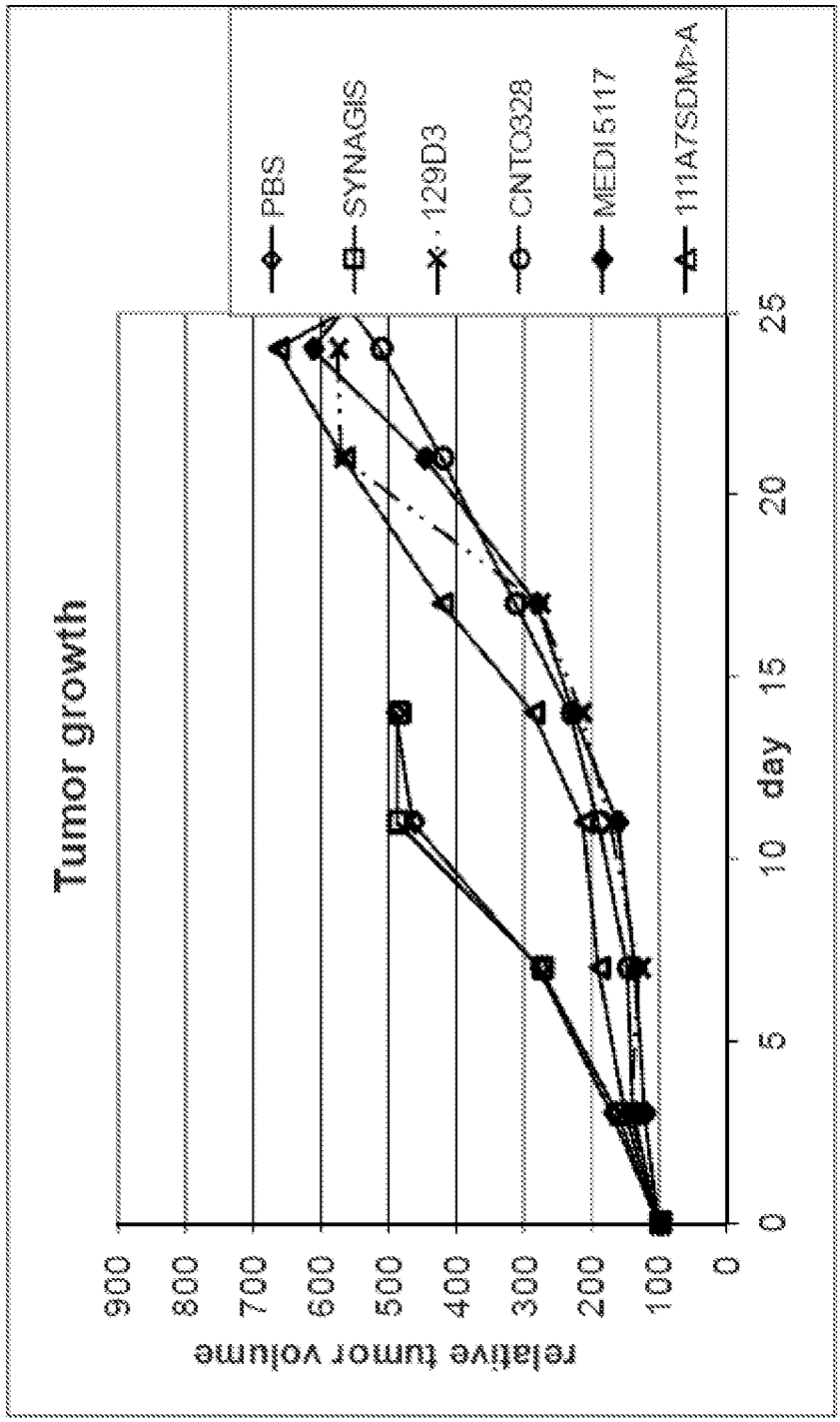
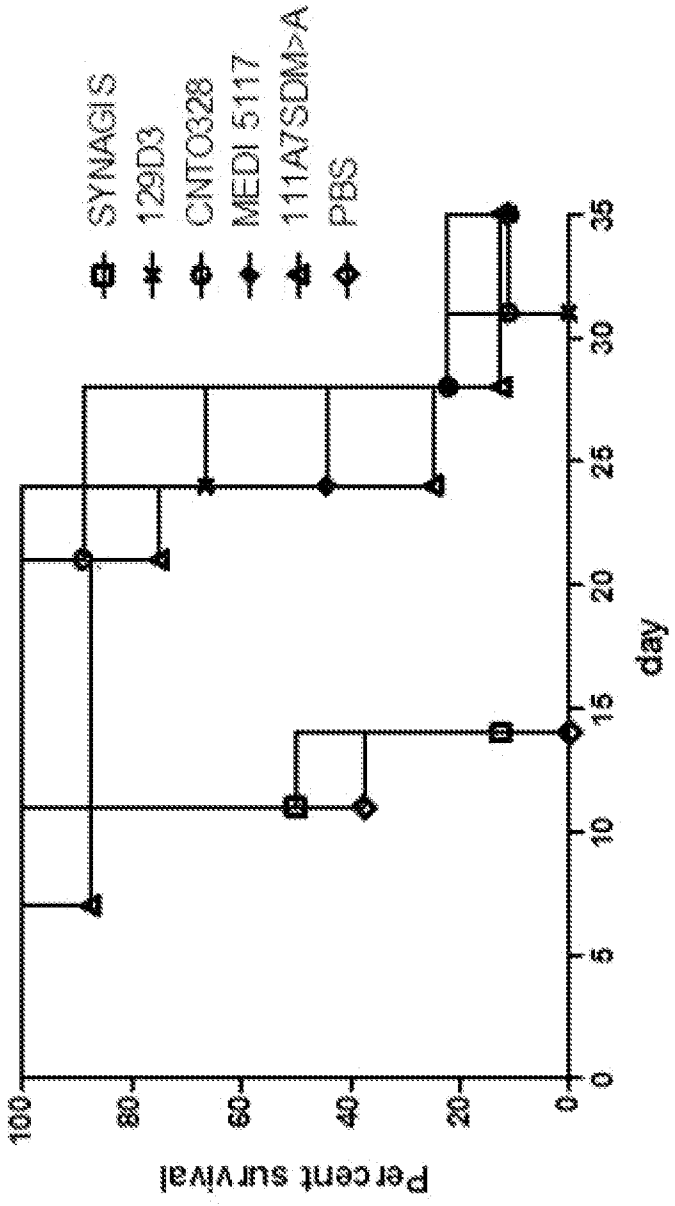

Tumor growth
relative tumor volume
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
25
day
PBS
SYNAGIS
129D3
CNTO328
MEDI5117
111A7SDMPA

Figure 18


SYNAGIS
129D3
CNTO328
MEDI 5117
111A7SDM>A
PBS
Percent survival
100
80
60
40
20
0
0
5
10
15
20
25
30
35
day

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/054271

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/24 A61K39/395
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/104529 A2 (ABLYNX NV [BE]; KOLKMAN JOOST ALEXANDER [BE]; HERMANS GUY [BE]; HOOGEN) 20 September 2007 (2007-09-20) page 11, line 9 - line 14 page 225; example 4 page 229; example 9 page 36, line 28 - page 37, column 2 -----	1-25
X	WO 2008/019061 A2 (VACCINEX INC [US]; SMITH ERNEST S [US]; WANG WEI [US]) 14 February 2008 (2008-02-14) page 46, paragraph 0159 page 71, paragraph 0210 page 73, paragraphs 0213, 0215 ----- -/--	1-25

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2013	08/10/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Malamoussi, A

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