

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(10) International Publication Number

WO 2017/201731 A1

(43) International Publication Date
30 November 2017 (30.11.2017)

(51) International Patent Classification:

C07K 16/28 (2006.01) *A61P 35/00* (2006.01)
C12N 15/13 (2006.01) *A61K 39/395* (2006.01)
A61P 29/00 (2006.01)

SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(21) International Application Number:

PCT/CN2016/083653

(22) International Filing Date:

27 May 2016 (27.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(71) Applicant: BEIJING VDJBIO CO., LTD. [CN/CN];
B311, #5 Kaituo Rd, Haidian District, Beijing 100085 (CN).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

(72) Inventor: LI, Ziqiang; Apt. #20-2-201, Guanlinyuan,
Baoshengli, Haidian District, Beijing 100192 (CN).

Published:

— with international search report (Art. 21(3))

(74) Agent: AFD CHINA INTELLECTUAL PROPERTY
LAW OFFICE; Suite B 1601A, 8 Xue Qing Rd., Haidian,
Beijing 100192 (CN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE,

(54) Title: ANTIBODIES, COMPOSITION AND KITS COMPRISING SAME, AND METHODS OF USE THEREOF

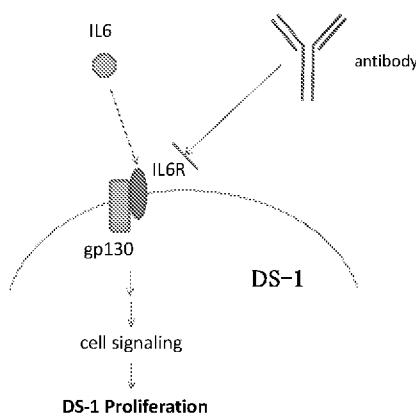


Fig. 1

(57) Abstract: In some aspects, the present disclosure provides antibodies with high target affinities, as well as compositions comprising the same, and methods of using the same. In some embodiments, antibodies against an IL6 receptor are provided.

ANTIBODIES, COMPOSITION AND KITS COMPRISING SAME, AND METHODS OF USE THEREOF

BACKGROUND OF THE INVENTION

[0001] Previously known as hepatocyte stimulating factor, B-cell stimulatory factor 2, cytotoxic T-

5 cell differentiation factor, B-cell differentiation factor, hybridoma/plasmacytoma growth factor, monocyte granulocyte inducer type 2 and thrombopoietin, Interleukin-6 (IL-6) is a pleiotropic cytokine produced by various types of cells, such as T cells, B cells, monocytes, fibroblasts, osteoblasts, keratinocytes, endothelial cells, mesangial cells and some tumor cells. IL-6 comprises four α -helical domains with a motif of four cysteine residues which are necessary for its tertiary

10 structure. Human IL-6 is a 26-kDa glycoprotein whose gene is found on chromosome 7.

[0002] IL-6 binds to a membrane bound or soluble IL-6 receptor (IL-6R) and this complex associates with two molecules of the signal transducing protein gp130, thereby initiating cellular events including activation of the JAK-STAT3 pathway and ras-mediated MAP kinase signaling. IL-6 elicits various effects such as proliferation and differentiation of B cells and monocytes, T cell activation,

15 hematopoiesis, osteoclast activation, keratinocyte growth, neuronal growth, hepatocyte activation and acute phase protein induction from hepatocytes.

[0003] IL-6 plays an important role in immune regulation, hematopoiesis, inflammation and oncogenesis. IL-6 is involved in and has been a drug discovery target for treating diseases or disorders such as infection, endotoxic shock associated with infection, arthritis, rheumatoid arthritis,

20 psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, pelvic inflammatory disease, Alzheimer's Disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, Castleman's disease, ankylosing spondylitis, dermatomyositis, uveitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme arthritis, meningoencephalitis, immune 25 mediated inflammatory disorders of the central and peripheral nervous system, autoimmune disorders, pancreatitis, trauma from surgery, graft-versus-host disease, transplant rejection, heart disease, bone resorption, burns patients, myocardial infarction, Paget's disease, osteoporosis, sepsis, liver/lung fibrosis, periodontitis, hypochlorhydia, solid tumors (renal cell carcinoma), prostatic and bladder cancers, pancreatic cancer, neurological cancers, and B-cell malignancies (e.g., Castleman's disease, 30 certain lymphomas, chronic lymphocytic leukemia, and multiple myeloma). Indirect evidence also suggests an association between IL-6 and chronic obstructive pulmonary disease and insulin resistance in type 2 diabetes.

[0004] Tocilizumab (Heavy chain as shown in SEQ ID NO. 1, light chain as shown in SEQ ID NO. 2), a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), is an IgG1 antibody

35 obtained by humanizing mouse antibody PM1. Tocilizumab is useful as a therapeutic agent for IL-6-

associated diseases, and has been marketed under the trade names of Actemra and RoActemra. As an antibody, target detection sensitivity (as in a detection assay), and therapeutic efficacy and dosing are related to affinity of the antibody for its target. Higher-affinity antibodies may enhance detection sensitivity, lower dose requirements, make production more efficient, and decrease the risk of side effects.

SUMMARY OF THE INVENTION

[0005] In view of the foregoing, there exists a considerable need for anti-IL-6 or anti-IL6R antibodies with improved target binding affinities, compositions and kits comprising the same, and methods of use thereof. The present disclosure addresses the above needs, and provides additional advantages as well.

[0006] The present disclosure provides antibodies capable of binding to IL-6R, uses thereof, and methods of making the same. In one aspect, the present disclosure provides an antibody, wherein the antibody: (a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90; (b) exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91; and (c) does not contain (a) SEQ ID NO. 3 and SEQ ID NO. 4, and (b) SEQ ID NO. 1 and SEQ ID NO. 2.

[0007] In another aspect, the present disclosure provides an antibody, wherein the antibody (a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID

5 NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, 10 SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, 15 SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ 20 ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90; (b) exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2; and (c) does not contain SEQ ID NO. 3 and SEQ ID NO. 4.

25 **[0008]** In another aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than an affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4; and (b) the antibody inhibits proliferation of DS-1 cells by at least 40% after 72 hours at a concentration of 0.032 μ g/mL or less in 30 an MTS cell-proliferation assay.

35 **[0009]** In another aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1; and/or (b) the light chain comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO. 2; and (c) the antibody comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to an antibody comprising a heavy chain of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11,

SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, 5 SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, 10 SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, or SEQ ID NO. 89 and a light chain of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, or SEQ ID NO. 90.

15 **[0010]** In another aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the heavy chain comprises one or more mutations with respect to SEQ ID NO. 1, wherein residue 57 is mutated to methionine (M); (b) the light chain comprises an amino acid sequence having at least 90% sequence identify to SEQ ID NO. 4 or SEQ ID NO. 2, or both; and (c) the antibody exhibits a binding affinity (K_D) for human IL-6R of 1 nM or less, as determined by 20 surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

25 **[0011]** In another aspect, the present disclosure provides a pharmaceutical composition comprising an antibody as described herein and a pharmaceutically acceptable excipient. In another aspect, the present disclosure provides a kit comprising an antibody as described herein in a container. In another aspect, the present disclosure provides a method of treating a disease or condition comprising 30 administering an antibody as described herein or a composition comprising an antibody as described herein. In another aspect, the present disclosure provides use of an antibody as described herein for the manufacture of a medicament for treating a condition of a subject. In another aspect, the present disclosure provides an isolated polynucleotide encoding an antibody as described herein. In another aspect, the present disclosure provides a vector comprising an isolated polynucleotide as described herein. In another aspect, the present disclosure provides a cell comprising a vector as described herein.

INCORPORATION BY REFERENCE

35 **[0012]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

5 [0014] FIG. 1 is an illustration of an IL-6R antibody inhibiting proliferation of DS-1 cells in the presence of IL-6.

[0015] FIGS. 2A and 2B are graphs illustrating results of DS-1 cell proliferation assay.

[0016] FIGS. 3A and 3B are graphs illustrating results of DS-1 cell proliferation assay showing the

10 inhibition% of exemplary antibodies as described herein on DS-1 cell proliferation.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The systems and methods of this disclosure as described herein may employ, unless otherwise indicated, conventional techniques and descriptions of molecular biology (including recombinant

15 techniques), cell biology, biochemistry, microarray and sequencing technology, which are within the skill of those who practice in the art. Such conventional techniques include polymer array synthesis, hybridization and ligation of oligonucleotides, sequencing of oligonucleotides, and detection of

hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the examples herein. However, equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as Green,

20 et al., Eds., *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV) (1999); Weiner, et al., Eds., *Genetic Variation: A Laboratory Manual* (2007); Dieffenbach, Dveksler, Eds., *PCR Primer: A*

Laboratory Manual (2003); Bowtell and Sambrook, *DNA Microarrays: A Molecular Cloning Manual* (2003); Mount, *Bioinformatics: Sequence and Genome Analysis* (2004); Sambrook and Russell, *Condensed Protocols from Molecular Cloning: A Laboratory Manual* (2006); and Sambrook and

25 Green, *Molecular Cloning: A Laboratory Manual*, 4th Edition (2012) (all from Cold Spring Harbor Laboratory Press); Stryer, L., *Biochemistry* (4th Ed.) W.H. Freeman, N.Y. (1995); Gait,

“*Oligonucleotide Synthesis: A Practical Approach*” IRL Press, London (1984); Nelson and Cox,

Lehninger, Principles of Biochemistry, 6th Ed., W.H. Freeman Pub., New York (2012); R.I. Freshney, *Culture of Animal Cells: A Manual of Basic Technique and Specialized Applications*, 6th Ed., Wiley-

30 Blackwell (2010); and Berg et al., *Biochemistry*, 5th Ed., W.H. Freeman Pub., New York (2002), all of which are herein incorporated by reference in their entirety for all purposes. Before the present compositions, research tools and systems and methods are described, it is to be understood that this disclosure is not limited to the specific systems and methods, compositions, targets and uses

described, as such may, of course, vary. It is also to be understood that the terminology used herein is

35 for the purpose of describing particular aspects only and is not intended to limit the scope of the present disclosure, which will be limited only by appended claims.

[0018] As used in the specification and claims, the singular form “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof.

[0019] The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term “about” meaning within an acceptable error range for the particular value should be assumed.

[0020] The terms “polypeptide”, “oligopeptide”, “peptide” and “protein” are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides as described herein are based upon an antibody, the polypeptides can occur as single chains or associated chains.

[0021] The term “amino acid” refers to natural, unnatural, and synthetic amino acids, including but not limited to both the D or L optical isomers, and amino acid analogs and peptidomimetics. Standard single or three letter codes are used to designate amino acids.

[0022] The term “natural L-amino acid” means the L optical isomer forms of glycine (G), proline (P), alanine (A), valine (V), leucine (L), isoleucine (I), methionine (M), cysteine (C), phenylalanine (F), tyrosine (Y), tryptophan (W), histidine (H), lysine (K), arginine (R), glutamine (Q), asparagine (N), glutamic acid (E), aspartic acid (D), serine (S), and threonine (T).

[0023] The term “non-naturally occurring,” as applied to sequences and as used herein, means polypeptide or polynucleotide sequences that do not have a counterpart to, are not complementary to, or do not have a high degree of homology with a wild-type or naturally-occurring sequence found in a mammal, or comprise non-naturally occurring residues (e.g. nucleotide analogues). For example, a non-naturally occurring polypeptide or fragment may share no more than 99%, 98%, 95%, 90%, 80%, 70%, 60%, 50% or even less amino acid sequence identity as compared to a natural sequence when suitably aligned.

[0024] The terms “hydrophilic” and “hydrophobic” refer to the degree of affinity that a substance has with water. A hydrophilic substance has a strong affinity for water, tending to dissolve in, mix with, or be wetted by water, while a hydrophobic substance substantially lacks affinity for water, tending to repel and not absorb water and tending not to dissolve in or mix with or be wetted by water. Amino

5 acids can be characterized based on their hydrophobicity. A number of scales have been developed.

An example is a scale developed by Levitt, M, et al., J Mol Biol (1976) 104:59, which is listed in Hopp, TP, et al., Proc Natl Acad Sci U S A (1981) 78:3824. Examples of “hydrophilic amino acids” are arginine, lysine, threonine, alanine, asparagine, and glutamine. Of particular interest are the hydrophilic amino acids aspartate, glutamate, and serine, and glycine. Examples of “hydrophobic

10 amino acids” are tryptophan, tyrosine, phenylalanine, methionine, leucine, isoleucine, and valine.

[0025] A “fragment” when applied to a protein, is a truncated form of a native biologically active protein that may or may not retain at least a portion of the therapeutic and/or biological activity. A “variant” when applied to a protein is a protein with sequence homology to the native biologically active protein that retains at least a portion of the therapeutic and/or biological activity of the

15 biologically active protein. For example, a variant protein may share at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity compared with the reference biologically active protein. As used herein, the term “biologically active protein moiety” includes proteins modified deliberately, as for example, by site directed mutagenesis, synthesis of the encoding gene, insertions, or accidentally through mutations.

20 **[0026]** In the context of polypeptides, a “linear sequence” or a “sequence” is an order of amino acids in a polypeptide in an amino to carboxyl terminus direction in which residues that neighbor each other in the sequence are contiguous in the primary structure of the polypeptide. A “partial sequence” is a linear sequence of part of a polypeptide that is known to comprise additional residues in one or both directions.

25 **[0027]** An “antibody” is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (ScFv), mutants thereof, fusion proteins comprising an antibody portion

30 (such as domain antibodies), and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class.

Depending on the antibody amino acid sequence of the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of

35 immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon,

gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0028] In some embodiments provided herein, the antibody is a monoclonal antibody. As used herein, “monoclonal antibody” refers to an antibody obtained from a population of substantially

5 homogeneous antibodies. In general, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant
10 on the antigen. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler and Milstein, 1975, *Nature*, 256:495, or may be made by recombinant DNA methods such
15 as described in U.S. Pat. No. 4,816,567. The monoclonal antibodies may also be isolated from phage libraries generated using the techniques described in McCafferty et al., 1990, *Nature*, 348:552-554, for example.

[0029] In some embodiments provided herein, the antibody is a humanized antibody. As used

herein, “humanized” antibodies refer to forms of non-human (e.g. murine) antibodies that are specific

20 chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non- human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody)
25 such as mouse, rat, or rabbit having the desired specificity, affinity, and, biological activity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will
30 comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more
35 CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs “derived from” one or more CDRs from the original antibody.

[0030] In some embodiments provided herein, the antibody is a human antibody. As used herein, “human antibody” means an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies known in the art or of the present invention. This definition of a human antibody includes 5 antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies can be produced using various techniques known in the art. In one embodiment, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., 1996, *Nature Biotechnology*, 14:309-314; Sheets et al., 1998, 10 *PNAS*, (USA) 95:6157-6162; Hoogenboom and Winter, 1991, *J. Mol. Biol.*, 227:381; Marks et al., 1991, *J. Mol. Biol.*, 222:581). Human antibodies can also be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016. Alternatively, the human 15 antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual or may have been immunized in vitro). See, e.g., Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., 1991, *J. Immunol.*, 147 (1):86-95; and U.S. Patent No. 5,750,373.

[0031] “Polynucleotide,” or “nucleic acid,” as used interchangeably herein, refer to polymers of 20 nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of 25 nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, “caps”, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with 30 charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the 35 polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to

solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-5 allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α -anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), (O)NR₂ ("amide"), P(O)R, P(O)OR', CO or CH₂ ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

10 15 [0032] A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, 20 contribute to the formation of the antigen-binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda MD)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-lazikani et al (1997) J. Molec. Biol. 273:927-948)). As used herein, a CDR may refer to CDRs 25 defined by either approach or by a combination of both approaches.

[0033] A "constant region" of an antibody refers to the constant region of the antibody light chain or the constant region of the antibody heavy chain, either alone or in combination.

30 [0034] An epitope that "preferentially binds" or "specifically binds" (used interchangeably herein) to an antibody or a polypeptide is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other 35 substances. For example, an antibody that specifically or preferentially binds to an IL-6R epitope is an antibody that binds this epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other IL-6R epitopes or non-IL6R epitopes. As a further example, an

antibody (or other moiety) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, “specific binding” or “preferential binding” does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

5 **[0035]** A “host cell” includes an individual cell or cell culture that can be or has been a recipient for vector(s) comprising exogenous polynucleotides. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of the present disclosure.

10 **[0036]** The term "Fc region" is used to define a C-terminal region of an immunoglobulin heavy chain. The "Fc region" may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3.

15 **[0037]** As used herein, "Fc receptor" and "FcR" describe a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an "activating receptor") and Fc γ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. FcRs are reviewed in Ravetch and Kinet, 1991, Ann. Rev. Immunol., 9:457-92; Capel et al., 1994, Immunomethods, 4:25-34; and de Haas et al., 1995, J. Lab. Clin. Med., 126:330-41. "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., 1976, J. Immunol., 117:587; and Kim et al., 1994, J. Immunol., 24:249).

20 **[0038]** "Complement dependent cytotoxicity" and "CDC" refer to the lysing of a target in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule (e.g. an antibody) complexed with a cognate antigen. To assess complement activation, a CDC assay, e.g. as described in Gazzano-Santoro et al., J. Immunol. Methods, 202:163 (1996), may be performed.

25 **[0039]** A “functional Fc region” possesses at least one effector function of a native sequence Fc region. Exemplary “effector functions” include C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down-regulation of cell surface receptors (e.g. B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (e.g. an antibody variable

domain) and can be assessed using various assays known in the art for evaluating such antibody effector functions.

[0040] A “native sequence Fc region” comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. A “variant Fc region” comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, yet retains at least one effector function of the native sequence Fc region. Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g. from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or

10 in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% sequence identity with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% sequence identity therewith, more preferably at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% sequence identity therewith.

15 **[0041]** As used herein “antibody-dependent cell-mediated cytotoxicity” and “ADCC” refer to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g. natural killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. ADCC activity of a molecule of interest can be assessed using an in vitro ADCC assay, such as that described in U.S. Patent No. 5,500,362 or 5,821,337.

20 Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and NK cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al., 1998, PNAS (USA), 95:652-656.

25 **[0042]** Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity.

30 **[0043]** Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins - Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J., 1990, *Unified Approach to Alignment and Phylogenies* pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M., 1989, CABIOS 5:151-153; Myers, E.W. and Muller W., 1988, CABIOS 4:11-17; Robinson, E.D., 1971, *Comb. Theor.* 11:105; Santou, N., Nes, M., 1987, *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R., 1973,

Numerical Taxonomy the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J., 1983, Proc. Natl. Acad. Sci. USA 80:726-730.

Alternative alignment programs are available, including but not limited to the BLAST algorithm, which may also be used to evaluate sequence identify, such as by using default parameters.

5 [0044] Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison (e.g. of at least 20 positions), wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps), such as gaps of 20 percent or less (e.g. 5 to 15 percent, or 10 to 12 percent), as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is typically calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

10 15 [0045] An "individual" or a "subject" is a mammal, more preferably a human. Mammals also include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats.

20 [0046] As used herein, "vector" means a construct, which is capable of delivering, and preferably expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

25 [0047] The term "effective amount" or "therapeutically effective amount" refers to the amount of an agent that is sufficient to effect beneficial or desired results. The therapeutically effective amount may vary depending upon one or more of: 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. An effective amount of an active agent may be administered in a single dose or in multiple doses. A component may be described 30 herein as having at least an effective amount, or at least an amount effective to produce a desired result, such as that associated with a particular goal or purpose, such as any described herein.

35 [0048] The term "effective amount" also applies to a dose that will provide an image for detection by an appropriate imaging method. The specific dose may vary depending on one or more of: the particular agent chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to be imaged, and the physical delivery system in which it is carried.

[0049] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutical acceptable excipient" includes any material which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Preferred diluents for aerosol or parenteral administration are phosphate buffered saline or normal (0.9%) saline. Compositions comprising such carriers are formulated by well-known conventional methods (see, for example, Remington's Pharmaceutical Sciences, 18th edition, A. Gennaro, ed., Mack Publishing Co., Easton, PA, 1990; and Remington, The Science and Practice of Pharmacy 20th Ed. Mack Publishing, 2000).

[0050] Antibody

[0051] The present disclosure provides antibodies capable of binding to IL-6R, uses thereof, and methods of making the same. In one aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89; (b) the antibody comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to an antibody comprising a heavy chain of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44,

SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, 5 SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, or SEQ ID NO. 89 and a light chain of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, or SEQ ID NO. 90; (c) the light chain comprises an amino acid sequence with about or 10 greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90; (d) the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1; (e) the light 15 chain comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO. 2; (f) the heavy chain comprises one or more mutations with respect to SEQ ID NO. 1, wherein residue 57 is mutated to methionine (M); (g) the antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91; (h) the antibody exhibits a binding affinity (K_D) 20 for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2; (i) the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4; (j) the antibody inhibits proliferation of DS-1 25 cells by at least 40% after 72 hours at a concentration of 0.032 µg/mL or less in an MTS cell-proliferation assay; (k) the antibody inhibits proliferation of DS-1 cells by an IC_{50} lower than the IC_{50} of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2 as determined in an MTS cell-proliferation assay; (l) the antibody inhibits proliferation of DS-1 cells by an IC_{50} lower than the IC_{50} of an antibody 30 comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4 as determined in an MTS cell-proliferation assay; (m) the antibody has a pH dependence of the binding affinity for IL-6R higher than the pH dependence of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4, and wherein the pH dependence is defined as the ratio between the 35 binding affinity for the IL-6R at pH7.4 and at pH6.0; (n) does not contain (1) SEQ ID NO. 3 and SEQ ID NO. 4, and/or (2) SEQ ID NO. 1 and SEQ ID NO. 2; or (o) any combination thereof.

[0052] In another aspect, the present disclosure provides an antibody, wherein the antibody: (a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID

5 NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, 10 SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, 15 SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ 20 ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90; (b) exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91; and (c) does not contain (a) SEQ ID NO. 3 and SEQ ID NO. 4, and (b) SEQ ID NO. 1 and SEQ ID NO. 2.

25 **[0053]** In yet another aspect, the present disclosure provides an antibody, wherein the antibody: (a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ 30 ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, 35 SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61,

SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%,

5 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90; (b) exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of

10 SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2; and (c) does not contain SEQ ID NO. 3 and SEQ ID NO. 4.

[0054] In still yet another aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than an affinity of an antibody comprising a heavy chain of an amino acid

15 sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4; and (b) the antibody inhibits proliferation of DS-1 cells by at least 40% after 72 hours at a concentration of 0.032 μ g/mL or less in an MTS cell-proliferation assay.

[0055] In still yet another aspect, the present disclosure provides an antibody comprising a heavy

chain and a light chain, wherein: (a) the heavy chain comprises one or more mutations at positions 51,

20 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1; and/or (b) the light chain comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO. 2; and (c) the antibody comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to an antibody comprising a heavy chain of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, or SEQ ID NO. 89 and a light chain of SEQ ID NO. 2, SEQ ID NO.

4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, or SEQ ID NO. 90.

[0056] In still yet another aspect, the present disclosure provides an antibody comprising a heavy chain and a light chain, wherein: (a) the heavy chain comprises one or more mutations with respect to

5 SEQ ID NO. 1, wherein residue 57 is mutated to methionine (M); (b) the light chain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO. 4 or SEQ ID NO. 2, or both; and (c) the antibody exhibits a binding affinity (K_D) for human IL-6R of 1 nM or less, as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

10 **[0057] SEQUENCE IDENTITY**

[0058] The sequence identity with respect to the amino acid sequences identified herein, is defined as the percentage of amino acid residues in a query sequence that are identical with the amino acid residues of a second, reference polypeptide sequence or a portion thereof, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not

15 considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment 20 over the full length of the sequences being compared. Percent identity may be measured over the length of an entire defined polypeptide sequence, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment 25 length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured. In some embodiments, percent identity is determined with respect to the full length of a noted reference sequence, such as a sequence provided herein. For example, sequence comparison between two amino acid sequences (or a shorter length thereof) of the present disclosure may be carried out by computer program Blastp 30 (protein-protein BLAST) provided online by Nation Center for Biotechnology Information (NCBI). The percentage amino acid sequence identity of a given amino acid sequence A to a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has a certain % amino acid sequence identity to a given amino acid sequence B) is calculated by the formula as follows:

$$\frac{X}{Y} \times 100\%$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program BLAST in that program's alignment of A and B, and where Y is the total number of amino acid residues in A or B, whichever is shorter.

[0059] In some embodiments provided herein, a subject antibody comprises a heavy chain that

5 exhibits high degree of sequence identity to a reference selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, 10 SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, 15 SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, and/or a light chain that exhibits high degree of sequence identity to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ 20 ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90. In some embodiments provided herein, a subject antibody comprises a heavy chain having an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, 25 SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, 30 SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, 35 SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89. In some embodiments provided herein, a subject antibody comprises a light chain having an amino acid sequence with about or greater than

70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90. In some embodiments provided herein, a subject antibody comprises a heavy chain having an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, and a light chain having an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90.

[0060] Embodied herein are any combinations of heavy chains and light chains exemplified in SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, and SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID

NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90.

[0061] In some embodiments provided herein, the antibody comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100%

5 sequence identity to an antibody comprising a heavy chain of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, 10 SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, 15 SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, or SEQ ID NO. 89 and a light chain of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID 20 NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, or SEQ ID NO. 90.

[0062] In some embodiments provided herein, a subject antibody comprises a heavy chain comprising an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 26. In some

embodiments provided herein, a subject antibody comprises a light chain comprising an amino acid 25 sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 4. In some embodiments provided herein, a subject antibody comprises a heavy chain comprising an amino acid sequence with greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 26 and a light chain comprising an amino acid sequence with greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 4. 30

[0063] In some embodiments provided herein, a subject antibody comprises a heavy chain comprising an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 28. In some

35 embodiments provided herein, a subject antibody comprises a light chain comprising an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 4. In some embodiments provided herein,

a subject antibody comprises a heavy chain comprising an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 28 and a light chain comprising an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence of SEQ ID NO. 4.

5 [0064] In some embodiments provided herein, a subject antibody does not contain SEQ ID NO. 3 and SEQ ID NO. 4. In some embodiments provided herein, a subject antibody does not contain SEQ ID NO. 1 and SEQ ID NO. 2. In some embodiments provided herein, a subject antibody does not contain (a) SEQ ID NO. 3 and SEQ ID NO. 4, and (b) SEQ ID NO. 1 and SEQ ID NO. 2.

10 [0065] **MUTATION**

[0066] In some embodiments provided herein, a subject antibody as described herein may have one or more mutations with respect to a reference sequence. A mutation may be a deletion, an insertion or addition, or a replacement or substitution to an amino acid residue. A “deletion” refers to a change in an amino acid sequence due to the absence of one or more amino acid residues. An “insertion” or “addition” refers to changes in an amino acid sequence resulting in the addition of one or more amino acid residues as compared to a reference sequence. A “replacement” or “substitution” refers to the replacement of one or more amino acids by different amino acids. In the context of the present disclosure, the mutations of a subject antibody or a fraction thereof with respect to a reference sequence may be determined by comparison of the subject antibody or a fraction thereof to the reference sequence. Optimal alignment of sequences for comparison may be conducted according to any of the known methods in the art.

15 [0067] A mutation may be identified by the mutation site. The mutation site is the position on a reference sequence where a deletion, an addition, or a substitution takes place. The amino acid residues on a reference sequence are numbered from the N-terminus to the C-terminus, and the mutation site is the numbering of the amino acid residue on which a deletion, an addition, or a substitution takes place. For example, position 26 on a reference sequence is the position where the 26th amino acid residue locates starting from the N-terminus.

20 [0068] In the context of the present disclosure, one mutation at a specific position is intended to mean an deletion of one amino acid residue at the specific position, a substitution of an amino acid residue at the specific position with another amino acid residue, or an addition of one or more amino acid residues between the specific position and the position after the specific position (or after the specific position when the amino acid residue at the specific position is the last amino acid residue) on the reference sequence.

25 [0069] For the purpose of describing a mutation with respect to a reference sequence, the one-letter amino acid code may be used. In this respect, for example, when a subject antibody is said to comprise a mutation from G to I at position 26, which may be described as “G26I”, with respect to a reference sequence, it is intended to mean that the 26th amino acid residue, which is a glycine (G)

residue according to the reference sequence, is substituted by an alanine residue in a subject antibody or a fraction thereof. In the context of the present disclosure, for example, when a subject antibody is said to comprise a deletion of a glycine (G) residue at position 26, which may be described as “G26del” with respect to a reference sequence, it is intended to mean that the 26th amino acid residue,

5 which is a glycine (G) residue according to the reference sequence, does not exist in a subject antibody or a fraction thereof. In the context of the present disclosure, for example, when a subject antibody is said to comprise an addition of one or more amino acid residues after the glycine (G) residue at position 26, which may be described by “G26_ins” followed by a list of the added amino acid residues, it is intended to mean that the listed one or more amino acid residues are added between 10 the 26th amino acid residue, which is glycine (G), and the 27th amino acid or (in a case where the 26th amino acid residue is the last amino acid residue according to the reference sequence) after the 26th amino acid residue, which is glycine (G).

[0070] In some embodiments, a subject antibody comprises one or more mutations in the heavy chain with respect to SEQ ID NO. 1. In further embodiments, the heavy chain of a subject antibody 15 comprises one or more mutations located in one or more of the Fv framework regions (FRs) and/or one or more of the complementarity determining regions (CDRs). In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, three, or four of HFR1, HFR2, HFR3, and HFR4. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, or three of HCDR1, HCDR2, and 20 HCDR3. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, three, or four of HFR1, HFR2, HFR3, and HFR4 and one or more mutations located in one, two, or three of HCDR1, HCDR2, and HCDR3. In still further 25 embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, three, four, five, or six of HFR1, HFR2, HCDR2, HFR3, HCDR3, and HFR4. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, three, or four of HFR1, HCDR2, HCDR3, and HFR4. In still further embodiments, the heavy chain of a 30 subject antibody comprises one or more mutations located in one, two, three, or four of HFR1, HCDR2, HCDR3, and HFR4. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, or three of HFR1, HCDR2, and HCDR3. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one, two, or three of HCDR2, HCDR3, and HFR4. In still further embodiments, the heavy chain of a subject antibody comprises one or more mutations located in one or two of HCDR2 and 35 HCDR3.

[0071] In some embodiments provided herein, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more mutations in the heavy chain with respect to SEQ ID NO. 1. In further

embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more mutations in the heavy chain at positions 25, 48, 51, 57, 58, 59, 69, 71, 99, 103, 106, 108, 116, 119, 123, 136, and 209 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more mutations in the heavy chain at

5 positions 25, 51, 57, 58, 59, 69, 71, 99, 103, 106, 108, 116, 119, 123, 136, and 209 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more mutations in the heavy chain at positions 25, 51, 57, 58, 59, 99, 103, 106, 108, 116, 119, 123, 136, and 209 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations in the heavy chain at

10 positions 51, 57, 58, 59, 99, 103, 106, 108, 116, 119, 123, 136, and 209 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations in the heavy chain at positions 51, 57, 58, 59, 99, 103, 106, 108, 116, 119, 123, 136, and 209 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations in the heavy chain at positions 25, 51, 57, 58, 59, 99, 103, 106, 108, 116, and 119 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or more mutations in the heavy chain at positions 25, 51, 57, 58, 59, 99, 103, 106, and 108 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3, 4, 5, 6, 7 or more mutations in the heavy chain at positions 51, 57, 58, 59, 99, 103, 106, and 108 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody

15 comprises 1, 2, 3, 4, 5 or more mutations in the heavy chain at positions 51, 57, 99, 103, 106, and 108 with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises 1, 2, 3 or more mutations in the heavy chain at positions 51, 57, 99, and 103 with respect to SEQ ID NO. 1.

[0072] In some embodiments, a subject antibody comprises 1, 2, 3, 4, 5 or more mutations in the heavy chain with respect to SEQ ID NO. 1 selected from Y51F, Y51W, Y51K, Y51R, or Y51H; I57M; T58I; P62A; T69S; L71V; S99C, S99T, or S99N; T103I, T103A, T103G, T103L, T103M, T103Y, or T103R; M106I; Y108F; T116I; S119A; K123E; S136N; and S209G. In some embodiments, a subject antibody comprises 1, 2, 3, 4, 5 or more mutations in the heavy chain with respect to SEQ ID NO. 1 selected from Y51F; I57M; T58I; S99C; T103I; M106I; and Y108F. In some embodiments, a subject antibody comprises 1, 2, 3, 4 or more mutations in the heavy chain with

20 respect to SEQ ID NO. 1 selected from Y51F; I57M; S99C; T103I; M106I; and Y108F.

[0073] In further embodiments, a subject antibody comprises a mutation I57M in the heavy chain with respect to SEQ ID NO. 1. In further embodiments, a subject antibody comprises a mutation T58I with respect to SEQ ID NO. 1. In further embodiments, a subject antibody comprises a mutation S99C or S99T in the heavy chain with respect to SEQ ID NO. 1. In further embodiments, a subject antibody comprises a mutation T103M, T103I, T103G, T103L, T103Y, or T103R in the heavy chain with respect to SEQ ID NO. 1. In further embodiments, a subject antibody comprises a mutation

25

30

35

M106I with respect to SEQ ID NO. 1. In further embodiments, a subject antibody comprises a mutation Y108F in the heavy chain with respect to SEQ ID NO. 1.

[0074] In still further embodiments, a subject antibody comprises Y51F, I57M, T58I, S99C, and T103I in the heavy chain with respect to SEQ ID NO. 1. In still further embodiments, a subject

5 antibody comprises Y51F, I57M, S99C, T103I, and T116I in the heavy chain with respect to SEQ ID NO. 1. In still further embodiments, a subject antibody comprises Y51F, I57M, S99C, and T103I in the heavy chain with respect to SEQ ID NO. 1. In yet further embodiments, a subject antibody comprises Y51F, I57M, S99T, and T103I in the heavy chain with respect to SEQ ID NO. 1. In still yet further embodiments, a subject antibody comprises Y51F, I57M, S99N, and T103I in the heavy

10 chain with respect to SEQ ID NO. 1.

[0075] In some embodiments, a subject antibody comprises one or more mutations in the light chain with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody

comprises one or more mutations located in one or more of the CDRs. In still further embodiments, the light chain of a subject antibody comprises one or more mutations located in one, two, or three of 15 LCDR1, LCDR2, and LCDR3. In still further embodiments, the light chain of a subject antibody comprises one or more mutations in LCDR1. In still further embodiments, the light chain of a subject antibody comprise one or more mutations in LCDR2. In still further embodiments, the light chain of a subject antibody comprises one or more mutations in LCDR3. In still further embodiments, the light chain of a subject antibody comprises no mutations with respect to SEQ ID NO. 2.

20 **[0076]** In some embodiments, the light chain of a subject antibody comprises one or more mutations with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody comprises 1, 2, 3, 4 or more mutations at positions 27, 33, 50, 55, 56, 89, 92, 93, and 97 with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody comprises 1, 2, 3, 4 or more mutations at positions 50, 55, 56, 89, 92, 93, and 97 with respect to SEQ ID NO. 2. In further 25 embodiments, the light chain of a subject antibody comprises 1, 2, 3 or more mutations at positions 89, 92, 93, and 97 with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody comprises one or more mutations at positions 89, and 93 with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody comprises mutations at positions 89 and 93 with respect to SEQ ID NO. 2.

30 **[0077]** In some embodiments, the light chain of a subject antibody comprises one or more mutations selected from Q27H; L33P; Y50S; H55Y, H55Q, or H55R; S56P; Q89G or Q89K; N92D; T93R; and T97N with respect to SEQ ID NO. 2. In further embodiments, the light chain of a subject antibody comprises one or more mutations selected from Y50S; H55Y, H55Q, or H55R; S56P; Q89G or Q89K; N92D; T93R; and T97N with respect to SEQ ID NO. 2. In further embodiments, the light 35 chain of a subject antibody comprises one or more mutations selected from Q89G or Q89K; N92D; T93R; and T97N with respect to SEQ ID NO. 2. In still further embodiments, the light chain of a

subject antibody comprises mutations (i) Q89G or Q89K, and (ii) N92D with respect to SEQ ID NO. 2.

[0078] In some embodiments, a subject antibody comprises one or more mutations in the heavy chain with respect to SEQ ID NO. 1 and one or more mutations in the light chain with respect to SEQ ID NO. 2. For this purpose, the mutation pattern in the heavy chain and the mutation pattern in the light chain could be combined in any desirable manner.

[0079] In some embodiments, a subject antibody can be any one of the following 1#, 2#, 3#, 5#, 6#, 7#, 8#, 9#, 11#, 12#, 13#, 14#, 15#, 16#, 17#, 18#, 20#, 24#, 26#, 27#, 28#, 29#, 30#, 31#, 35#, 45#, 49#, 50#, 51#, 56#, 57#, 58#, 60#, 61#, 62#, 64#, 66#, 68#, 201#, 202#, 203#, 204#, 205#, 206#, 208#, 10 52#, 54#, 55#, 59#, 69#, 209#, 214#, 215#, 216#, 217#, 218#, 219#, 220#, 221#, 222#, 223#, 224#, 225#, 226#, 227#, 228#, 229#, 230#, 231#, 232#, 233#, 234#, 235#, 236#, 237#, 238#, 239#, 240#, 241#, 242#, 243#, 244#, 245#, 246#, 247#, 248#, 249#, 250#, 251#, 252#, 253#, 254#, 255#, 256#, 257#, 258#, 259#, 260#, 261#, 262#, 263#, 264#, 265#, and 266#.

[0080] A subject antibody typically exhibits high binding affinity to IL-6 receptor. In some 15 embodiments, the IL-6 receptor is human IL-6R. In some embodiments provided herein, the IL-6 receptor has an amino acid sequence of SEQ ID NO. 91.

[0081] Binding affinity of molecules to an IL-6R in solution or immobilized on an array can be detected using detection techniques known in the art. Examples of such techniques include immunological techniques such as competitive binding assays and sandwich assays; fluorescence 20 detection using instruments such as confocal scanners, confocal microscopes, or CCD-based systems and techniques such as fluorescence, fluorescence polarization (FP), fluorescence resonant energy transfer (FRET), total internal reflection fluorescence (TIRF), fluorescence correlation spectroscopy (FCS); colorimetric/spectrometric techniques; surface plasmon resonance (SPR), by which changes in mass of materials adsorbed at surfaces are measured; techniques using radioisotopes, including 25 conventional radioisotope binding and scintillation proximity assays (SPA); mass spectroscopy, such as matrix-assisted laser desorption/ionization mass spectroscopy (MALDI) and MALDI-time of flight (TOF) mass spectroscopy; ellipsometry, which is an optical method of measuring thickness of protein films; quartz crystal microbalance (QCM), a very sensitive method for measuring mass of materials adsorbing to surfaces; scanning probe microscopies, such as atomic force microscopy (AFM), 30 scanning force microscopy (SFM) or scanning electron microscopy (SEM); and techniques such as electrochemical, impedance, acoustic, microwave, and IR/Raman detection. See, e.g., *Mere L, et al., "Miniaturized FRET assays and microfluidics: key components for ultra-high-throughput screening," Drug Discovery Today 4(8):363-369 (1999)*, and references cited therein; *Lakowicz JR, Principles of Fluorescence Spectroscopy, 2nd Edition, Plenum Press (1999)*, or *Jain KK: Integrative Omics, Pharmacoproteomics, and Human Body Fluids. In: Thongboonkerd V, ed., ed. Proteomics of Human Body Fluids: Principles, Methods and Applications. Volume 1: Totowa, N.J.: Humana Press, 2007*, each of which is herein incorporated by reference in its entirety.

[0082] In some embodiments provided herein, binding affinity of a subject antibody to IL-6R is measured by surface plasmon resonance. Biacore® surface plasmon resonance (SPR) system (GE Healthcare, Chicago IL) may be used to measure binding affinity of a subject antibody. Exemplary SPR analysis systems include, but are not limited to, Biacore X100, Biacore T200, Biacore 3000 or Biacore 4000 instrument, and commercial sensor chips series. In a typical application of the Biacore systems, interaction kinetics are analyzed by monitoring the interaction as a function of time over a range of analyte concentrations, and then fitting the whole data set to a mathematical model describing the interaction. The association phase (during sample injection) contains information on both association and dissociation processes, while only dissociation occurs during the dissociation phase (after sample injection, when buffer flow removes dissociated analyte molecules). Those skilled in the art can choose or determine appropriate parameters and/or conditions for carrying out the binding affinity assay according to manufacturer's manual. In some embodiments, the binding affinity of a subject antibody is determined by surface plasmon resonance at 37°C.

[0083] The binding affinity of a subject antibody for IL-6 receptor may be characterized by k_a , k_d or K_D . The term " k_a ", as used herein, is intended to refer to the rate constant for association of an antibody to an antigen. The term " k_d ", as used herein, is intended to refer to the rate constant for dissociation of an antibody from the antibody/antigen complex. The term " K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of an antibody-antigen interaction. For purposes of the present disclosure, K_D is defined as the ratio of the two kinetic rate constants k_a/k_d .

The smaller the equilibrium dissociation constant the tighter the subject antibody and the IL-6R bind to each other. In biological systems a good, specific binder typically has a dissociation constant in the range of 10^9 to 10^{-7} M.

[0084] In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.05 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.01 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.005 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for human IL-6

receptor (IL-6R) of 0.001 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

[0085] In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an

5 amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is at least 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, or 1000 times greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2.

10 **[0086]** In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is comparable to an affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4.

15 In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than an affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4. In some embodiments provided herein, a subject antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100 times greater than an affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO.

20 4.

[0087] In some embodiments, the binding of a subject antibody has pH dependence. In the context of the present disclosure, pH dependence is defined as the ratio between the binding affinity for IL-6R at pH7.4 and at pH6.0. The pH dependence can be in the form of the fold of decrease of binding affinity from pH7.4 to pH6.0, or the fold of increase of binding affinity from pH7.4 to pH6.0. In

25 some embodiments, the pH dependence is calculated as the ratio between the K_D value at pH 6.0 and the K_D value at pH 7.4, and the pH dependence, i.e., the ratio, indicates the fold of affinity decrease from the pH7.4 to pH6.0. If the pH dependence of a subject antibody described herein is over 1, it means that the antibody binds to IL-6R in such a pH-dependent manner that its binding to IL-6R at

30 pH7.4 is higher than at pH6.0. If the pH dependence of a subject antibody described herein is lower than 1, it means that the antibody binds to IL-6R in such a pH-dependent manner that its binding to IL-6R at pH6.0 is higher than at pH7.4. The ability to maintain binding under neutral condition but significantly reduce under acidic conditions allows a subject antibody's dissociation from antigen in acidic condition, thus escaping the degradation by lysosomes and returning to the plasma where it can bind to an antigen again. A subject antibody having such pH dependent binding pattern has superior

35 properties in terms of antigen neutralization and clearance relative to its counterpart that binds in a pH-independent mode.

[0088] In some embodiments, a subject antibody provided herein has a pH dependence of binding affinity for IL-6R higher than 1, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40 or more. In some embodiments, a subject antibody has a pH dependence of binding affinity for IL-6R higher than that of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a

5 light chain of an amino acid sequence of SEQ ID NO. 2. In some embodiments, a subject antibody has a pH dependence of binding affinity for IL-6R at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times higher than that of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2. In some embodiments, a subject antibody has a pH dependence of binding affinity for IL-6R higher than that of an antibody comprising a heavy 10 chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4. In some embodiments, a subject antibody has a pH dependence of binding affinity for IL-6R at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times higher than that of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4.

15 **[0089]** In some embodiments, a subject antibody exhibits inhibitory activity against its IL-6 receptor. Inhibition of IL-6 receptor may be evaluated by measuring downstream biomarkers or cell proliferation. Inhibitory activity of a subject antibody against IL-6 receptor can be evaluated by DS-1 cell (ATCC Accession No. CRL 11102) proliferation. As shown in Fig. 1, DS-1 cell proliferation depends upon the binding of IL-6 to IL-6R, and the subsequent activation of cell signaling pathways.

20 Binding of a subject antibody provided herein to IL-6R reduces the amounts of available IL-6R, and thus correlates to the inhibition of DS-1 cell proliferation.

[0090] Different types of assays are available to evaluate the proliferation of cells, comprising but not limited to DNA synthesis cell proliferation assays, metabolic cell proliferation assays, assays detecting proliferation markers and assays measuring ATP concentration. In a DNA synthesis cell 25 proliferation assay, DNA of proliferating cells are labeled to be radioactive, and the label can be washed, adhered to filters and then measured using a scintillation counter. In a metabolic cell proliferation assay, tetrazolium salts such as MTT, XTT, MTS and WSTs may be used which are reduced in metabolically active cells, forming a formazan dye that subsequently changes the color of the media. In an assay detecting proliferation markers, a monoclonal antibody may be used to target 30 common markers for cell proliferation and/or cell cycle regulation such as Ki-67, PCNA, topoisomerase IIB, and phospho-histone H3. For a measurement of ATP concentration, a bioluminescence-based detection of ATP may be used using the enzyme luciferase and its substrate luciferin.

[0091] An MTS cell-proliferation assay may be used to measure the proliferation of DS-1 cells. 35 MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), in the presence of phenazine methosulfate (PMS), produces a colored formazan product. The colored formazan product has an absorbance maximum at 490-500 nm in phosphate-buffered saline,

measurement of which provides an evaluation of the proliferation of DS-1 cells, and thus an evaluation of the inhibitory activity of a subject antibody.

[0092] In some embodiments, a subject antibody inhibits proliferation of DS-1 cells at least as effectively as an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2. In further embodiments, a subject antibody inhibits proliferation of DS-1 cells at least as effectively as an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4. In some embodiments, a subject antibody as described herein inhibits proliferation of DS-1 cells by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more at a concentration of 0.5 μ g/ml, 0.25 μ g/ml, 0.1 μ g/ml, 0.05 μ g/ml, 0.04 μ g/ml, 0.035 μ g/ml, 0.034 μ g/ml, 0.033 μ g/ml, 0.032 μ g/ml, 0.031 μ g/ml, 0.03 μ g/ml, 0.02 μ g/ml, 0.01 μ g/ml or less.

[0093] An antibody embodied herein may be a monoclonal antibody, a chimeric antibody, a human or humanized antibody. The term “human antibody,” as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human

15 germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term “human antibody,” as used herein, is not intended to include 20 antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The term “humanized antibody” is intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

Additional framework region modifications may be made within the human framework sequences.

25 The term “chimeric antibody” is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

[0094] Furthermore, the subject antibody can be of any isotype. The choice of isotype typically will 30 be guided by the desired effector functions, such as ADCC induction. Exemplary isotypes are IgG1, IgG2, IgG3, and IgG4. Either of the human light chain constant regions, kappa or lambda, may be used. If desired, the class of an antibody may be switched by known methods. For example, an antibody that was originally IgM may be class switched to an IgG antibody. Further, class switching techniques may be used to convert one IgG subclass to another, for instance from IgG1 to IgG2. Thus, 35 the effector function of the antibodies as described herein may be changed by isotype switching to, e.g., an IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody for various therapeutic uses. In one embodiment an antibody is an IgG1 antibody.

[0095] In some embodiments, the subject antibody provided herein is a monoclonal antibody. The subject antibody can be prepared by the hybridoma process or the recombinant DNA process. A typical example of the hybridoma process is the method of Kohler & Milstein (Nature, 256:495 (1975)). Antibody-producing cells used in the cell fusion step of this method are spleen cells, lymph 5 node cells, peripheral blood leukocytes, etc. of an animal (e.g., mouse, rat, hamster, rabbit, monkey, goat) immunized with an antigen (human IL-6 receptor, its partial peptide, or cells expressing them). It is also possible to use antibody-producing cells obtained by allowing an antigen to act in a culture medium on the above cells or lymphocytes isolated in advance from an unimmunized animal. As 10 myeloma cells, publicly known various cell strains can be used. The antibody-producing cells and myeloma cells may originate in different animal species, if they are mutually fusible; preferably, however, they are of the same animal species origin. Hybridomas, for example, are produced by cell 15 fusion between spleen cells obtained from an antigen-immunized mouse and mouse myeloma cells, and subsequent screening can obtain hybridomas producing a monoclonal antibody against human IL-6R. The monoclonal antibody against human IL-6R can be produced by a culture of the hybridomas, or from an ascitic fluid of a mammal administered the hybridomas.

[0096] In some embodiments, the subject antibody is a humanized antibody. In making humanized antibodies, the choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any HuAb can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to 20 significant loss of binding affinity to the antigen. Glaser et al. (1992) J. Immunol. 149:2606; Tempest et al. (1992) Biotechnology 9:266; and Shalaby et al. (1992) J. Exp. Med. 17:217. The more homologous a HuAb is to the original muAb, the less likely that the human framework will introduce 25 distortions into the murine CDRs that could reduce affinity. Based on a sequence homology search against an antibody sequence database, the HuAb IC4 provides good framework homology to muM4TS.22, although other highly homologous HuAbs would be suitable as well, especially kappa L chains from human subgroup I or H chains from human subgroup III. Kabat et al. (1987). Various computer programs such as ENCUD (Levitt et al. (1983) J. Mol. Biol. 168:595) are available to predict the ideal sequence for the V region. The invention thus encompasses HuAbs with different V regions. It is within the skill of one in the art to determine suitable V region sequences and to optimize 30 these sequences. Methods for obtaining antibodies with reduced immunogenicity are also described in U.S. Pat. No. 5,270,202 and EP 699,755.

[0097] It is important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, in one example, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized 35 products using three dimensional models of the parental and humanized sequences. Three dimensional immunoglobulin models are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected

candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, and of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and import sequence so that the desired antibody

5 characteristic, such as increased affinity for the target antigen(s), is achieved.

[0098] In some embodiments, a subject antibody or fragment thereof is fused to serum albumins.

Fusion to serum albumins can improve the pharmacokinetics of a subject antibody as described herein. For example, the subject antibody or fragment thereof may be fused with a serum albumin. Serum albumin is a globular protein that is the most abundant blood protein in mammals.

10 Serum albumin is produced in the liver and constitutes about half of the blood serum proteins. It is monomeric and soluble in the blood. In some embodiments, the subject antibody or fragment thereof may be fused to a serum albumin. In further embodiments, serum albumin is human serum albumin (HSA).

[0099] In some embodiments, a subject antibody described herein or fragment thereof may be

15 fused to an albumin-binding peptide that displays binding activity to serum albumin to increase the half-life of the subject antibody or fragment thereof. Albumin-binding peptides that can be used herein include but are not limited to those described in e.g., Dennis et al., *J. Biol. Chem.* 277:35035-35043, 2002 and Miyakawa et al., *J. Pharm. Sci.* 102:3110-3118, 2013. In some embodiments, an albumin-binding peptide is fused genetically to a subject 20 antibody or fragment thereof described herein. In further embodiments, an albumin-binding peptide is attached to a subject antibody described herein or fragment thereof through chemical means, e.g., chemical conjugation. In some embodiments, an albumin-binding peptide may be fused to the N- or C-terminus of a subject antibody or fragment thereof described herein. The C-terminus of the albumin-binding peptide may be directly fused to the N-terminus of the 25 subject antibody through a peptide bond. Alternatively, the N-terminus of the albumin-binding peptide may be directly fused to the C-terminus of the subject antibody or fragment thereof through a peptide bond. In further embodiments, the carboxylic acid at the C-terminus of the albumin-binding peptide may be fused to an internal amino acid residue of the subject antibody or fragment thereof using conventional chemical conjugation techniques.

30 **[00100]** In some embodiments, a subject antibody described herein or fragment thereof is fused to a polymer, e.g., polyethylene glycol (PEG). An antibody or fragment thereof can be pegylated to, for example, increase the biological (e.g., serum) half life of the antibody or fragment thereof. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more

PEG groups become attached to the antibody or antibody fragment. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. Methods for pegylating proteins such as those disclosed in for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al may be used. In some embodiments, a polymer, e.g., PEG, may be covalently attached to a subject antibody, or fragment thereof, described herein, either at the N- or C-terminus or at an internal location, using conventional chemical methods, e.g., chemical conjugation. Without being bound by a theory, PEG moieties may contribute to, once attached to the antibody as described herein, the water solubility, high mobility in solution, lack of toxicity and low immunogenicity, extended circulating life, increased stability, ready clearance from the body, and altered distribution in the body.

[00101] Other half-life extension technologies that may be used to increase the serum half-life of the subject antibodies, or fragment thereof, include, but are not limited to, XTEN (Schellenberger et al., *Nat. Biotechnol.* 27:1186-1192, 2009) and Albu tag (Trussel et al., *Bioconjug Chem.* 20:2286-2292, 2009).

[00102] In some embodiments, a subject antibody or fragment thereof is conjugated to a chemically functional moiety. Typically, the moiety is a label capable of producing a detectable signal. These conjugated antibodies or fragments thereof are useful, for example, in detection systems such as quantitation of tumor burden, and imaging of metastatic foci and tumor imaging. Such labels are known in the art and include, but are not limited to, radioisotopes, enzymes, fluorescent compounds, chemiluminescent compounds, bioluminescent compounds substrate cofactors and inhibitors. See, for examples of patents describing the use of such labels, U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. The moieties can be covalently linked to antibody or fragment thereof as described herein, recombinantly linked, or conjugated to an antibody or fragment thereof through a secondary reagent, such as a second antibody, protein A, or a biotin-avidin complex.

[00103] Other functional moieties include signal peptides, agents that enhance or reduce immunologic reactivity, agents that facilitate coupling to a solid support, vaccine carriers, bioresponse modifiers, paramagnetic labels and drugs. A signal peptide is a short amino acid sequence that directs a newly synthesized protein through a cellular membrane, usually the endoplasmic reticulum in eukaryotic cells, and either the inner membrane or both inner and outer membranes of bacteria. Signal peptides are typically at the N-terminal portion of a polypeptide and are typically removed enzymatically between biosynthesis and secretion of the polypeptide from the cell. Such a peptide can be

incorporated into the subject antibody or fragment thereof to allow secretion of the synthesized molecules.

[00104] Agents that enhance immunologic reactivity include, but are not limited to, bacterial superantigens. Agents that facilitate coupling to a solid support include, but are not limited to, biotin or avidin. Immunogen carriers include, but are not limited to, any physiologically acceptable buffers. Bioresponse modifiers include cytokines, particularly tumor necrosis factor (TNF), interleukin-2, interleukin-4, granulocyte macrophage colony stimulating factor and gamma.-interferons.

[00105] Agents that reduce immunologic reactivity include, but are not limited to anti-inflammatory agents and immunosuppressants. Anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. NSAIDs include but are not limited to, salicylates, such as acetylsalicylic acid; diflunisal, salicylic acid, and salsalate; propionic acid derivatives, such as ibuprofen; naproxen; dexibuprofen, dexketoprofen, flurbiprofen, oxaprozin, fenoprofen, loxoprofen, and ketoprofen; acetic acid derivatives, such as indomethacin, diclofenac, tolmetin, aceclofenac, sulindac, nabumetone, etodolac, and ketorolac; enolic acid derivatives, such as piroxicam, lornoxicam, meloxicam, isoxicam, tenoxicam, phenylbutazone, and droxicam; anthranilic acid derivatives, such as mefenamic acid, flufenamic acid, meclofenamic acid, and tolfenamic acid; selective COX-2 inhibitors, such as celecoxib, lumiracoxib, rofecoxib, etoricoxib, valdecoxib, firocoxib, and parecoxib; sulfonanilides, such as nimesulide; and others such as clonixin, and licofelone. Corticosteroids include but are not limited to, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone. The immunosuppressants include but are not limited to hydroxychloroquine, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab, D-penicillamine, oral gold compound, injectable gold compound (intramuscular injection), minocycline, sodium gold thiomalate, auranofin, D-penicillamine, lobenzarit, bucillamine, actarit, cyclophosphamide, azathioprine, methotrexate, mizoribine, cyclosporine, and tacrolimus.

[00106] Suitable drug moieties include antineoplastic agents. Non-limiting examples are radioisotopes, vinca alkaloids such as the vinblastine, vincristine and vindesine sulfates, adriamycin, bleomycin sulfate, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, duanorubicin hydrochloride, doxorubicin hydrochloride, etoposide, fluorouracil, lomustine, mechlororethamine hydrochloride, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, procarbazine hydrochloride, streptozotocin, taxol, thioguanine, and uracil mustard.

[00107] Immunotoxins, including single chain molecules, can be produced by recombinant means. A variety of immunotoxins are available, and methods can be found, for example, in Monoclonal Antibody-toxin Conjugates: Aiming the Magic Bullet, Thorpe et al. (1982) Monoclonal Antibodies in Clinical Medicine, Academic Press, pp. 168-190; Vitatta (1987) Science 238:1098-1104; and Winter and Milstein (1991) Nature 349:293-299. Suitable toxins include, but are not limited to, ricin, radionuclides, pokeweed antiviral protein, *Pseudomonas* exotoxin A, diphtheria toxin, ricin A chain,

fungal toxins such as restrictocin and phospholipase enzymes. See, generally, "Chimeric Toxins," Olsnes and Pihl, *Pharmac. Ther.* 15:355-381 (1981); and "Monoclonal Antibodies for Cancer Detection and Therapy," eds. Baldwin and Byers, pp. 159-179, 224-266, Academic Press (1985).

[00108] The chemically functional moieties can be made recombinantly for instance by creating a

5 fusion gene encoding the antibody and the functional moiety. Alternatively, the antibody or fragment thereof can be chemically bonded to the moiety by any of a variety of well-established chemical procedures. For example, when the moiety is a protein, a variety of coupling agents may be used such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as 10 dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an 15 acid-labile linker, peptidase-sensitive linker, dimethyl linker, or disulfide-containing linker (Chari et al. *Cancer Research*, 52: 127-131 (1992)) may be used. The moieties may be covalently linked, or conjugated, through a secondary reagent, such as a second antibody, protein A, or a biotin-avidin complex. For examples of paramagnetic moieties and the conjugation thereof to antibodies, see, e.g., Miltenyi et al. (1990) *Cytometry* 11:231-238.

20 **[00109]** In some embodiments, a subject antibody as provided herein is a bispecific antibody.

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes.

A bispecific antibody as described herein may be a bispecific antibody that recognizes different

epitopes on the IL-6 receptor molecule, or a bispecific antibody in which one of the antigen-binding sites recognizes the IL-6 receptor and the other antigen-binding site recognizes an antigen other than

25 the IL-6 receptor. Examples of the second antigens that bind to the other antigen-binding site of a bispecific antibody that comprises an IL-6 receptor-recognizing antibody include IL-6, TNF α ,

TNFR1, TNFR2, CD80, CD86, CD28, CD20, CD19, IL-1 α , IL- β , IL-1R, RANKL, RANK, IL-17, IL-17R, IL-23, IL-23R, IL-15, IL-15R, BlyS, lymphotoxin α , lymphotoxin β , LIGHT ligand, LIGHT, VLA-4, CD25, IL-12, IL-12R, CD40, CD40L, BAFF, CD52, CD22, IL-32, IL-21, IL-21R, GM-CSF,

30 GM-CSFR, M-CSF, M-CSFR, IFN-alpha, VEGF, VEGFR, EGF, EGFR, CCR5, APRIL, and APRILR. Bispecific antibodies can be prepared as full-length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies).

[00110] Exemplified antibodies of the present disclosure include but are not limited to those as shown in the following table.

Table 1. Antibodies disclosed herein

Ref #	Seq ID No: (Heavy Chain)	Seq ID No: (Light Chain)
25	1	2
202	3	4
1	5	2
2	6	2
3	7	2
5	8	2
6	9	2
7	10	2
8	11	2
9	12	2
11	13	2
12	14	2
13	15	2
14	16	2
15	17	2
16	18	2
17	19	2
18	20	2
20	21	2
24	22	2
26	23	2
27	24	2
28	25	2
29	26	2
30	27	2
31	28	2
34	29	2
35	30	2
37	31	2
40	32	2
42	33	2
43	34	2
45	35	2
46	36	2
48	37	2
49	38	2
50	39	2
51	40	2
52	41	2
54	42	2
55	43	2
56	44	2

57	45	2
58	46	2
59	47	2
60	48	2
61	49	2
62	50	2
64	51	2
66	52	2
68	53	2
69	54	2
201	55	2
203	56	4
204	26	4
205	27	4
206	28	4
208	57	2
209	58	2
214	59	2
215	60	2
216	61	2
217	62	2
218	63	2
219	59	4
220	60	4
221	61	4
222	62	4
223	63	4
224	64	2
225	65	2
226	66	2
227	67	2
228	68	2
229	69	2
230	70	2
231	71	2
232	72	2
233	73	2
234	74	2
235	75	2
236	76	2
237	64	4
238	65	4
239	66	4
240	67	4

241	68	4
242	69	4
243	70	4
244	71	4
245	72	4
246	73	4
247	74	4
248	75	4
249	76	4
250	77	2
251	78	2
252	76	4
253	77	4
254	1	79
255	1	80
256	1	81
257	1	82
258	1	83
259	1	84
260	1	85
261	1	86
262	1	87
263	1	88
264	89	85
265	89	88
266	1	90

[00111] A subject antibody can be produced as a recombinant antibody by cloning DNA encoding the subject antibody or peptide from hybridomas or B cells or any form of antibody and/or antibody fragment libraries , integrating the clone into a suitable vector, and transducing the vector into host

5 cells (for example, P. J. Delves, Antibody Production: Essential Techniques, 1997 WILEY, P. Shepherd and C. Dean Monoclonal Antibodies, 2000 OXFORD UNIVERSITY PRESS, Vandamme A. M. et al., Eur. J. Biochem. 192:767-775 (1990)). Thus, in one aspect, provided herein is an isolated polynucleotide encoding an antibody or fragment thereof of the present disclosure.

[00112] Nucleotide sequences corresponding to various regions of L or H chains of an existing

10 antibody can be readily obtained and sequenced using convention techniques including but not limited to hybridization, PCR, and DNA sequencing. Hybridoma cells that produce monoclonal antibodies serve as a preferred source of antibody nucleotide sequences. A vast number of hybridoma cells producing an array of monoclonal antibodies may be obtained from public or private repositories. The largest depository agent is American Type Culture Collection, which offers a diverse collection of 15 well-characterized hybridoma cell lines. Alternatively, antibody nucleotides can be obtained from

immunized or non-immunized rodents or humans, and from organs such as spleen and peripheral blood lymphocytes. Specific techniques applicable for extracting and synthesizing antibody nucleotides are described in Orlandi et al. (1989) Proc. Natl. Acad. Sci. U.S.A 86: 3833-3837, Larrick et al. 1989) biochem. Biophys. Res. Commun. 160: 1250-1255; Sastry et al. (1989) Proc. Natl. Acad. Sci., U.S.A. 86: 5728-5732; and U.S. Pat. No. 5,969,108.

[00113] The antibody nucleotide sequences may also be modified, for example, by substituting the coding sequence for human heavy and light chain constant regions in place of the homologous non-human sequences. In that manner, chimeric antibodies are prepared that retain the binding specificity of the original antibody.

[00114] Additionally, polynucleotides encoding the heavy and/or light chains of the antibody or functional fragment thereof can be subjected to codon optimization to achieve optimized expression of a subject antibody or functional fragment thereof in a desired host cell. For example, in one method of codon optimization, a native codon is substituted by the most frequent codon from a reference set of genes, wherein the rate of codon translation for each amino acid is designed to be high. Additional exemplary methods for generating codon optimized polynucleotides for expression of a desired protein, which can be applied to the heavy and/or light chains of the antibody or a functional fragment thereof, are described in Kanaya et al., Gene, 238:143-155 (1999), Wang et al., Mol. Biol. Evol., 18(5):792-800 (2001), U.S. Pat. No. 5,795,737, U.S. Publication 2008/0076161 and WO 2008/000632.

[00115] Polynucleotides of the present disclosure include those coding for functional equivalents and fragments thereof of the exemplified polypeptides. Functional equivalents may be polypeptides having conservative amino acid substitutions, analogs including fusions, and mutants.

[00116] Due to the degeneracy of the genetic code, there can be considerable variation in nucleotides of the L and H sequences, as well as the heterodimerization sequences suitable for construction of the polynucleotide and vectors of the present disclosure. These variation are encompassed by the present disclosure.

[00117] Where desired, the recombinant polynucleotides may comprise heterologous sequences that facilitate detection of the expression and purification of the gene product. Examples of such sequences include those encoding reporter proteins such as β -galactosidase, β -lactamase, chloramphenicol acetyltransferase (CAT), luciferase, green fluorescent protein (GFP) and their derivatives. Other heterologous sequences that facilitate purification may code for epitopes such as Myc, HA (derived from influenza virus hemagglutinin), His-6, FLAG, or the Fc portion of immunoglobulin, glutathione S-transferase (GST), and maltose-binding protein (MBP).

[00118] The polynucleotides can be conjugated to a variety of chemically functional moieties as described above. Commonly employed moieties include labels capable of producing a detectable signal, signal peptides, agents that enhance or reduce immunologic reactivity, agents that facilitate coupling to a solid support, vaccine carriers, bioresponse modifiers, paramagnetic labels and drugs.

The moieties can be covalently linked to a polynucleotide recombinantly or by other means known in the art.

[00119] The polynucleotides can comprise additional sequences, such as additional encoding sequences within the same transcription unit, controlling elements such as promoters, ribosome

5 binding sites, and polyadenylation sites, additional transcription units under control of the same or a different promoter, sequences that permit cloning, expression, and transformation of a host cell, and any such construct as may be desirable in accordance with any of the various embodiments described herein.

[00120] The polynucleotides can be obtained using chemical synthesis, recombinant cloning methods,

10 PCR, or any combination thereof. One of skill in the art can use the sequence data provided herein to obtain a desired polynucleotide by employing a DNA synthesizer or ordering from a commercial service.

[00121] Polynucleotides comprising a desired sequence can be inserted into a suitable vector which in turn can be introduced into a suitable host cell for replication, amplification and expression.

15 Accordingly, in one aspect, provided herein are a variety of vectors comprising one or more of the polynucleotides of the present disclosure. Also provided is a selectable library of expression vectors comprising at least one vector encoding the subject antibody.

[00122] Vectors of the present disclosure are generally categorized into cloning and expression vectors. Cloning vectors are useful for obtaining replicate copies of the polynucleotides they contain, 20 or as a means of storing the polynucleotides in a depository for future recovery. Expression vectors (and host cells containing these expression vectors) can be used to obtain polypeptides produced from the polynucleotides they contain. Suitable cloning and expression vectors include any known in the art, e.g., those for use in bacterial, mammalian, yeast, insect and phage display expression systems.

[00123] Suitable cloning vectors can be constructed according to standard techniques, or selected from 25 a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors will generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, or may carry marker genes. Suitable examples include plasmids and bacterial viruses, e.g., pBR322, pMB9, ColE1, pCR1, RP4, pUC18, mp18, mp19, phage DNAs (including filamentous and non-filamentous phage 30 DNAs), and shuttle vectors such as pSA3 and pAT28. These and other cloning vectors are available from commercial vendors such as Clontech, BiORad, Stratagene, and Invitrogen.

[00124] Expression vectors containing these nucleic acids are useful to obtain host vector systems to produce proteins and polypeptides. Typically, these expression vectors are replicable in the host organisms either as episomes or as an integral part of the chromosomal DNA. Suitable expression 35 vectors include plasmids, viral vectors, including phagemids, adenoviruses, adeno-associated viruses, retroviruses, cosmids, etc. A number of expression vectors suitable for expression in eukaryotic cells including yeast, avian, and mammalian cells are available. One example of an expression vector is

pcDNA3 (Invitrogen, San Diego, Calif.), in which transcription is driven by the cytomegalovirus (CMV) early promoter/enhancer. Two types of particularly useful expression vectors for expressing the subject antibody as described herein are the phage display vector and bacterial display vector.

[00125] For example techniques for constructing phage display vectors, see e.g. the review article by

5 Winter G. et al. (1994) Ann. Rev. Immunol. 12:433-55. Both filamentous and non-filamentous phage sequences are applicable for constructing a display vector. Filamentous phage vectors are preferred because the genomes of many representative phages of this class have been sequenced, and their genomes are found to be much smaller than that of non-filamentous phages. Representative phages of this class include M13, f1, fd, If1, Ike, Xf, Pf1, and Pf3. The phage vector typically is constructed to
10 express heteromultimers, e.g. antibody peptides, by fusion to a part or all of a phage coat protein. Suitable coat proteins include pIII, VIII, VI, VII and IX of M13. The heteromultimer sequence is typically inserted into the phage vector in such a way that the integrity of the expressed phage coat is not undermined, and the heteromultimer is preferably biologically functional.

[00126] For constructing pIII fusion vector, commonly employed fusion sites are located at the amino

15 terminus, in between the flexible spacer between the two domains of pIII (see e.g. Smith et al. Science 288:1315-17), or any other alternative fusion sites described in U.S. Pat. Nos. 5,969,108, 5,837,500. The pIII fusion and other proteins of the phage can be encoded entirely within the same phage replicon or on different replicons. When at least two replicons are used, the pIII fusion is generally encoded on a phagemid, a plasmid containing a phage origin of replication. Phagemids can be packaged into
20 phage particles by "rescue" with a helper phage such as M13KO7, which provides all the phage proteins, including pIII, but due to a defect origin is itself poorly packaged in competition with the phagemids. Other multivalent helper phages (e.g. M13.DELTA.gIII) that lack or contain altered pIII to enhance the package efficiency can also be employed (Rondot et al. Nature Biotechnology 19:75-78).

25 [00127] Similar constructions can be made with other filamentous phage. Pf3 is a well-known filamentous phage that infects *Pseudomonas aeruginosa* cells that harbor an IncP-1 plasmid. The entire genome has been sequenced and the genetic signals involved in replication and assembly are characterized. The major coat protein of PF3 is unusual in having no signal peptide to direct its secretion. The sequence has charged residues ASP₇, ARG₃₇, LYS₄₀, and PHE₄₄-COO⁻ which is
30 consistent with the amino terminus being exposed. To construct a display Pf3 vector, it is generally desirable to engineer a signal sequence known to cause secretion in *P. aeruginosa* fused in-frame to a gene fragment encoding a heterologous polypeptide, which in turn is fused in-frame with a DNA encoding the mature Pf3 coat protein.

[00128] The same general construction scheme applies to generating display vectors containing

35 sequences derived from non-filamentous phages including bacteriophage X174, λ, T4 and T7 phages. A corresponding display vector that expresses the subject heteromultimers using the unique heterodimerization sequences can be generated.

[00129] In addition to phage display vector, another class of preferred vector is a bacterial display vector. The general scheme outlined above is equally applicable for constructing such vectors. Briefly, the vectors facilitate expression of a heteromultimer, antibody of the present disclosure in particular, as a fusion with a bacterial surface protein. A variety of bacterial surface proteins are applicable for expressing such fusions. Non-limiting examples of bacterial surface proteins include LamB (Bremer et al. Proc. Natl. Acad. Sci U.S.A. (1984) 81:3830-34; Gene (1987) 52:165-73); OmpA (Prog Biophys Molec Biol (1987) 49:89-115); OmpC; OmpF (Pages et al. Biochemimie (1990) 72:169-76); PhoE (van der Ley et al. J. Biol. Chem. 261:12222-5); pilin (So et al. Curr Top in Microbiol & Immunol (1985) 118:13-28); pldA (de Geus et al. EMBO J. (1984) 3(8): 1799-1802) and their homologs. Characterization of these and other surface proteins, and the methods of using these proteins for displaying heterologous polypeptides are detailed in U.S. Pat. No. 5,837,500 as well as the references cited therein.

[00130] The vectors of the present disclosure typically comprise transcriptional or translational control sequences required for expressing the encoded antibody. Suitable transcription or translational control sequences include but are not limited to replication origin, promoter, enhancer, repressor binding regions, transcription initiation sites, ribosome binding sites, translation initiation sites, and termination sites for transcription and translation.

[00131] The expression vector can be transferred to a host cell and the transfected cells are then cultured to produce a subject antibody or functional fragment thereof. Thus, in one aspect, provided herein are host cells containing a polynucleotide encoding a subject antibody or functional fragment thereof operably linked to a heterologous promoter. The host cell can be co-transfected with two expression vectors, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors can contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector can be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain can be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, 1986, Nature 322:52; and Kohler, 1980, Proc. Natl. Acad. Sci. USA 77:2197-2199).

[00132] A variety of host-expression vector systems can be utilized to express the subject antibody or functional fragment thereof (see, e.g., U.S. Pat. No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also represent cells which can, when transformed or transfected with the appropriate nucleotide coding sequences, express a subject antibody molecule in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression

vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, NSO, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies

5 (Foecking et al., 1986, Gene 45:101; and Cockett et al., 1990, Bio/Technology 8:2). In some embodiments, antibodies or fragments thereof are produced in CHO cells.

[00133] For bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such an antibody or fragment thereof is to be produced, for the generation of

10 pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified can be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., 1983, EMBO 12:1791), in which the antibody coding sequence can be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic

15 Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 24:5503-5509); and the like.

20 pGEX vectors can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa

25 protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[00134] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) can be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody or functional fragment coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for

30 example the polyhedrin promoter).

[00135] In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest can be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene can then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (e.g., see Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 81:355-359). Specific

initiation signals can also be used for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a

5 variety of origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., 1987, Methods in Enzymol. 153:51-544).

[00136] For plant cells, a variety of vector delivery techniques is available in the art. The host cells may be in the form of whole plants, isolated cells or protoplasts. Illustrative procedures for

10 introducing vectors into plant cells include Agrobacterium-mediated plant transformation, protoplast transformation, gene transfer into pollen, injection into reproductive organs and injection into immature embryos. As is evident to one skilled in the art, each of these methods has distinct advantages and disadvantages. Thus, one particular method of introducing vectors into a particular plant species may not necessarily be the most effective for another plant species.

15 [00137] In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products can be important for the function of the antibody or functional fragment. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of 20 proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product can be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT2O 25 and T47D, NSO (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O and HsS78Bst cells.

[00138] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express an antibody or functional fragment thereof can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells 30 can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells can be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the 35 plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express the antibody molecule.

[00139] A number of selection systems can be used, including but not limited to, systems using the herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, Proc. Natl. Acad. Sci. USA 89:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:8-17) genes in tk-, hgprt- or aprt-cells, 5 respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., 1980, Proc. Natl. Acad. Sci. USA. 77(6):3567-70; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); glutamine synthetase (GS), which is an enzyme responsible for the biosynthesis of glutamine using glutamate and ammonia (Bebbington et al., 1992, Biotechnology 10:169); gpt, which confers resistance to mycophenolic acid 10 (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; May, 1993, TIB TECH 11(5):155-215); and hygro, which 15 confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147). Recombinant DNA technology methods can be applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds.), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., 1981, J. Mol. Biol. 150:1, which are incorporated by 20 reference herein in their entireties. The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3 (Academic Press, New York, 1987)). When a marker in the vector system expressing an antibody or 25 functional fragment thereof is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., 1983, Mol. Cell. Biol. 3:257).

[00140] Once an antibody molecule has been produced by recombinant expression, it can be purified by any suitable method for purification of an immunoglobulin molecule, for example, by 30 chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the subject antibodies or functional fragments thereof can be fused to heterologous polypeptide sequences provided herein or otherwise known in the art to facilitate purification. For example, a subject antibody or functional fragment 35 thereof can be purified through recombinantly adding a poly-histidine tag (His-tag), FLAG-tag, hemagglutinin tag (HA-tag) or myc-tag among others that are commercially available and utilizing suitable purification methods.

[00141] Method of treatment

[00142] In another aspect, provided herein are methods of using the subject antibody or a functional fragment thereof to treat conditions, diseases or disorders implicated by IL-6/IL-6 receptor malfunction.

5 **[00143]** In some embodiments, the present disclosure provides a method of treating an inflammatory disorder in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of an antibody of the present disclosure. In some cases, the inflammatory disorder is multiple sclerosis. In other cases, the inflammatory disorder is an autoimmune disease. Examples of autoimmune diseases include but are not limited to acute 10 disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, Crohn's disease, Diabetes mellitus (type 1), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid 15 arthritis, inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), psoriatic arthritis, systemic lupus erythematosus (SLE), asthma, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, 20 ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thrombosis.

25 **[00144]** In further embodiments, the present disclosure provides a method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of an antibody of the present disclosure. In some cases, the cancer is hepatocellular carcinoma. In other cases, the cancer is acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, 30 retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS related (e.g. Lymphoma and Kaposi's Sarcoma) or Viral-Induced cancer.

35 **[00145]** In still further embodiments, an antibody of the present disclosure is used for the treatment of bursitis, lupus, acute disseminated encephalomyelitis (ADEM), addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, crohn's disease , diabetes mellitus (type 1), goodpasture's syndrome, graves' disease, guillain-barré syndrome (GBS), hashimoto's disease, inflammatory bowel disease, lupus erythematosus, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, ord's thyroiditis,osteoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, reiter's syndrome, takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, wegener's granulomatosis, alopecia universalis,

chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, 5 endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrosis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradenitis, ileitis, iritis, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, 10 vaginitis, vasculitis, or vulvitis.

[00146] In some embodiments, an antibody of the present disclosure is used for the treatment of infection, endotoxic shock associated with infection, arthritis, rheumatoid arthritis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, pelvic inflammatory disease, Alzheimer's Disease, Crohn's disease, ulcerative colitis, irritable bowel

15 syndrome, Castleman's disease, ankylosing spondylitis, dermatomyositis, uveitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme arthritis, meningoencephalitis, immune mediated inflammatory disorders of the central and peripheral nervous system, autoimmune disorders, pancreatitis, trauma from surgery, graft-versus-host disease, transplant rejection, heart disease, bone 20 resorption, burns patients, myocardial infarction, Paget's disease, osteoporosis, sepsis, liver/lung fibrosis, periodontitis, hypochlorhydia, solid tumors (renal cell carcinoma), prostatic and bladder cancers, pancreatic cancer, neurological cancers, and B-cell malignancies (e.g., Casteleman's disease, certain lymphomas, chronic lymphocytic leukemia, and multiple myeloma).

[00147] In some embodiments, the subject to be treated is a mammal, such as a human. In other 25 cases, the mammal is a mouse, a rat, a cat, a dog, a rabbit, a pig, a sheep, a horse, a bovine, a goat, a gerbil, a hamster, a guinea pig, a monkey or any other mammal. Many such mammals may be subjects that are known to the art as preclinical models for certain diseases or disorders, including inflammatory diseases, solid tumors and/or other cancers (e.g., Talmadge et al., 2007 Am. J. Pathol. 170:793; Kerbel, 2003 Canc. Biol. Therap. 2(4 Suppl 1):S134; Man et al., 2007 Canc. Met. Rev. 30 26:737; Cespedes et al., 2006 Clin. TransL Oncol. 8:318).

[00148] In another aspect, the disclosure provides methods of using an antibody of the present disclosure to treat diseases, conditions or disorders in a mammal in conjunction with a second agent. The second agent could be administered together with, before, or after the antibody. In some 35 embodiments, the second agent is an antiviral agent. Antiviral agents include but are not limited to telaprevir, boceprevir, semiprevir, sofosbuvir, daclastavir, asunaprevir, lamivudine, adefovir, entecavir, tenofovir, telbivudine, interferon alpha and PEGylated interferon alpha. In other embodiments, the second agent is an agent that acts to relieve the symptoms of inflammatory

conditions described herein. Anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. NSAIDs include but are not limited to, salicylates, such as acetylsalicylic acid; diflunisal, salicylic acid, and salsalate; propionic acid derivatives, such as ibuprofen; naproxen; dexibuprofen, dexketoprofen, flurbiprofen, oxaprozin, fenoprofen, loxoprofen, 5 and ketoprofen; acetic acid derivatives, such as indomethacin, diclofenac, tolmetin, aceclofenac, sulindac, nabumetone, etodolac, and ketorolac; enolic acid derivatives, such as piroxicam, lornoxicam, meloxicam, isoxicam, tenoxicam, phenylbutazone, and droxicam; anthranilic acid derivatives, such as mefenamic acid, flufenamic acid, meclofenamic acid, and tolfenamic acid; selective COX-2 inhibitors, such as celecoxib, lumiracoxib, rofecoxib, etoricoxib, valdecoxib, firocoxib, and parecoxib; 10 sulfonanilides, such as nimesulide; and others such as clonixin, and licofelone. Corticosteroids include but are not limited to, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone.

[00149] In some embodiments, the second agent is an immunosuppressant. The immunosuppressants that can be used in combination with the subject antibody include but are not limited to

15 hydroxychloroquine, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab, D-penicillamine, oral gold compound, injectable gold compound (intramuscular injection), minocycline, sodium gold thiomalate, auranofin, D-penicillamine, lobenzarit, bucillamine, actarit, cyclophosphamide, azathioprine, methotrexate, mizoribine, cyclosporine, and tacrolimus.

[00150] In further embodiments, the second agent is an anti-cancer agent (e.g. a chemotherapeutic

20 agent). The chemotherapeutic can be selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples of chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules include Gleevec® (Imatinib Mesylate), Velcade®

25 (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine,

30 triethylenephosphoramide, triethylenethiophosphoramide and trimethylololomelamine; nitrogen mustards such as chlorambucil, chloraphazine, chlophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin,

35 authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins,

mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, 5 thiamiprime, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; 10 defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside 15 ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for 20 example tamoxifen, (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; 25 vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the subject antibody or fragment thereof can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin[®], Avastin[®], Erbitux[®], Rituxan[®], Taxol[®], Arimidex[®], Taxotere[®], ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 30 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Bircodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, 35 Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan,

Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, 5 ZD6126, and Zosuquidar.

[00151] The specific dose will vary depending on the particular antibody chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried. In some 10 embodiments, an antibody is administered to a subject within a range of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70 mg per week on average over the course of a treatment cycle. For example, the antibody is administered to a subject within a range of about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 15 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55 mg per week. In some embodiments, the antibody is administered to a subject within a range of about 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55 mg per week.

[00152] In some embodiments, an antibody is administered to a subject in an amount greater than 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 mg per day on average over the course of a treatment cycle. For example, the antibody is administered to a subject in an amount 20 between about 6 and 10 mg, between about 6.5 and 9.5 mg, between about 6.5 and 8.5 mg, between about 6.5 and 8 mg, or between about 7 and 9 mg per day on average over the course of a treatment cycle.

[00153] In some embodiments, an antibody is administered to a subject within a range of about 0.01mg/kg-50mg/kg per day, such as about, less than about, or more than about, 0.01 mg/kg, 0.02 25 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1mg/kg, 0.2mg/kg, 0.3mg/kg, 0.4mg/kg, 5mg/kg, 6mg/kg, 7mg/kg, 8mg/kg, 9mg/kg, 10mg/kg, 11mg/kg, 12mg/kg, 13mg/kg, 14mg/kg, 15mg/kg, 16mg/kg, 17mg/kg, 18mg/kg, 19mg/kg, 20mg/kg, 25mg/kg, 30mg/kg, 35mg/kg, 40mg/kg, 45mg/kg, or 50mg/kg per day. In some embodiments, an antibody is administered to a subject within a range of about 0.1mg/kg-400mg/kg per week, such as 30 about, less than about, or more than about 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1mg/kg, 5mg/kg, 10mg/kg, 15mg/kg, 20mg/kg, 25mg/kg, 30mg/kg, 35mg/kg, 40mg/kg, 45mg/kg, 50mg/kg, 100mg/kg, 150mg/kg, 200mg/kg, 250mg/kg, 300mg/kg, 350mg/kg, or 400mg/kg per week. In some embodiments, an antibody is administered to a subject within a range of about 0.4mg/kg-1500mg/kg per month, such as about, less than about, or 35 more than about 0.4 mg/kg, 0.5 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50mg/kg, 100mg/kg, 150mg/kg, 200mg/kg, 250mg/kg, 300mg/kg, 350mg/kg, 400mg/kg, 450mg/kg, 500mg/kg, 550mg/kg, 600mg/kg, 650mg/kg, 700mg/kg,

750mg/kg, 800mg/kg, 850mg/kg, 900mg/kg, 950mg/kg, or 1000mg/kg per month. In some embodiments, an antibody is administered to a subject within a range of about 0.1mg/m²-200mg/m² per week, such as about, less than about, or more than about 1 mg/m², 5mg/m², 10mg/m², 15mg/m², 20mg/m², 25mg/m², 30mg/m², 35mg/m², 40mg/m², 45mg/m², 50mg/m², 55mg/m², 60mg/m², 65mg/m²,

5 70mg/m², 75mg/m², 100mg/m², 125mg/m², 150mg/m², 175mg/m², or 200mg/m² per week. The target dose may be administered in a single dose. Alternatively, the target dose may be administered in about or more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, or more doses. For example, a dose of about 1mg/kg per week may be delivered weekly at a dose of about 1mg/kg every week, about 2 mg/kg administered every two weeks, or about 4mg/kg
10 administered every four weeks over the course of the week. The administration schedule may be repeated according to any regimen as described herein, including any administration schedule described herein. In some embodiments, an antibody is administered to a subject in the range of about 0.1mg/m²-500mg/m², such as about, less than about, or more than about 1mg/m², 5mg/m², 10
mg/m², 15mg/m², 20mg/m², 25mg/m², 30mg/m², 35mg/m², 40mg/m², 45mg/m², 50mg/m², 55mg/m²,
15 60mg/m², 65mg/m², 70mg/m², 75mg/m², 100mg/m², 130mg/m², 135mg/m², 155mg/m², 175mg/m²,
200mg/m², 225mg/m², 250mg/m², 300mg/m², 350mg/m², 400mg/m², 420mg/m², 450mg/m², or
500mg/m².

[00154] A dose of the antibody may be about, at least about, or at most about 0.1, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225,
25 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725,
750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000 mg or mg/kg, or any range derivable therein. It
is contemplated that a dosage of mg/kg refers to the mg amount of antibody per kg of total body
weight of the subject. It is contemplated that when multiple doses are given to a patient, the doses
may vary in amount or they may be the same.

25 **[00155]** Pharmaceutical composition

[00156] In another aspect, provided herein are pharmaceutical compositions comprising the subject antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, excipient, or stabilizer including but not limited to inert solid diluents and fillers, diluents, sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. (Remington's
30 Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)).

[00157] The subject pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. Suitable examples of sustained release
35 preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or

poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. Some 5 sustained release formulations enable release of molecules over a few weeks to a few months, or even up to a few years. In some embodiments, the subject pharmaceutical composition release the subject antibody as described herein for at least a few weeks, such as for at least 1 week, 2 weeks, 3 weeks or 4 weeks. In further embodiments, the subject pharmaceutical composition release the subject antibody as described herein over a few months, such as for at least 1 month, 2 months, 3 months, 4 10 months, 5 months, or 6 months.

[00158] The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition can further comprise an antibody or a functional fragment thereof as an active ingredient and may include a conventional pharmaceutical carrier or excipient. Further, it may include other medicinal or pharmaceutical agents, 15 carriers, adjuvants, etc.

[00159] Exemplary parenteral administration forms include solutions or suspensions of active polypeptide and/or PEG-modified polypeptide in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered with salts such as histidine and/or phosphate, if desired.

[00160] In some embodiments, the disclosure provides a pharmaceutical composition for injection containing a subject antibody or a functional fragment thereof and a pharmaceutical excipient suitable for injection. Example components and amounts of agents in such compositions are as described herein.

[00161] The forms in which the compositions of the present disclosure may be incorporated for 25 administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00162] Aqueous solutions in saline can be used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and 30 vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00163] Sterile injectable solutions can be prepared by incorporating an antibody of the present disclosure or functional fragment thereof in the desired amount in the appropriate solvent with various other ingredients as enumerated above, followed by filtered sterilization. Generally, dispersions are 35

prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and other ingredients. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient 5 from a previously sterile-filtered solution thereof.

[00164] In some embodiments, the disclosure provides a pharmaceutical composition for oral administration containing an antibody of the present disclosure or a functional fragment thereof, and a pharmaceutical excipient suitable for oral administration.

[00165] In some embodiments, a solid pharmaceutical composition for oral administration is provided 10 herein containing: (i) an effective amount of an antibody of the present disclosure or a functional fragment thereof; optionally (ii) an effective amount of a second agent; and (iii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains: (iv) an effective amount of a third agent.

[00166] In some embodiments, the pharmaceutical composition is a liquid pharmaceutical 15 composition suitable for oral consumption. Pharmaceutical compositions suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods 20 of pharmacy, and typically include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

[00167] This disclosure further encompasses anhydrous pharmaceutical compositions and dosage 25 forms comprising an active ingredient, since water can facilitate the degradation of some polypeptides. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions.

30 Pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary 35 kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00168] An antibody of the present disclosure can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual

5 pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of
10 lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00169] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its
15 derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00170] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline
20 cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00171] Disintegrants may be used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter
25 the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to
30 about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

35 [00172] Lubricants which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate,

talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof.

Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight

5 percent of the pharmaceutical composition.

[00173] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

10 **[00174]** The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or 15 as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00175] Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be

20 employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00176] Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those

25 compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10.

However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

30 **[00177]** Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00178] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00179] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine,

10 lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

15 [00180] Hydrophilic non-ionic surfactants may include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; 20 polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; 25 polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00181] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30

cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose

5 monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00182] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and 10 sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic 15 transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00183] In one embodiment, the composition includes a solubilizer to ensure good solubilization and/or dissolution of the compound and to minimize precipitation of the compound. This can be 20 especially advantageous for compositions for non-oral use, e.g., compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00184] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and 25 polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of 30 polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurool) or methoxy PEG ; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and 35 polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ -caprolactone and isomers thereof, δ -valerolactone and isomers thereof, β -butyrolactone and isomers thereof; and other solubilizers known in the art, such as

dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00185] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-

5 hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurool, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurool and propylene glycol.

[00186] The amount of solubilizer that can be included is not particularly limited. The amount of a 10 given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a subject using conventional 15 techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00187] The composition can further include one or more pharmaceutically acceptable additives and 20 excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00188] In addition, an acid or a base may be incorporated into the composition to facilitate 25 processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, 30 triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic 35 acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate,

disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

5 [00189] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

10

[00190] In another aspect of the disclosure, provided are kits comprising the unit doses containing the antibody compositions of the disclosure and instructions for use. The kit can further comprise one or more unit doses containing one or more additional reagents, such as an immunosuppressive reagent, a cytotoxic agent or a radiotoxic agent as described above, or one or more additional antibodies as described herein (e.g., a human antibody having a complementary activity which binds to an epitope in the antigen distinct from a first human antibody). Kits typically include a label indicating the intended use of the contents of the kit. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

20 [00191] A kit of the present disclosure may also include diagnostic agents and/or other therapeutic agents. In one embodiment, a kit includes an antibody of the present disclosure and a diagnostic agent that may be used in a diagnostic method for diagnosing the state or existence of a disease, condition or disorder in a subject as described herein.

EXAMPLES

[00192] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

35 **Example 1: Binding Affinity Assay of Antibodies**

[00193] All SPR measurements were performed on a **BIAcore** 3000 instrument (GE Biosciences, Piscataway, N.J.). **BIAcore** Software-**BIAcore** 3000 Control Software V3.2 was used for the

operation and control of the **BIAcore** 3000 instrument. BiaEvaluation Software V4.1 was used for the analysis of SPR data from the **BIAcore** 3000 instrument and data was plotted using Graph Pad Prism Software Version 5. The binding affinity of antibodies to IL-6R was measured in HBS-EP buffer (10 mM HEPES, 150 mM NaCl, 3.4 mM EDTA, 0.005% P20) at 25°C. The flow rate for the affinity 5 study was 30 μ L/minute. The indicated antibodies were used as the ligand for the construction of the reference channel of the chip. Analyte (sIL-6R; SBH Sciences, Natick, MA 01760 USA) binding to the immobilized ligand was measured and the concentration of the sIL-6R is from 1.2 to 100 nM (3x dilution). Each sample was injected for 3 min at a flow rate of 30 μ L/min to allow for binding to chip-bound antibody. Next, binding buffer without analyte was sent over the chip at the same flow rate to 10 allow for dissociation of bound analyte. After 500s, remaining bound analyte was removed by injecting regeneration solution (1M Formic acid). Data was analyzed by using the Kinetics Wizard and the manual fitting programs that are both included with the BiaEvaluation Software V4.1. The k_a , k_d , K_D and the affinity relative to Tocilizumab (sample #25) are shown in Table 2.

Table 1-1. Binding Affinity of Exemplary Antibodies

Sample #	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative Affinity
25(control)	1.88E+05	2.52E-04	1.34E-09	1
1	2.44E+05	1.01E-04	4.13E-10	3.2
2	1.97E+05	8.51E-05	4.32E-10	3.1
3	2.13E+05	5.80E-05	2.73E-10	4.9
5	2.66E+05	2.34E-04	8.82E-10	1.5
6	2.33E+05	6.22E-05	2.67E-10	5.0
7	2.32E+05	1.77E-04	7.63E-10	1.8
8	2.70E+05	2.41E-04	8.93E-10	1.5
9	2.39E+05	5.94E-05	2.49E-10	5.4
11	2.75E+05	2.38E-05	8.63E-11	15.5
12	2.89E+05	8.32E-05	2.88E-10	4.6
13	2.69E+05	1.00E-04	3.73E-10	3.6
14	3.14E+05	5.69E-05	1.81E-10	7.4
15	3.10E+05	4.49E-05	1.45E-10	9.2
16	2.96E+05	4.04E-05	1.36E-10	9.8
17	2.87E+05	8.71E-05	3.04E-10	4.4
18	3.35E+05	4.73E-05	1.41E-10	9.5
20	2.10E+05	1.58E-04	7.51E-10	1.8
24	2.54E+05	7.13E-05	2.81E-10	4.8
26	2.43E+05	1.02E-04	4.20E-10	3.2
27	3.39E+05	3.46E-05	1.02E-10	13.1

28	2.84E+05	7.61E-05	2.68E-10	5.0
29	4.17E+05	3.99E-05	9.57E-11	14.0
30	2.99E+05	7.03E-05	2.35E-10	5.7
31	2.92E+05	2.92E-05	1.00E-10	13.4

Table 2-2. Binding Affinity of Exemplary Antibodies

Sample #	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative Affinity
25(control)	2.07E+05	3.53E-04	1.71E-09	1
1	2.29E+05	6.76E-05	2.95E-10	5.8
2	2.00E+05	1.17E-04	5.85E-10	2.9
3	2.04E+05	8.87E-05	4.35E-10	3.9
6	2.19E+05	8.10E-05	3.70E-10	4.6
9	1.96E+05	6.28E-05	3.20E-10	5.3
11	2.76E+05	3.08E-05	1.12E-10	15.3
12	3.02E+05	1.26E-04	4.18E-10	4.1
14	3.74E+05	9.75E-05	2.61E-10	6.6
15	2.98E+05	5.97E-05	2.34E-10	8.6
16	3.36E+05	6.30E-05	1.87E-10	9.1
17	3.31E+05	1.17E-04	3.54E-10	4.8
18	3.25E+05	5.42E-05	1.67E-10	10.2
24	2.52E+05	7.99E-05	3.17E-10	5.4
27	3.39E+05	4.27E-05	1.26E-10	13.6
28	3.63E+05	1.48E-04	4.08E-10	4.2
29	4.40E+05	5.37E-05	1.22E-10	14.0
30	3.27E+05	8.33E-05	2.55E-10	6.7
31	3.85E+05	5.99E-05	1.56E-10	11.0
35	2.25E+05	1.46E-04	6.48E-10	2.6
45	1.75E+05	1.06E-04	6.05E-10	2.8

Table 2-3. Binding Affinity of Exemplary Antibodies

Sample #	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative Affinity
25(control)	1.22E+05	3.49E-04	2.85E-09	1
49	1.32E+05	2.18E-04	1.65E-09	1.7
50	1.44E+05	1.02E-04	7.07E-10	4.0
51	1.36E+05	5.72E-05	4.20E-10	6.8

56	2.30E+05	5.59E-05	2.43E-10	11.7
57	2.45E+05	2.41E-05	9.84E-11	29.0
58	2.58E+05	2.67E-05	1.03E-10	27.7
60	2.24E+05	4.59E-05	2.05E-10	13.9
61	2.38E+05	1.29E-05	5.44E-11	52.4
62	2.56E+05	6.61E-06	2.58E-11	110.5
64	2.14E+05	2.85E-05	1.33E-10	21.4
66	2.39E+05	3.38E-05	1.41E-10	20.2
68	2.91E+05	8.60E-06	2.96E-11	96.3
201	2.18E+05	1.47E-05	6.74E-11	42.3
202	8.53E+04	2.46E-06	2.88E-11	99.0
203	9.50E+04	3.17E-05	3.34E-10	8.5
204	2.29E+05	3.28E-06	1.43E-11	199.3
205	1.75E+05	2.14E-06	1.22E-11	233.6
206	1.89E+05	1.41E-07	7.50E-13	3800.0
208	2.21E+05	2.79E-05	1.26E-10	22.6

Table 2-4. Binding Affinity of Exemplary Antibodies

Sample #	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative Affinity
25(control)	1.08E+05	3.41E-04	3.16E-09	1
52	1.07E+05	1.99E-04	1.86E-09	1.7
54	1.99E+05	1.39E-05	6.97E-11	45.3
55	1.87E+05	7.24E-05	3.87E-10	8.2
59	1.72E+05	4.86E-05	2.83E-10	11.2
69	1.45E+05	4.14E-05	2.86E-10	11.0
209	2.04E+05	1.37E-07	6.69E-13	4723.5
214	1.27E+05	4.69E-05	3.69E-10	8.7
215	1.57E+05	1.61E-04	1.03E-09	3.1
216	1.45E+05	2.66E-04	1.83E-09	1.7
217	1.88E+05	1.09E-04	5.81E-10	5.4
218	1.07E+05	6.63E-05	6.21E-10	5.1
219	1.21E+05	5.96E-05	4.91E-10	6.4
220	1.31E+05	6.34E-05	4.83E-10	6.5
221	1.36E+05	9.01E-05	6.63E-10	4.8
222	1.28E+05	3.66E-05	2.86E-10	11.0

223	1.33E+05	4.91E-05	3.68E-10	8.6
224	1.60E+05	7.99E-05	5.00E-10	6.3
225	1.63E+05	1.05E-04	6.45E-10	4.9
226	1.56E+05	1.60E-05	1.02E-10	31.0
227	1.44E+05	6.90E-05	4.77E-10	6.6
228	1.49E+05	3.04E-05	2.04E-10	15.5
229	1.24E+05	7.49E-05	6.05E-10	5.2
230	1.37E+05	6.15E-05	4.48E-10	7.1
231	1.32E+05	1.48E-07	1.12E-12	2821.4
232	1.51E+05	4.81E-05	3.19E-10	9.9
233	1.49E+05	5.75E-05	3.87E-10	8.2
234	1.54E+05	5.69E-05	3.70E-10	8.5
235	1.28E+05	3.81E-05	2.97E-10	10.6
236	1.85E+05	1.53E-05	8.29E-11	38.1
237	1.66E+05	1.01E-05	6.05E-11	52.2
238	1.35E+05	1.50E-05	1.11E-10	28.5
239	1.44E+05	2.36E-05	1.64E-10	19.3
240	1.54E+05	2.30E-05	1.50E-10	21.1
241	1.79E+05	3.61E-05	2.02E-10	15.6
242	7.02E+04	8.71E-05	1.24E-09	2.6
243	7.10E+04	1.94E-05	2.73E-10	11.6
244	1.40E+05	2.33E-05	1.66E-10	19.0
245	1.41E+05	3.53E-05	2.50E-10	12.6
246	1.25E+05	9.86E-06	7.89E-11	40.1

Table 2-5. Binding Affinity of Exemplary Antibodies

Sample #	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative Affinity
25(control)	1.25E+05	3.50E-04	2.80E-09	1
202	1.34E+05	3.17E-06	2.36E-11	118.6
206	2.30E+05	1.35E-07	5.87E-13	4770.0
247	1.67E+05	3.54E-05	2.12E-10	13.2
248	9.12E+04	1.73E-05	1.89E-10	14.8
249	1.41E+05	3.39E-05	2.41E-10	11.6
250	2.62E+05	9.27E-05	3.54E-10	7.9
251	1.73E+05	1.40E-04	8.05E-10	3.5

252	1.52E+05	2.44E-05	1.60E-10	17.5
253	1.76E+05	2.73E-05	1.55E-10	18.1

Example 2: Determination of pH Dependence of the Binding Affinity for IL-6R

[00194] SPR measurements at pH 7.4 and pH 6.0 were performed in parallel and K_D values calculated according to the protocol as detailed in Example 1. The pH dependence is calculated as the ratio

5 between the K_D value at pH 6.0 and the K_D value at pH 7.4, which indicates the fold of affinity decrease from the pH7.4 to pH6.0. If the pH dependence of a subject antibody described herein is over 1, it means that the antibody binds to IL-6R in such a pH-dependent manner that its binding to IL-6R at pH7.4 is higher than at pH6.0. If the pH dependence of a subject antibody described herein is lower than 1, it means that the antibody binds to IL-6R in such a pH-dependent manner that its 10 binding to IL-6R at pH6.0 is higher than at pH7.4. Two batches of SPR measurements were performed on antibodies #202, #205, and #206 and antibodies #209, #231, and #237, and antibody #25 was used as a reference antibody in both batches. The KD values obtained is provided below in Tables 3-1 to 3-2, respectively. pH dependence thus determined by comparing the binding affinity at pH 7.4 and that at pH 6.0 is provided in Table 3-3. It can be seen from Table 3-3 below that the 15 indicated antibodies have a much higher pH dependence than Tocilizumab, indicating a more significant decrease in binding affinity from pH7.4 to pH6.0, and thus superior properties in terms of antigen neutralization and clearance.

Table 3-1. Binding Affinity of Exemplary Antibodies

Sample	pH 7.4			pH 6.0		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
25(control)	1.22E+05	3.49E-04	2.85E-09	2.83E+05	5.64E-04	2.00E-09
202	8.53E+04	2.46E-06	2.88E-11	2.84E+05	6.10E-06	2.14E-11
205	1.75E+05	2.14E-06	1.22E-11	3.84E+05	2.15E-05	5.60E-11
206	1.89E+05	1.41E-07	7.50E-13	4.12E+05	8.78E-06	2.13E-11

20

Table 3-2. Binding Affinity of Exemplary Antibodies

Sample	pH 7.4			pH 6.0		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
25(control)	1.08E+05	3.41E-04	3.16E-09	3.16E+05	5.66E-04	1.79E-09
209	2.04E+05	1.37E-07	6.69E-13	6.83E+05	2.99E-05	4.38E-11
231	1.32E+05	1.48E-07	1.12E-12	2.91E+05	3.10E-05	1.07E-10
237	1.66E+05	1.01E-05	6.05E-11	2.92E+05	4.62E-05	1.59E-10

Table 1. Summary of pH Dependence of Exemplary Antibodies

Sample #	pH dependence (Fold of affinity decrease)
25 (control)	0.48* **
202	0.74*
205	4.59
206	28.4
209	65.47
231	95.54
237	2.63

*pH dependence of lower than 1 means the affinity at pH 6.0 is higher than the affinity at pH7.4.

** Value averaged between the two batches.

5 Example 3: Evaluation of IL-6 Receptor Neutralizing Activity

[00195] After two washes with PBS, DS-1 cells (ATCC Accession No. CRL 11102) were suspended in RPMI1640 containing 10% FBS (feeding without IL6), cultured at 37°C for 18 hours. The cell suspensions were dispensed 25,000 cells/90µl/well at 96-well plate (Corning), then added 8µl/well (1.25mg/mL) of the indicated antibody to arrive at a final concentration of 100µg/mL. The 10 suspension was then cultured at 37°C for 6 hours. IL6 of 3 concentrations with the highest final concentration at 250ng/mL (5x dilution) was added, and the suspension was then cultured at 37°C for 72 hours. MTS (Promega) and PMS were mixed at the ratio of 20:1, added 20µl/well, and then 15 incubated at 37°C for 4 hours. Absorbance at 490nm was recorded using Multiskan Fc (Thermo). As shown in Figs. 2A and 2B, some representative antibodies significantly inhibited the proliferation of DS-1 cells.

Example 4: Evaluation of Inhibition% and IC₅₀ for representative antibodies in DS-1 cells

[00196] After two washes with PBS, DS-1 cells were suspended in RPMI1640 containing 10% FBS (feeding without IL6), cultured at 37°C for 18 hours. The cell suspensions were dispensed 25,000 cells/90µl/well at 96-well plate (Corning), then added 8µl/well anti-IL6R-mAb at 4-fold dilutions 20 over 9 concentrations with highest concentration at 100µg/mL, cultured at 37°C for 6 hours. IL6 and controls were added 2µl/well with final concentration at 2ng/mL, cultured at 37°C for 72 hours. Mixed MTS (Promega) and PMS at the ratio of 20:1, added 20µl/well, incubated at 37°C for 4 hours. Record the absorbance at 490nm using Multiskan Fc (Thermo). Inhibition% curves for some 25 representative antibodies are shown in Figs. 3A and 3B. IC₅₀ values are calculated and provided below.

Table 1. Binding Affinity of Exemplary Antibodies

Sample #	IC ₅₀ (μg/ml)
25#	0.32965
57#	0.06383
58#	0.06966
202#	0.06863
204#	0.03615
206#	0.0339

[00197] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

SEQUENCES LISTING

Seq ID No.:	SEQUENCE
1	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
2	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTISSLQP EDIATYYCQQ GNRLPYTFGQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGEc
3	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARVL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
4	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTISSLQP EDIATYYCQQ GNRLPYTFGQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGEc
5	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
6	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKNTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPGN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
7	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
8	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG

		51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
9		1 QVQLQESGPG LVRPSQTL 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STEGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
10		1 QVQLQESGPG LVRPSQTL 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAIDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
11		1 QVQLQESGPG LVRPSQTL 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
12		1 QVQLQESGPG LVRPSQTL 51 YISYSGITTY NASLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
13		1 QVQLQESGPG LVRPSQTL 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
14		1 QVQLQESGPG LVRPSQTL 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLT 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWE 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG

	351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
15	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
16	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
17	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
18	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
19	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
20	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
21	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKNTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY

	201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
22	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
23	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
24	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
25	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
26	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
27	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
28	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG

		51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
29		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARLTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
30		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
31		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARRTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
32		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 RISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
33		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 HISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARR 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
34		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 HISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV

	351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
35	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARTL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
36	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARNL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
37	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
38	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NASLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
39	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
40	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
41	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY

	201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
42	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
43	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
44	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
45	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
46	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
47	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNKA TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
48	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG

		51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
49		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAMDYWG QGSLVIVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
50		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
51		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
52		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
53		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAIDYFG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
54		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV

	351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
55	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARITAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
56	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
57	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
58	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 FISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
59	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
60	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
61	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY

	201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
62	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
63	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
64	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
65	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
66	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
67	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
68	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG

		51 YISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
69		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARMTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
70		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
71		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGITTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARTL 101 ARMTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
72		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARTL 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
73		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARTL 101 ARTTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWEESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
74		1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMTTY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVSVLTW LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV

	351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
75	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARTL 101 ARMTAIDFWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
76	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARATAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
77	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
78	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARS 101 ARITAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHPKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 301 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
79	1 DIQMTQSPSS LSASVGDRVT ITCRASHDIS SYLNWYQQKP GKAPKLLIY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTLPYTFQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWK 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGE C
80	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYPNWYQQKP GKAPKLLIY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTLPYTFQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWK 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGE C
81	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTLPYTFQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWK 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGE C
82	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIY 51 TSRLYSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTLPYTFQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWK 151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGE C
83	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIY 51 TSRLQSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTLPYTFQ

	101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
84	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHPGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTPYTFQG 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
85	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTPYTFQG 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
86	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GDTPYTFQG 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
87	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTPYNFGQ 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
88	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLRSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNTPYTFQG 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
89	1 QVQLQESGPG LVRPSQTL SL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG 51 YISYSGMITY NPSLKSRTVM LRDTSKNQFS LRLSSVTAAD TAVYYCARCL 101 ARMTAIDFWG QGSLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 201 ICNVNHKPSN TKVDKKVEPK SCDKHTCPP CPAPELLGGP SVFLFPPKPK 251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAAK TKPREEQYNS 301 TYRUVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 351 YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPPVL 401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG
90	1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY 51 TSRLHSGVPS RFSGSGSGTD FFTTISSLQP EDIATYYCQQ GNRLPYTFQG 101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLNNFY PREAKVQWKV 151 DNALQSGNSQ ESVTEQDSKD STYSLSSLT LSKADYEKHK VYACEVTHQG 201 LSSPVTKSFN RGECA
91	1 LAPRRCPAQE VARGVLTSLP GDSVLTCPG VEPEDNATVH WVLRKPAAGS 51 HPSRWAGMGR RLLLRSQLH DSGNYSCYRA GRPAGTVHLL VDVPPEPQL 101 SCFRKSPLSN VVCEWGPRST PSLTTKAVLL VRKFQNPAE DFQEPCQYSQ 151 ESQKFSCQLA VPEGDSSFYI VSMCVASSVG SKFSKTQTFQ GCGILQPDPP 201 ANITVTAVAR NWRWLSVTWQ DPHSWNSSFY RLRFELRYRA ERSKTFITWM 251 VKDLQHHCVI HDAWSGLRHV VQLRAQEEFG QGEWSEWSPE AMGTPWTESR 301 SPPAENEVST PMQALTTNKD DDNILFRDSA NATSLPVQDS SSVPLP

CLAIMS

WHAT IS CLAIMED IS:

1. An antibody, wherein the antibody:

(a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90;

(b) exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 1 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91; and

(c) does not contain (a) SEQ ID NO. 3 and SEQ ID NO. 4, and (b) SEQ ID NO. 1 and SEQ ID NO. 2.

2. The antibody of claim 1, wherein the heavy chain comprises an amino acid with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to SEQ ID NO. 26.

3. The antibody of claim 1, wherein the light chain comprises an amino acid with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to SEQ ID NO. 4.

35 4. The antibody of claim 1, wherein the heavy chain comprises an amino acid with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to SEQ ID NO. 28, and wherein the light chain comprises an amino acid with about or greater

than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to SEQ ID NO. 4.

5. The antibody of claim 1, wherein the antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.1 nM or less as determined by surface plasmon resonance at 37°C, wherein
5 the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

6. The antibody of claim 1, wherein the antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.05 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

7. The antibody of claim 1, wherein the antibody exhibits a binding affinity (K_D) for human
10 IL-6 receptor (IL-6R) of 0.01 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

8. The antibody of claim 1, wherein the antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.005 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

15 9. The antibody of claim 1, wherein the antibody exhibits a binding affinity (K_D) for human IL-6 receptor (IL-6R) of 0.001 nM or less as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

10. An antibody, wherein the antibody:

(a) comprises a heavy chain and a light chain, wherein the heavy chain comprises an
20 amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID

NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90;

(b) exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than the affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2; and

(c) does not contain SEQ ID NO. 3 and SEQ ID NO. 4.

11. The antibody of claim 10, wherein the heavy chain comprises an amino acid of SEQ ID NO. 26.

12. The antibody of claim 10, wherein the light chain comprises an amino acid of SEQ ID

10 NO. 4.

13. The antibody of claim 10, wherein the heavy chain comprises an amino acid of SEQ ID NO. 28, and wherein the light chain comprises an amino acid of SEQ ID NO. 4.

14. The antibody of any of claims 10-13, wherein the binding affinity (K_D) for IL-6 receptor (IL-6R) is determined by surface plasmon resonance at 37°C.

15 15. The antibody of claim 10, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.1 nM or less as determined by surface plasmon resonance at 37°C.

16. The antibody of claim 10, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.05 nM or less as determined by surface plasmon resonance at 37°C.

20 17. The antibody of claim 10, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.01 nM or less as determined by surface plasmon resonance at 37°C.

18. The antibody of claim 10, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.005 nM or less as determined by surface plasmon resonance at 37°C.

19. The antibody of claim 10, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.001 nM or less as determined by surface plasmon resonance at 37°C.

25 20. The antibody of any of claims 10 to 19, wherein the IL-6 receptor is human IL-6 receptor.

21. The antibody of any of claims 10 to 19, wherein the IL-6 receptor has an amino acid sequence shown in SEQ ID NO. 91.

22. An antibody comprising a heavy chain and a light chain, wherein:

30 (a) the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) that is greater than an affinity of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4; and

(b) the antibody inhibits proliferation of DS-1 cells by at least 40% after 72 hours at a concentration of 0.032 μ g/mL or less in an MTS cell-proliferation assay.

35 23. The antibody of claim 22, wherein the heavy chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID

NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, 5 SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, 10 SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, wherein the light chain comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identify to a sequence 15 selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90.

24. The antibody of claim 22, wherein the heavy chain comprises an amino acid sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, 30 SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89.

25. The antibody of claim 22, wherein the light chain comprises an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90.

35 26. The antibody of claim 22, wherein the heavy chain comprises an amino acid sequence selected from SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ

ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39,

5 SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, 10 SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, and SEQ ID NO. 89, and wherein the light chain comprises an amino acid sequence selected from SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, and SEQ ID NO. 90.

15 27. The antibody of claim 22, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.1 nM or less as determined by surface plasmon resonance at 37°C.

28. The antibody of claim 22, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.05 nM or less as determined by surface plasmon resonance at 37°C.

29. The antibody of claim 22, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.01 nM or less as determined by surface plasmon resonance at 37°C.

30. The antibody of claim 22, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.005 nM or less as determined by surface plasmon resonance at 37°C.

31. The antibody of claim 22, wherein the antibody exhibits a binding affinity (K_D) for IL-6 receptor (IL-6R) of 0.001 nM or less as determined by surface plasmon resonance at 37°C.

25 32. The antibody of any of claims 22 to 31, wherein the IL-6 receptor is human IL-6 receptor.

33. The antibody of any of claims 22 to 31, wherein the IL-6 receptor has an amino acid sequence shown in SEQ ID NO. 91.

34. An antibody comprising a heavy chain and a light chain, wherein:

30 (a) the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1; and/or

(b) the light chain comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO. 2; and

(c) the antibody comprises an amino acid sequence with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to an

35 antibody comprising a heavy chain of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20,

SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 29, SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 40, SEQ ID NO. 41, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, 5 SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 56, SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 71, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, 10 SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, SEQ ID NO. 78, or SEQ ID NO. 89 and a light chain of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 81, SEQ ID NO. 82, SEQ ID NO. 83, SEQ ID NO. 84, SEQ ID NO. 85, SEQ ID NO. 86, SEQ ID NO. 87, SEQ ID NO. 88, or SEQ ID NO. 90.

35. The antibody of claim 34, wherein the heavy chain comprises two or more mutations at

15 positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1.

36. The antibody of claim 34, wherein the heavy chain comprises three or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1.

37. The antibody of claim 34, wherein the heavy chain comprises four or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1.

20 38. The antibody of claim 34, wherein the heavy chain comprises five or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1.

39. The antibody of any of claims 34 to 39, wherein the mutation at position 51 of the heavy chain is selected from the group consisting of from Y to F, from Y to R, from Y to W and from Y to K.

25 40. The antibody of any of claims 34 to 40, wherein the mutation at position 57 of the heavy chain is from I to M.

41. The antibody of any of claims 34 to 41, wherein the mutation at position 58 of the heavy chain is selected from the group consisting of from T to I and from T to M.

30 42. The antibody of any of claims 34 to 42, wherein the mutation at position 99 of the heavy chain is selected from the group consisting of from S to C, from S to T, from S to N, and from S to V.

43. The antibody of any of claims 34 to 43, wherein the mutation at position 103 of the heavy chain is selected from the group consisting of from T to I, from T to A, from T to G, from T to L, from T to M, from T to Y, and from T to R.

35 44. The antibody of any of claims 34 to 44, wherein the mutation at position 106 of the heavy chain is from M to I.

45. The antibody of any of claims 34 to 45, wherein the mutation at position 116 of the heavy chain is from T to I.

46. The antibody of any of claims 34 to 46, wherein the light chain comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO: 2.

47. The antibody of any of claims 34 to 47, wherein the mutation at position 89 is from Q to G with respect to SEQ ID NO: 2.

5 48. The antibody of any of claims 34 to 48, wherein the mutation at position 93 is from T to R with respect to SEQ ID NO: 2.

49. The antibody of claim 34, wherein the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1, and wherein the light chain comprises a mutation at position 89 with respect to SEQ ID NO: 2.

10 50. The antibody of claim 34, wherein the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1, and wherein the light chain comprises a mutation at position 93 with respect to SEQ ID NO: 2.

51. The antibody of claim 34, wherein the heavy chain comprises one or more mutations at positions 51, 57, 58, 99, 103, 106, and 116 with respect to SEQ ID NO. 1, and wherein the light chain 15 comprises one or more mutations at positions 89 and 93 with respect to SEQ ID NO: 2.

52. An antibody comprising a heavy chain and a light chain, wherein:

(a) the heavy chain comprises one or more mutations with respect to SEQ ID NO. 1, wherein residue 57 is mutated to methionine (M);

20 (b) the light chain comprises an amino acid sequence having at least 90% sequence identify to SEQ ID NO. 4 or SEQ ID NO. 2, or both; and

(c) the antibody exhibits a binding affinity (K_D) for human IL-6R of 1 nM or less, as determined by surface plasmon resonance at 37°C, wherein the IL-6R has as an amino acid sequence shown in SEQ ID No. 91.

53. The antibody of claim 53, wherein the heavy chain comprises an amino acid sequence 25 with about or greater than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% and 100% sequence identity to a sequence selected from SEQ ID NO. 23, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 37, SEQ ID NO. 42, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 46, SEQ ID NO. 47, SEQ ID NO. 48, SEQ ID NO. 49, SEQ ID NO. 50, SEQ ID NO. 51, SEQ ID NO. 52, SEQ ID NO. 53, SEQ ID NO. 54, SEQ ID NO. 55, 30 SEQ ID NO. 57, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 61, SEQ ID NO. 62, SEQ ID NO. 63, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 69, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 77, and SEQ ID NO. 78.

35 54. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of binding affinity for IL-6R higher than 5, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0.

55. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of binding affinity for IL-6R higher than 10, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0.

5 56. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of binding affinity for IL-6R higher than 15, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0.

57. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of binding affinity for IL-6R higher than 20, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0.

10 58. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of the binding affinity for IL-6R higher than the pH dependence of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 1 and a light chain of an amino acid sequence of SEQ ID NO. 2, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0.

15 59. The antibody of any of the preceding claims, wherein the antibody has a pH dependence of the binding affinity for IL-6R higher than the pH dependence of an antibody comprising a heavy chain of an amino acid sequence of SEQ ID NO. 3 and a light chain of an amino acid sequence of SEQ ID NO. 4, and wherein the pH dependence is defined as the ratio between the binding affinity for the IL-6R at pH7.4 and at pH6.0

20 60. The antibody of any of claims 55 to 60, wherein the pH dependence of the binding affinity is for human IL-6 receptor, and wherein the pH dependence is defined as the ratio between the binding affinity for the human IL-6R at pH7.4 and at pH6.0.

61. The antibody of any of the preceding claims, wherein the antibody has mutations selected from:

25 (a) Y51F, I57M, T58I, S99C, and T103I in the heavy chain with respect to SEQ ID NO. 1;

(b) Y51F, I57M, S99T, and T103I in the heavy chain with respect to SEQ ID NO. 1;

(c) Y51F, I57M, S99N, and T103I in the heavy chain with respect to SEQ ID NO. 1;

(d) Y51F, I57M, S99C, T103I, and T116I in the heavy chain with respect to SEQ ID

30 NO. 1;

(e) Y51F, I57M, S99C, and T103I in the heavy chain; and Q89G and T93R in the light chain with respect to SEQ ID NO. 1; and

(f) Y51F, I57M, and T103I in the heavy chain; and Q89G and T93R in the light chain with respect to SEQ ID NO. 2.

35 62. The antibody of any of the preceding claims, wherein the antibody is a monoclonal antibody.

63. The antibody of any of the preceding claims, wherein the antibody is a human or humanized antibody.
64. The antibody of any of the preceding claims, wherein the antibody is an IgG, an IgM, an IgE, an IgA, or an IgD molecule, or is derived from one of these.
- 5 65. The antibody of any of the preceding claims, wherein the antibody comprises an Fc region.
 66. The antibody of claim 65, wherein the Fc region comprises an impaired effector function.
 67. The antibody of any of the preceding claims, wherein the antibody is attached to serum albumins, albumin-binding peptide, or a polymer.
- 10 68. The antibody of claim 67, wherein the polymer is polyethylene glycol.
69. The antibody of any of the preceding claims, wherein the antibody is a bi-specific antibody.
70. The antibody of claim 69, wherein the bi-specific antibody binds to a second antigen selected from IL-6, TNF α , TNFR1, TNFR2, CD80, CD86, CD28, CD20, CD19, IL-1 α , IL- β , IL-1R, RANKL, RANK, IL-17, IL-17R, IL-23, IL-23R, IL-15, IL-15R, BlyS, lymphotoxin α , lymphotoxin β , LIGHT ligand, LIGHT, VLA-4, CD25, IL-12, IL-12R, CD40, CD40L, BAFF, CD52, CD22, IL-32, IL-21, IL-21R, GM-CSF, GM-CSFR, M-CSF, M-CSFR, IFN-alpha, VEGF, VEGFR, EGF, EGFR, CCR5, APRIL, and APRILR.
- 20 71. A method of treating a disease or condition comprising administering the antibody of any one of claims 1-67 to a subject in need thereof.
72. The method of claim 68, wherein the disease or condition comprises infection, endotoxic shock associated with infection, arthritis, rheumatoid arthritis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), asthma, pelvic inflammatory disease, Alzheimer's Disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, multiple sclerosis, ankylosing spondylitis, dermatomyositis, uveitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme arthritis, meningoencephalitis, immune mediated inflammatory disorders of the central and peripheral nervous system, autoimmune disorders, pancreatitis, trauma from surgery, graft-versus-host disease, transplant rejection, heart disease, bone resorption, burns patients, myocardial infarction, Paget's disease, osteoporosis, sepsis, liver/lung fibrosis, periodontitis, hypochlorhydia, solid tumors (renal cell carcinoma), liver cancer, multiple myeloma, prostatic cancer, bladder cancer, pancreatic cancer, neurological cancers, and B-cell malignancies (e.g., Castleman's disease, certain lymphomas, chronic lymphocytic leukemia, and multiple myeloma).
- 30 73. A pharmaceutical composition comprising the antibody of any one of claims 1-67 and a pharmaceutically acceptable excipient.
74. A kit comprising the antibody of any one of claims 1-67 in a container.

75. The antibody of any one of claims 1-67 for use in treating a condition of a subject.
76. Use of an antibody of any one of claims 1-67 for the manufacture of a medicament for treating a condition of a subject.
77. An isolated polynucleotide encoding the antibody of any one of claims 1-67.
- 5 78. A vector comprising the isolated polynucleotide of claim 74.
79. A cell comprising the vector of claim 75.
80. The cell of claim 76 wherein the cell is a eukaryotic cell.
81. The cell of claim 76, wherein the cell is a prokaryotic cell.
82. The cell of claim 76, wherein said cell is a mammalian cell, bacterial cell, fungal cell, or
- 10 an insect cell.

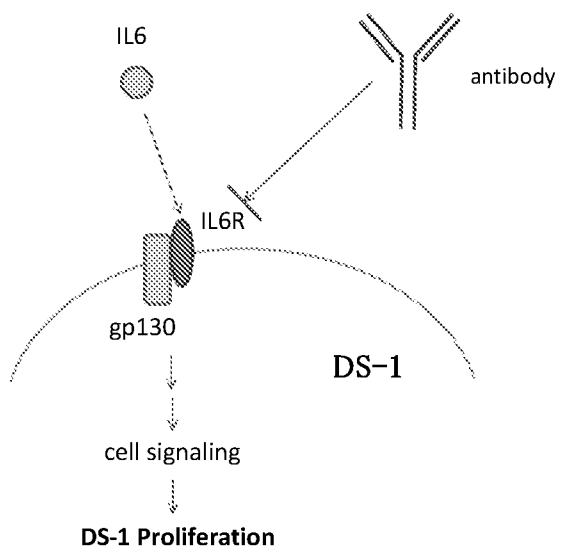


Fig. 1

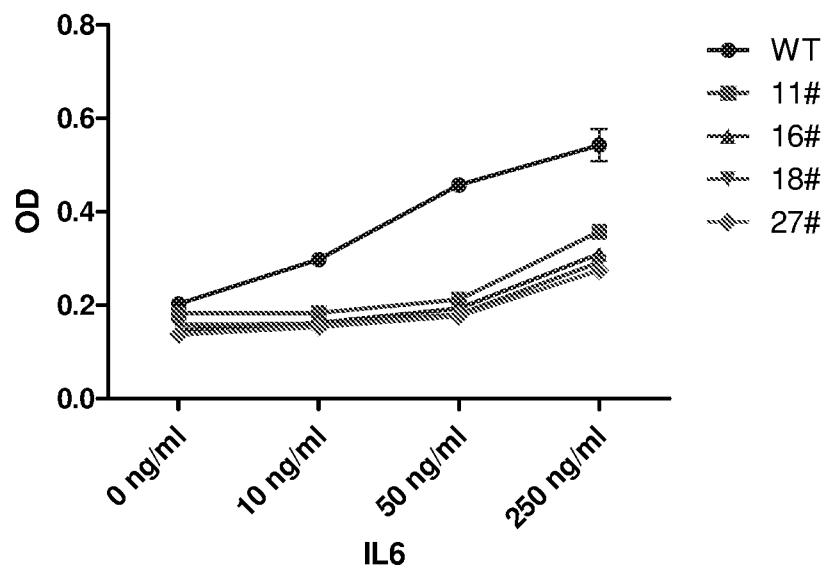


Fig. 2A

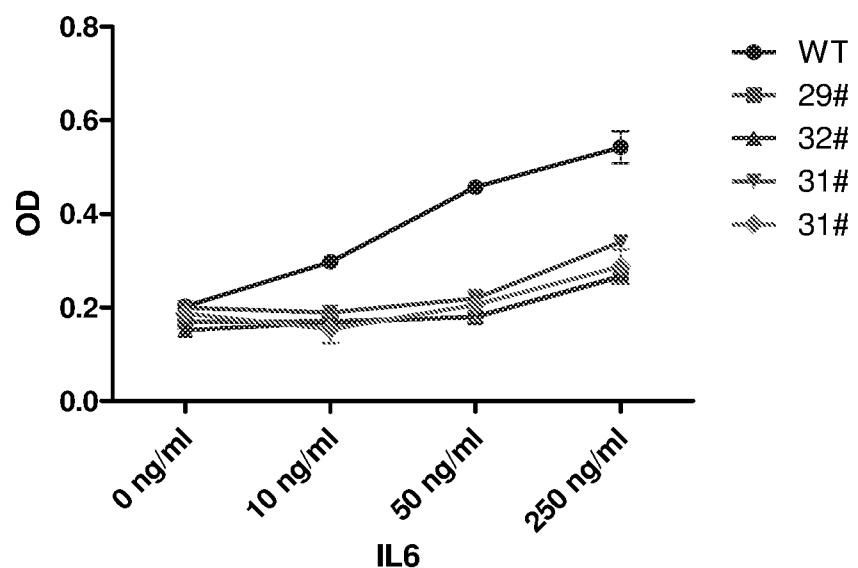


Fig. 2B

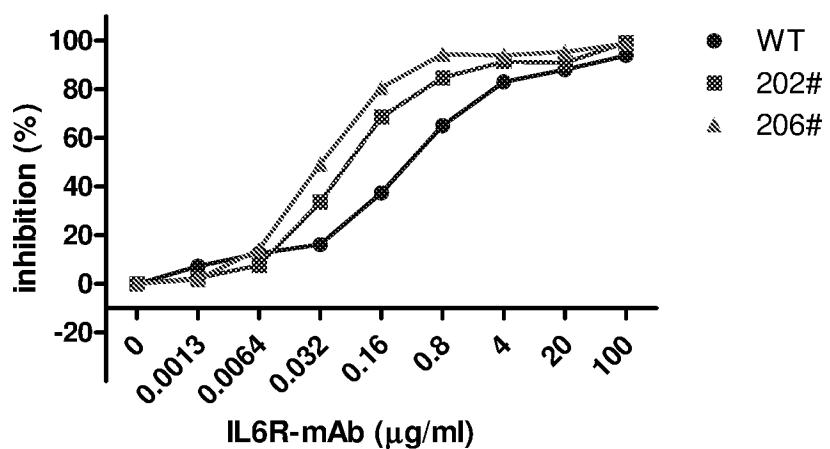


Fig. 3A

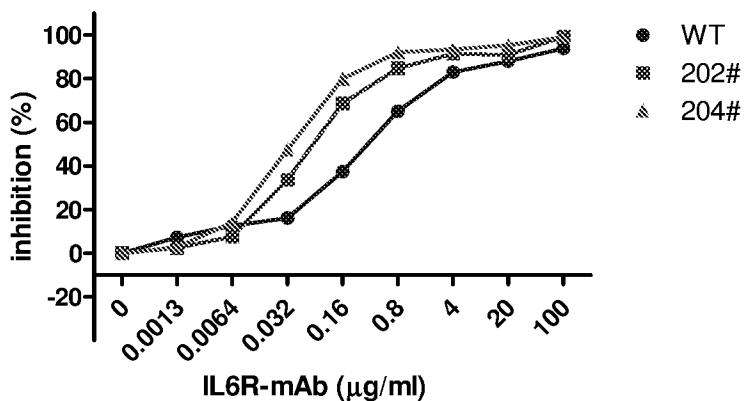


Fig. 3B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083653

A. CLASSIFICATION OF SUBJECT MATTER

C07K 16/28(2006.01)i; C12N 15/13(2006.01)i; A61P 29/00(2006.01)i; A61P 35/00(2006.01)i; A61K 39/395(2006.01)i

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)

C07K, C12N, A61P, A61K

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)

CNABS, CPRSABS, DWPI, SIPOABS, ISI Web of Knowledge, CNKI, BAIDU, Google Scholar and searched terms: anti-IL-6R, IL-6R, IL-6 receptor, antibod+, modif+, alterat+, site-directed mutagenesis, monoclonal antibody, MAb, immunoglobulin etc. GENBANK, EMBL and searched sequences: SEQ ID NOS: 2 and 5

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011098450 A1 (CHUGAI PHARMACEUTICAL CO LTD) 28 April 2011 (2011-04-28) see examples 1-6	1, 3, 5-10, 12, 14-35, 42, 43, 46-51, 54-60, 62-70, 73-82
A	US 2011098450 A1 (CHUGAI PHARMACEUTICAL CO LTD) 28 April 2011 (2011-04-28) see the whole document	2, 4, 11, 13, 36-41, 44, 45, 52, 53, 61
X	CN 101874042 A (CHUGAI PHARMACEUTICAL CO LTD) 27 October 2010 (2010-10-27) see examples 28-30	1, 3, 5-10, 12, 14-35, 42, 43, 46-51, 54-60, 62-70, 73-82
A	CN 101874042 A (CHUGAI PHARMACEUTICAL CO LTD) 27 October 2010 (2010-10-27) see the whole document	2, 4, 11, 13, 36-41, 44, 45, 52, 53, 61

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
 "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "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

21 February 2017

Date of mailing of the international search report

02 March 2017

Name and mailing address of the ISA/CN

**STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China**

Authorized officer

MA,Zhenlian

Faxsimile No. (86-10)62019451

Telephone No. (86-10)62412131

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083653**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007114319 A1 (CHUGAI PHARMACEUTICAL CO LTD ET AL.) 11 October 2007 (2007-10-11) see the whole document	1-70, 73-82
A	Sang Jick Kim et al. "Antibody Engineering for the Development of Therapeutic Antibodies" <i>«Molecules and Cells»</i> , Vol. 20, No. 1, 31 August 2005 (2005-08-31), see pages 17-29	1-70, 73-82

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083653**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **71 and 72**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] PCT Rule 39.1(iv) - Method for treatment of the human or animal body by surgery or therapy.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- [1] The application concerns antibodies comprising a heavy chain amino acid sequence with certain identity to a sequence selected from SEQ ID NOs: 5-78 and 89, and a light chain amino acid sequence with certain identity to a sequence selected from SEQ ID NO. 2, 4, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88 and 90. The authority considers that there are $75*13=975$ separate inventions covered by the claims of the present application. The common or corresponding technical feature among the 975 inventions lies in that the antibodies exhibit higher binding affinity relative to TOCILIZUMAB, which is resulted from site mutations within SEQ ID NO. 1 and SEQ ID NO. 2. The technical feature has been disclosed by the prior art, such as CN 101849006 A, which discloses anti-IL-6R antibodies that are superior to TOCILIZUMAB by combining amino acid sequences alterations (see claim 5 and examples 1-6). Thus, the 975 inventions are not linked by common or corresponding special technical features and define 975 separate inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 PCT.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083653**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-70, 73-82**

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/083653

Patent document cited in search report				Publication date (day/month/year)		Patent family member(s)		Publication date (day/month/year)	
US	2011098450	A1	28 April 2011	KR	20110046385	A		04 May 2011	
				JP	5661291	B2		28 January 2015	
				CA	2699834	C		13 March 2012	
				ZA	201103027	B		26 June 2012	
				HK	1185887	A1		29 January 2016	
				MX	2010003256	A		04 August 2010	
				TW	1440469	B		11 June 2014	
				KR	101044180	B1		24 June 2011	
				HK	1147107	A1		25 October 2013	
				US	8562991	B2		22 October 2013	
				EP	2330193	A1		08 June 2011	
				RU	2430111	C1		27 September 2011	
				CA	2763039	C		27 October 2015	
				PT	2330193	E		21 September 2015	
				IL	211850	D0		30 June 2011	
				BR	PI0905076	A2		07 July 2015	
				CR	20110204	A		03 June 2011	
				MY	153908	A		15 April 2015	
				DK	2330193	T3		24 August 2015	
				EP	2330193	B1		17 June 2015	
				CN	103254310	A		21 August 2013	
				AU	2009290162	B2		10 November 2011	
				TW	201021829	A		16 June 2010	
				CA	2699834	A1		01 April 2010	
				WO	2010035769	A1		01 April 2010	
				AR	073404	A1		03 November 2010	
				EC	SP11011003	A		31 May 2011	
				SI	2330193	T1		30 October 2015	
				CN	103254310	B		12 August 2015	
				ES	2546800	T3		29 September 2015	
				JP	4550938	B2		22 September 2010	
				CO	6362048	A2		20 January 2012	
				HR	P20150857	T1		09 October 2015	
				JP	2010239958	A		28 October 2010	
				PE	00792012	A1		29 February 2012	
				CN	101849006	B		22 May 2013	
				NZ	592214	A		28 September 2012	
				US	2012253016	A1		04 October 2012	
				MA	32707	B1		02 October 2011	
				CA	2763039	A1		01 April 2010	
				US	2015166666	A1		18 June 2015	
				EP	2330193	A4		25 July 2012	
				KR	20100061834	A		09 June 2010	
				AU	2009290162	A1		15 April 2010	
				CN	101849006	A		29 September 2010	
CN	101874042	A	27 October 2010	RU	2010116208	A		10 November 2011	
				RU	2510400	C2		27 March 2014	
				JP	2013216660	A		24 October 2013	
				EP	2202245	A1		30 June 2010	
				BR	PI0817294	A2		17 March 2015	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/083653

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)		Publication date (day/month/year)
		AU	2008304778	A1 02 April 2009
		AR	070716	A1 28 April 2010
		US	2015284465	A1 08 October 2015
		US	2011076275	A1 31 March 2011
		MX	2010003443	A 21 April 2010
		PE	02682010	A1 21 April 2010
		AR	070633	A1 21 April 2010
		AU	2008304778	B9 08 May 2014
		DK	2202245	T3 21 November 2016
		MX	336725	B 28 January 2016
		EP	2202245	B1 24 August 2016
		RU	2510400	C9 20 July 2014
		JP	5731573	B2 10 June 2015
		CA	2700701	A1 02 April 2009
		SI	2202245	T1 28 October 2016
		JP	2015130883	A 23 July 2015
		US	9096651	B2 04 August 2015
		KR	20100074220	A 01 July 2010
		JP	5334319	B2 06 November 2013
		ES	2595638	T3 02 January 2017
		IL	246040	D0 31 July 2016
		EP	2202245	A4 03 November 2010
		KR	101575914	B1 08 December 2015
		WO	2009041643	A1 02 April 2009
		AU	2008304778	B2 09 January 2014
WO	2007114319	A1	11 October 2007	EP 2006381 B1 03 February 2016
				DK 2006381 T3 22 February 2016
				AU 2007232873 B2 20 February 2014
				KR 20090005111 A 12 January 2009
				EP 3056568 A1 17 August 2016
				CA 2647846 C 21 June 2016
				JP 5882247 B2 09 March 2016
				KR 101463631 B1 19 November 2014
				HK 1130833 A1 30 October 2015
				IN 10515DEN2014 A 21 August 2015
				JP 5624276 B2 12 November 2014
				HK 1208229 A1 26 February 2016
				EP 2006381 A1 24 December 2008
				JP 2015134817 A 27 July 2015
				ES 2568436 T3 29 April 2016
				CN 101479381 B 29 April 2015
				EP 2006381 A4 29 April 2009
				CN 101479381 A 08 July 2009
				AU 2007232873 A1 11 October 2007
				JP 2013165716 A 29 August 2013
				CN 104761637 A 08 July 2015
				US 2009324589 A1 31 December 2009
				CA 2647846 A1 11 October 2007