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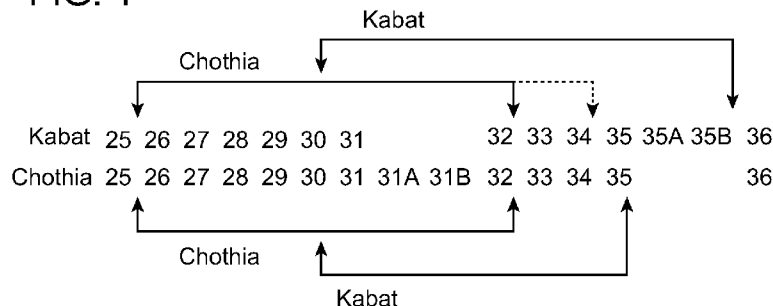
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(54) Title: ANTI-PD-1 ANTIBODIES, COMPOSITIONS COMPRISING ANTI-PD-1 ANTIBODIES AND METHODS OF USING ANTI-PD-1 ANTIBODIES

FIG. 1



(57) Abstract: Provided herein are antibodies that selectively bind to PD-1 and its isoforms and homologs, and compositions comprising the antibodies. Also provided are methods of using the antibodies, such as therapeutic and diagnostic methods.

ANTI-PD-1 ANTIBODIES, COMPOSITIONS COMPRISING ANTI-PD-1 ANTIBODIES AND METHODS OF USING ANTI-PD-1 ANTIBODIES

FIELD

[0001] Provided herein are antibodies with binding specificity for PD-1 and compositions comprising the antibodies, including pharmaceutical compositions, diagnostic compositions and kits. Also provided are methods of using anti-PD-1 antibodies for therapeutic and diagnostic purposes.

BACKGROUND

[0002] Programmed cell death protein 1 (PD-1, also known as CD279) is a cell surface protein molecule that belongs to the immunoglobulin superfamily. It is expressed on T and B lymphocytes and macrophages, and plays a role in cell fate and differentiation. *See* Ishida et al., *EMBO J.*, 1992, 11:3887-3895, incorporated by reference in its entirety. Activation of PD-1 is thought to negatively regulate the immune response. *See* Blank et al., *Cancer Immunol. Immunother.*, 2007, 56:739-745; and Freeman et al., *J. Exp. Med.*, 2000, 192:1027-1034, each of which is incorporated by reference in its entirety.

[0003] PD-1 has two known ligands, PD-L1 and PD-L2, which are both members of the B7 family. *See* Freeman et al., *supra*; and Latchman et al., *Nat. Immunol.*, 2001, 2:261-268, each of which is incorporated by reference in its entirety. The interaction between PD-1 and these ligands is thought to play a role in a variety of diseases, including cancer (*see* Ribas and Tumei, *Clin. Cancer Res.*, 2014, June 26, PMID: 24970841 [Epub ahead of print]), autoimmune disease (*see* Dai et al., *Cell Immunol.*, 2014, 290:72-79), and infection (*see* Day et al., *Nature*, 2006, 443:350-354). Each of the references cited in the preceding sentence is incorporated by reference in its entirety. In particular, the engagement of PD-1 by one of its ligands is thought to inhibit T-cell effector functions in an antigen-specific manner.

[0004] In view of the role of PD-1 in multiple disease processes, there is a need for improved methods of modulating the interaction of PD-1 with its ligands and the downstream signaling processes activated by PD-1. Moreover, given the role of PD-1 in several diseases, there is also a need for therapeutics that specifically target cells and tissues that express PD-1.

SUMMARY

[0005] Provided herein are antibodies that selectively bind PD-1. In some embodiments, the antibodies bind human PD-1. In some embodiments, the antibodies also bind homologs of human PD-1. In some aspects, the homolog is a cynomolgus monkey homolog. In some aspects, the homolog is a murine homolog. In some embodiments, the antibodies bind to human PD-1, a cynomolgus monkey homolog, and a murine homolog.

[0006] In some embodiments, the antibodies comprise at least one CDR sequence defined by a consensus sequence provided in this disclosure. In some embodiments, the antibodies comprise an illustrative CDR, V_H, or V_L sequence provided in this disclosure, or a variant thereof. In some aspects, the variant is a variant with one or more conservative amino acid substitutions.

[0007] Also provided are compositions and kits comprising the antibodies. In some embodiments, the compositions are pharmaceutical compositions. Any suitable pharmaceutical composition may be used. In some embodiments, the pharmaceutical composition is a composition for parenteral administration.

[0008] This disclosure also provides methods of using the anti-PD-1 antibodies provided herein. In some embodiments, the method is a method of treatment. In some embodiments, the method is a diagnostic method. In some embodiments, the method is an analytical method. In some embodiments, the method is a method of purifying and/or quantifying PD-1.

[0009] In some embodiments, the antibodies are used to treat a disease or condition. In some aspects, the disease or condition is selected from a cancer, autoimmune disease, and infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIG. 1** provides a comparison of the Kabat and Chothia numbering systems for CDR-H1. *Adapted from* Martin A.C.R. (2010). Protein Sequence and Structure Analysis of Antibody Variable Domains. In R. Kontermann & S. Dübel (Eds.), *Antibody Engineering* vol. 2 (pp. 33-51). Springer-Verlag, Berlin Heidelberg.

[0011] **FIG. 2** provides a chart of tumor volume over 17-days of treatment with various anti-PD-1 antibodies, as described in Example 15.

[0012] **FIG. 3** provides a chart of interferon gamma (IFN- γ) secretion in a

cytomegalovirus (CMV) recall assay, as described in Example 16.

[0013] **FIG. 4** provides a chart of interferon gamma (IFN-g) secretion in a mixed lymphocyte response (MLR) assay, as described in Example 17.

[0014] **FIG. 5** provides a chart of mouse survival in a model of graft versus host disease, as described in Example 18.

DETAILED DESCRIPTION

1. Definitions

[0015] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a difference over what is generally understood in the art. The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodologies by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 2nd ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. As appropriate, procedures involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer defined protocols and/or parameters unless otherwise noted.

[0016] As used herein, the singular forms “a,” “an,” and “the” include the plural referents unless the context clearly indicates otherwise.

[0017] The term “about” indicates and encompasses an indicated value and a range above and below that value. In certain embodiments, the term “about” indicates the designated value $\pm 10\%$, $\pm 5\%$, or $\pm 1\%$. In certain embodiments, the term “about” indicates the designated value $\pm$ one standard deviation of that value.

[0018] The term “combinations thereof” includes every possible combination of elements to which the term refers to. For example, a sentence stating that “if α_2 is A, then α_3 is not D; α_5 is not S; or α_6 is not S; or combinations thereof” includes the following combinations when α_2 is A: (1) α_3 is not D; (2) α_5 is not S; (3) α_6 is not S; (4) α_3 is not D; α_5 is not S; and α_6 is not S; (5) α_3 is not D and α_5 is not S; (6) α_3 is not D and α_6 is not S; and (7)

α_5 is not S and α_6 is not S.

[0019] The terms “PD-1” and “PD-1 antigen” are used interchangeably herein. Unless specified otherwise, the terms include any variants, isoforms and species homologs of human PD-1 that are naturally expressed by cells, or that are expressed by cells transfected with a PD-1 gene. PD-1 proteins include full-length PD-1 (e.g., human PD-1; GI: 167857792; SEQ ID NO: 1; extracellular domain: Pro21-Gln167), as well as alternative splice variants of PD-1, such as PD-1 Δ ex2, PD-1 Δ ex3, PD-1 Δ ex2,3, and PD-1 Δ ex2,3,4. See Nielsen et al., *Cellular Immunology*, 2005, 235:109-116, incorporated by reference in its entirety. In some embodiments, PD-1 proteins include murine PD-1 (e.g., SEQ ID NO: 299; extracellular domain: Leu25-Gln167). In some embodiments, PD-1 proteins include cynomolgus PD-1 (e.g., SEQ ID NO: 300; extracellular domain: Pro21-Gln167).

[0020] The term “immunoglobulin” refers to a class of structurally related proteins generally comprising two pairs of polypeptide chains: one pair of light (L) chains and one pair of heavy (H) chains. In an “intact immunoglobulin,” all four of these chains are interconnected by disulfide bonds. The structure of immunoglobulins has been well characterized. See, e.g., Paul, *Fundamental Immunology* 7th ed., Ch. 5 (2013) Lippincott Williams & Wilkins, Philadelphia, PA. Briefly, each heavy chain typically comprises a heavy chain variable region (V_H) and a heavy chain constant region (C_H). The heavy chain constant region typically comprises three domains, C_{H1} , C_{H2} , and C_{H3} . Each light chain typically comprises a light chain variable region (V_L) and a light chain constant region. The light chain constant region typically comprises one domain, abbreviated C_L .

[0021] The term “antibody” describes a type of immunoglobulin molecule and is used herein in its broadest sense. An antibody specifically includes intact antibodies (e.g., intact immunoglobulins), and antibody fragments. Antibodies comprise at least one antigen-binding domain. One example of an antigen-binding domain is an antigen binding domain formed by a V_H - V_L dimer. A “PD-1 antibody,” “anti-PD-1 antibody,” “PD-1 Ab,” “PD-1-specific antibody” or “anti-PD-1 Ab” is an antibody, as described herein, which binds specifically to the antigen PD-1. In some embodiments, the antibody binds the extracellular domain of PD-1.

[0022] The V_H and V_L regions may be further subdivided into regions of hypervariability (“hypervariable regions (HVRs);” also called “complementarity determining regions” (CDRs)) interspersed with regions that are more conserved. The more conserved

regions are called framework regions (FRs). Each V_H and V_L generally comprises three CDRs and four FRs, arranged in the following order (from N-terminus to C-terminus): FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. The CDRs are involved in antigen binding, and confer antigen specificity and binding affinity to the antibody. See Kabat et al., *Sequences of Proteins of Immunological Interest* 5th ed. (1991) Public Health Service, National Institutes of Health, Bethesda, MD, incorporated by reference in its entirety.

[0023] The light chain from any vertebrate species can be assigned to one of two types, called kappa and lambda, based on the sequence of the constant domain.

[0024] The heavy chain from any vertebrate species can be assigned to one of five different classes (or isotypes): IgA, IgD, IgE, IgG, and IgM. These classes are also designated α , δ , ϵ , γ , and μ , respectively. The IgG and IgA classes are further divided into subclasses on the basis of differences in sequence and function. Humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0025] The amino acid sequence boundaries of a CDR can be determined by one of skill in the art using any of a number of known numbering schemes, including those described by Kabat et al., *supra* ("Kabat" numbering scheme); Al-Lazikani et al., 1997, *J. Mol. Biol.*, 273:927-948 ("Chothia" numbering scheme); MacCallum et al., 1996, *J. Mol. Biol.* 262:732-745 ("Contact" numbering scheme); Lefranc et al., *Dev. Comp. Immunol.*, 2003, 27:55-77 ("IMGT" numbering scheme); and Honegge and Plückthun, *J. Mol. Biol.*, 2001, 309:657-70 ("Aho" numbering scheme), each of which is incorporated by reference in its entirety.

[0026] Table 1 provides the positions of CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3 as identified by the Kabat and Chothia schemes. For CDR-H1, residue numbering is provided using both the Kabat and Chothia numbering schemes. FIG. 1 provides a comparison of the Kabat and Chothia numbering schemes for CDR-H1. *See* Martin (2010), *supra*.

[0027] Unless otherwise specified, the numbering scheme used for identification of a particular CDR herein is the Kabat/Chothia numbering scheme. Where the residues encompassed by these two numbering schemes diverge, the numbering scheme is specified as either Kabat or Chothia.

Table 1. Residues in CDRs according to Kabat and Chothia numbering schemes.

CDR	Kabat	Chothia
L1	L24-L34	L24-L34
L2	L50-L56	L50-L56
L3	L89-L97	L89-L97
H1 (Kabat Numbering)	H31-H35B	H26-H32 or H34*
H1 (Chothia Numbering)	H31-H35	H26-H32
H2	H50-H65	H52-H56
H3	H95-H102	H95-H102

* The C-terminus of CDR-H1, when numbered using the Kabat numbering convention, varies between H32 and H34, depending on the length of the CDR, as illustrated in FIG. 1.

[0028] The “EU numbering scheme” is generally used when referring to a residue in an antibody heavy chain constant region (e.g., as reported in Kabat et al., *supra*). Unless stated otherwise, the EU numbering scheme is used to refer to residues in antibody heavy chain constant regions described herein.

[0029] An “antibody fragment” comprises a portion of an intact antibody, such as the antigen binding or variable region of an intact antibody. Antibody fragments include, for example, Fv fragments, Fab fragments, F(ab')₂ fragments, Fab' fragments, scFv (sFv) fragments, and scFv-Fc fragments.

[0030] “Fv” fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[0031] “Fab” fragments comprise, in addition to the heavy and light chain variable domains, the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain. Fab fragments may be generated, for example, by papain digestion of a full-length antibody.

[0032] “F(ab')₂” fragments contain two Fab' fragments joined, near the hinge region, by disulfide bonds. F(ab')₂ fragments may be generated, for example, by pepsin digestion of an intact antibody. The F(ab') fragments can be dissociated, for example, by treatment with β-mercaptoethanol.

[0033] “Single-chain Fv” or “sFv” or “scFv” antibody fragments comprise a V_H domain and a V_L domain in a single polypeptide chain. The V_H and V_L are generally linked by a peptide linker. See Plückthun A. (1994). Antibodies from *Escherichia coli*. In Rosenberg M. & Moore G.P. (Eds.), *The Pharmacology of Monoclonal Antibodies* vol. 113 (pp. 269-315). Springer-Verlag, New York, incorporated by reference in its entirety. “scFv-Fc”

fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the V_H or V_L , depending on the orientation of the variable domains in the scFv (i.e., V_H - V_L or V_L - V_H). Any suitable Fc domain known in the art or described herein may be used. In some cases, the Fc domain is an IgG1 Fc domain (e.g., SEQ ID NO: 295). In some embodiments, the linker is $(G_4S)_3$ (see SEQ ID NO: 298).

[0034] The term “monoclonal antibody” refers to an antibody from a population of substantially homogeneous antibodies. A population of substantially homogeneous antibodies comprises antibodies that are substantially similar and that bind the same epitope(s), except for variants that may normally arise during production of the monoclonal antibody. Such variants are generally present in only minor amounts. A monoclonal antibody is typically obtained by a process that includes the selection of a single antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, yeast clones, bacterial clones, or other recombinant DNA clones. The selected antibody can be further altered, for example, to improve affinity for the target (“affinity maturation”), to humanize the antibody, to improve its production in cell culture, and/or to reduce its immunogenicity in a subject.

[0035] The term “chimeric antibody” refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0036] “Humanized” forms of non-human antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human immunoglobulin (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody). The donor antibody can be any suitable non-human antibody, such as a mouse, rat, rabbit, chicken, or non-human primate antibody having a desired specificity, affinity, or biological effect. In some instances, selected framework region residues of the recipient antibody are replaced by the corresponding framework region residues from the donor antibody. Humanized antibodies may also comprise residues that are not found in either the recipient antibody or the donor antibody. Such modifications may be made to further refine antibody function. For further details, see Jones et al., *Nature*, 1986, 321:522-525; Riechmann et al., *Nature*, 1988, 332:323-329; and Presta, *Curr. Op. Struct. Biol.*, 1992, 2:593-596, each of which is incorporated by reference in its entirety.

[0037] A “human antibody” is one which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed *de novo*). Human antibodies specifically exclude humanized antibodies.

[0038] An “isolated antibody” is one that has been separated and/or recovered from a component of its natural environment. Components of the natural environment may include enzymes, hormones, and other proteinaceous or nonproteinaceous materials. In some embodiments, an isolated antibody is purified to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, for example by use of a spinning cup sequenator. In some embodiments, an isolated antibody is purified to homogeneity by gel electrophoresis (e.g., SDS-PAGE) under reducing or nonreducing conditions, with detection by Coomassie blue or silver stain. An isolated antibody includes an antibody *in situ* within recombinant cells, since at least one component of the antibody's natural environment is not present. In some aspects, an isolated antibody is prepared by at least one purification step.

[0039] In some embodiments, an isolated antibody is purified to at least 80%, 85%, 90%, 95%, or 99% by weight. In some embodiments, an isolated antibody is provided as a solution comprising at least 85%, 90%, 95%, 98%, 99% to 100% by weight of an antibody, the remainder of the weight comprising the weight of other solutes dissolved in the solvent.

[0040] “Affinity” refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Affinity can be determined, for example, using surface plasmon resonance (SPR) technology, such as a Biacore[®] instrument.

[0041] With regard to the binding of an antibody to a target molecule, the terms “specific binding,” “specifically binds to,” “specific for,” “selectively binds,” and “selective for” a particular antigen (e.g., a polypeptide target) or an epitope on a particular antigen mean binding that is measurably different from a non-specific or non-selective interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to

binding of a control molecule. Specific binding can also be determined by competition with a control molecule that is similar to the target, such as an excess of non-labeled target. In that case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by the excess non-labeled target.

[0042] The term “ k_d ” (sec^{-1}), as used herein, refers to the dissociation rate constant of a particular antibody-antigen interaction. This value is also referred to as the k_{off} value.

[0043] The term “ k_a ” ($\text{M}^{-1} \times \text{sec}^{-1}$), as used herein, refers to the association rate constant of a particular antibody-antigen interaction. This value is also referred to as the k_{on} value.

[0044] The term “ K_D ” (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction. $K_D = k_d/k_a$.

[0045] The term “ K_A ” (M^{-1}), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction. $K_A = k_a/k_d$.

[0046] An “affinity matured” antibody is one with one or more alterations in one or more CDRs or FRs that result in an improvement in the affinity of the antibody for its antigen, compared to a parent antibody which does not possess the alteration(s). In one embodiment, an affinity matured antibody has nanomolar or picomolar affinity for the target antigen. Affinity matured antibodies may be produced using a variety of methods known in the art. For example, Marks et al. (*Bio/Technology*, 1992, 10:779-783, incorporated by reference in its entirety) describes affinity maturation by V_H and V_L domain shuffling. Random mutagenesis of CDR and/or framework residues is described by, for example, Barbas et al. (*Proc. Nat. Acad. Sci. U.S.A.*, 1994, 91:3809-3813); Schier et al., *Gene*, 1995, 169:147-155; Yelton et al., *J. Immunol.*, 1995, 155:1994-2004; Jackson et al., *J. Immunol.*, 1995, 154:3310-3319; and Hawkins et al., *J. Mol. Biol.*, 1992, 226:889-896, each of which is incorporated by reference in its entirety.

[0047] When used herein in the context of two or more antibodies, the term “competes with” or “cross-competes with” indicates that the two or more antibodies compete for binding to an antigen (e.g., PD-1). In one exemplary assay, PD-1 is coated on a plate and allowed to bind a first antibody, after which a second, labeled antibody is added. If the presence of the first antibody reduces binding of the second antibody, then the antibodies compete. The term “competes with” also includes combinations of antibodies where one antibody reduces binding of another antibody, but where no competition is observed when the

antibodies are added in the reverse order. However, in some embodiments, the first and second antibodies inhibit binding of each other, regardless of the order in which they are added. In some embodiments, one antibody reduces binding of another antibody to its antigen by at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%.

[0048] The term “epitope” means a portion of an antigen capable of specific binding to an antibody. Epitopes frequently consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an antibody binds can be determined using known techniques for epitope determination such as, for example, testing for antibody binding to PD-1 variants with different point-mutations.

[0049] Percent “identity” between a polypeptide sequence and a reference sequence, is defined as the percentage of amino acid residues in the polypeptide sequence that are identical to the amino acid residues in the reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent 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, MEGALIGN (DNASTAR), CLUSTALW, or CLUSTAL OMEGA software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0050] A “conservative substitution” or a “conservative amino acid substitution,” refers to the substitution of one or more amino acids with one or more chemically or functionally similar amino acids. Conservative substitution tables providing similar amino acids are well known in the art. Polypeptide sequences having such substitutions are known as “conservatively modified variants.” Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles. By way of example, the following groups of amino acids are considered conservative substitutions for one another.

<i>Acidic Residues</i>	D and E
<i>Basic Residues</i>	K, R, and H
<i>Hydrophilic Uncharged Residues</i>	S, T, N, and Q
<i>Aliphatic Uncharged Residues</i>	G, A, V, L, and I
<i>Non-polar Uncharged Residues</i>	C, M, and P
<i>Aromatic Residues</i>	F, Y, and W

<i>Alcohol Group-Containing Residues</i>	S and T
<i>Aliphatic Residues</i>	I, L, V, and M
<i>Cycloalkenyl-associated Residues</i>	F, H, W, and Y
<i>Hydrophobic Residues</i>	A, C, F, G, H, I, L, M, R, T, V, W, and Y
<i>Negatively Charged Residues</i>	D and E
<i>Polar Residues</i>	C, D, E, H, K, N, Q, R, S, and T
<i>Positively Charged Residues</i>	H, K, and R
<i>Small Residues</i>	A, C, D, G, N, P, S, T, and V
<i>Very Small Residues</i>	A, G, and S
<i>Residues Involved in Turn Formation</i>	A, C, D, E, G, H, K, N, Q, R, S, P, and T
<i>Flexible Residues</i>	Q, T, K, S, G, P, D, E, and R

<i>Group 1</i>	A, S, and T
<i>Group 2</i>	D and E
<i>Group 3</i>	N and Q
<i>Group 4</i>	R and K
<i>Group 5</i>	I, L, and M
<i>Group 6</i>	F, Y, and W

<i>Group A</i>	A and G
<i>Group B</i>	D and E
<i>Group C</i>	N and Q
<i>Group D</i>	R, K, and H
<i>Group E</i>	I, L, M, V
<i>Group F</i>	F, Y, and W
<i>Group G</i>	S and T
<i>Group H</i>	C and M

Additional conservative substitutions may be found, for example, in Creighton, *Proteins: Structures and Molecular Properties* 2nd ed. (1993) W. H. Freeman & Co., New York, NY. An antibody generated by making one or more conservative substitutions of amino acid residues in a parent antibody is referred to as a “conservatively modified variant.”

[0051] The term “amino acid” refers to the twenty common naturally occurring amino acids. Naturally occurring amino acids include alanine (Ala; A), arginine (Arg; R), asparagine (Asn; N), aspartic acid (Asp; D), cysteine (Cys; C); glutamic acid (Glu; E),

glutamine (Gln; Q), Glycine (Gly; G); histidine (His; H), isoleucine (Ile; I), leucine (Leu; L), lysine (Lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V).

[0052] “Treating” or “treatment” of any disease or disorder refers, in certain embodiments, to ameliorating a disease or disorder that exists in a subject. In another embodiment, “treating” or “treatment” includes ameliorating at least one physical parameter, which may be indiscernible by the subject. In yet another embodiment, “treating” or “treatment” includes modulating the disease or disorder, either physically (e.g., stabilization of a discernible symptom) or physiologically (e.g., stabilization of a physical parameter) or both. In yet another embodiment, “treating” or “treatment” includes delaying or preventing the onset of the disease or disorder.

[0053] As used herein, the term “therapeutically effective amount” or “effective amount” refers to an amount of an antibody or composition that when administered to a subject is effective to treat a disease or disorder.

[0054] As used herein, the term “subject” means a mammalian subject. Exemplary subjects include, but are not limited to humans, monkeys, dogs, cats, mice, rats, cows, horses, camels, avians, goats and sheep. In certain embodiments, the subject is a human. In some embodiments, the subject has cancer, an autoimmune disease or condition, and/or an infection that can be treated with an antibody provided herein. In some embodiments, the subject is a human that is suspected to have cancer, an autoimmune disease or condition, and/or an infection.

2. Antibodies

[0055] Provided herein are antibodies that selectively bind human PD-1. In some aspects, the antibody selectively binds to the extracellular domain of human PD-1. In some aspects, the antibody selectively binds to one or more of full-length human PD-1, PD-1 Δ ex2, PD-1 Δ ex3, PD-1 Δ ex2,3, and PD-1 Δ ex2,3,4. *See Nielsen et al., Cellular Immunology, 2005, 235:109-116, incorporated by reference in its entirety.*

[0056] In some embodiments, the antibody binds to homologs of human PD-1. In some aspects, the antibody binds to a homolog of human PD-1 from a species selected from monkeys, mice, dogs, cats, rats, cows, horses, goats and sheep. In some aspects, the homolog is a cynomolgus monkey homolog. In some aspects, the homolog is a murine homolog.

[0057] In some embodiments, the antibody has one or more CDRs having particular

lengths, in terms of the number of amino acid residues. In some embodiments, the Chothia CDR-H1 of the antibody is 6, 7, 8, or 9 residues in length. In some embodiments, the Kabat CDR-H1 of the antibody is 4, 5, 6, or 7 residues in length. In some embodiments, the Chothia CDR-H2 of the antibody is 5, 6, or 7 residues in length. In some embodiments, the Kabat CDR-H2 of the antibody is 15, 16, 17, or 18 residues in length. In some embodiments, the Kabat/Chothia CDR-H3 of the antibody is 5, 6, 7, 8, 9, 10, 11, or 12 residues in length.

[0058] In some aspects, the Kabat/Chothia CDR-L1 of the antibody is 9, 10, 11, 12, 13, 14, 15, or 16 residues in length. In some aspects, the Kabat/Chothia CDR-L2 of the antibody is 6, 7, or 8 residues in length. In some aspects, the Kabat/Chothia CDR-L3 of the antibody is 8, 9, 10, 11, or 12 residues in length.

[0059] In some embodiments, the antibody comprises a light chain. In some aspects, the light chain is a kappa light chain. In some aspects, the light chain is a lambda light chain.

[0060] In some embodiments, the antibody comprises a heavy chain. In some aspects, the heavy chain is an IgA. In some aspects, the heavy chain is an IgD. In some aspects, the heavy chain is an IgE. In some aspects, the heavy chain is an IgG. In some aspects, the heavy chain is an IgM. In some aspects, the heavy chain is an IgG1. In some aspects, the heavy chain is an IgG2. In some aspects, the heavy chain is an IgG3. In some aspects, the heavy chain is an IgG4. In some aspects, the heavy chain is an IgA1. In some aspects, the heavy chain is an IgA2.

[0061] In some embodiments, the antibody is an antibody fragment. In some aspects, the antibody fragment is an Fv fragment. In some aspects, the antibody fragment is a Fab fragment. In some aspects, the antibody fragment is a F(ab')₂ fragment. In some aspects, the antibody fragment is a Fab' fragment. In some aspects, the antibody fragment is an scFv (sFv) fragment. In some aspects, the antibody fragment is an scFv-Fc fragment.

[0062] In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a polyclonal antibody.

[0063] In some embodiments, the antibody is a chimeric antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a human antibody.

[0064] In some embodiments, the antibody is an affinity matured antibody. In some aspects, the antibody is an affinity matured antibody derived from an illustrative sequence provided in this disclosure.

[0065] In some embodiments, the antibody inhibits the binding of PD-1 to its ligands. In some aspects, the antibody inhibits the binding of PD-1 to PD-L1. In some aspects, the antibody inhibits the binding of PD-1 to PD-L2. In some aspects, the antibody inhibits the binding of PD-1 to PD-L1 and PD-L2.

[0066] The antibodies provided herein may be useful for the treatment of a variety of diseases and conditions, including cancers, autoimmune diseases, and infections.

2.1. CDR-H3 Sequences

[0067] In some embodiments, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 113. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 114. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 115. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 116. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 117. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 118. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 119. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 120. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 121. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 122. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 123. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 124. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 125. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 126. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 127. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially

of SEQ ID NO: 128. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 129. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 130. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 131. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 309. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 310. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 311. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 312. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 313. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 314. In some aspects, the antibody comprises a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 315.

[0068] In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-H3 sequence provided in this disclosure. In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-H3 sequences provided in this disclosure. In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-H3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0069] In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 132-136. In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 132. In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 133. In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 134. In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 135. In some aspects, the CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 136.

2.2. V_H Sequences Comprising Illustrative CDRs

[0070] In some embodiments, the antibody comprises a V_H sequence comprising one or more CDR-H sequences comprising, consisting of, or consisting essentially of one or more illustrative CDR-H sequences provided in this disclosure, and variants thereof.

2.2.1. V_H Sequences Comprising Illustrative Kabat CDRs

[0071] In some embodiments, the antibody comprises a V_H sequence comprising one or more Kabat CDR-H sequences comprising, consisting of, or consisting essentially of one or more illustrative Kabat CDR-H sequences provided in this disclosure, and variants thereof.

2.2.1.1. Kabat CDR-H3

[0072] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 113. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 114. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 115. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 116. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 117. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 118. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 119. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 120. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 121. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 122. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 123. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 124. In some aspects, the

antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 125. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 126. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 127. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 128. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 129. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 130. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 131. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 309. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 310. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 311. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 312. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 313. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 314. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 315.

2.2.1.2. Kabat CDR-H2

[0073] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 84-102 or 331. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 84. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of

[illegible]

2.2.1.3. Kabat CDR-H1

[0074] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 31-49. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 31. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 32. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 33. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 34. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 35. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 36. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 37. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 38. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 39. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 40. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 41. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 42. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 43. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 44. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 45. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 46. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of,

or consisting essentially of SEQ ID NO: 47. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 48. In some aspects, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 49.

2.2.1.4. Kabat CDR-H3 + Kabat CDR-H2

[0075] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315, and a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 84-102 or 331. In some aspects, the Kabat CDR-H3 sequence and the Kabat CDR-H2 sequence are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Kabat CDR-H3 and Kabat CDR-H2 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.1.5. Kabat CDR-H3 + Kabat CDR-H1

[0076] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315, and a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 31-49. In some aspects, the Kabat CDR-H3 sequence and the Kabat CDR-H1 sequence are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Kabat CDR-H3 and Kabat CDR-H1 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.1.6. Kabat CDR-H1 + Kabat CDR-H2

[0077] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 31-49 and a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 84-102 or 331. In some aspects, the Kabat CDR-H1 sequence and the Kabat CDR-H2 sequence are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Kabat CDR-H1 and Kabat CDR-H2 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264.

2.2.1.7. Kabat CDR-H1 + Kabat CDR-H2 + Kabat CDR-H3

[0078] In some embodiments, the antibody comprises a V_H sequence comprising a Kabat CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 31-49, a Kabat CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 84-102 or 331, and a Kabat CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315. In some aspects, the Kabat CDR-H1 sequence, Kabat CDR-H2 sequence, and Kabat CDR-H3 sequence are all from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Kabat CDR-H1, Kabat CDR-H2, and Kabat CDR-H3 are all from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.1.8. Variants of V_H Sequences Comprising Illustrative Kabat CDRs

[0079] In some embodiments, the V_H sequences provided herein comprise a variant of an illustrative Kabat CDR-H3, CDR-H2, and/or CDR-H1 sequence provided in this disclosure.

[0080] In some aspects, the Kabat CDR-H3 sequence comprises, consists of, or consists essentially of a variant of an illustrative Kabat CDR-H3 sequence provided in this disclosure. In some aspects, the Kabat CDR-H3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Kabat CDR-H3 sequences provided in this disclosure. In some aspects, the Kabat CDR-H3 sequence comprises, consists of, or consists essentially of any of the illustrative Kabat CDR-H3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0081] In some aspects, the Kabat CDR-H2 sequence comprises, consists of, or consists essentially of a variant of an illustrative Kabat CDR-H2 sequence provided in this disclosure. In some aspects, the Kabat CDR-H2 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Kabat CDR-H2 sequences provided in this disclosure. In some aspects, the Kabat CDR-H2 sequence comprises, consists of, or consists essentially of any of the illustrative Kabat CDR-H2 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0082] In some aspects, the Kabat CDR-H1 sequence comprises, consists of, or consists essentially of a variant of an illustrative Kabat CDR-H1 sequence provided in this disclosure. In some aspects, the Kabat CDR-H1 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Kabat CDR-H1 sequences provided in this disclosure. In some aspects, the Kabat CDR-H1 sequence comprises, consists of, or consists essentially of any of the illustrative Kabat CDR-H1 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.2.1.9. Excluded V_H Sequences Comprising Kabat CDRs

[0083] In some embodiments, the V_H sequences provided herein do not comprise certain Kabat CDR-H3, CDR-H2, and/or CDR-H1 sequences.

[0084] In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 108-112 or 132-136. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 108. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 109. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 110. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 111. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 112. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 132. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 133. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 134. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 135. In some aspects, the Kabat CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 136.

[0085] In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 55-59 or 103-107. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 55. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 56. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 57. In some aspects, the Kabat

CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 58. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 59. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 103. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 104. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 105. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 106. In some aspects, the Kabat CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 107.

[0086] In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 2-6 or 50-54. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 2. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 3. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 4. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 5. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 6. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 50. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 51. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 52. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 53. In some aspects, the Kabat CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 54.

2.2.2. V_H Sequences Comprising Illustrative Chothia CDRs

[0087] In some embodiments, the antibody comprises a V_H sequence comprising one or more Chothia CDR-H sequences comprising, consisting of, or consisting essentially of one or more illustrative Chothia CDR-H sequences provided in this disclosure, and variants thereof.

2.2.2.1. Chothia CDR-H3

[0088] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315. In some aspects, the antibody comprises a

[illegible]

comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 131. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 309. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 310. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 311. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 312. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 313. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 314. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 315.

2.2.2.2. Chothia CDR-H2

[0089] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 60-78. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 60. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 61. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 62. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 63. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 64. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 65. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 66. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially

of SEQ ID NO: 67. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 68. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 69. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 70. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 71. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 72. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 73. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 74. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 75. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 76. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 77. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 78.

2.2.2.3. Chothia CDR-H1

[0090] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 7-25. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 7. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 8. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 9. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 10. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising,

consisting of, or consisting essentially of SEQ ID NO: 11. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 12. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 13. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 14. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 15. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 16. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 17. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 18. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 19. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 20. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 21. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 22. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 23. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 24. In some aspects, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 25.

2.2.2.4. Chothia CDR-H3 + Chothia CDR-H2

[0091] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315, and a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 60-78. In some aspects, the Chothia CDR-H3 sequence and the Chothia CDR-H2 sequence

are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Chothia CDR-H3 and Chothia CDR-H2 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.2.5. Chothia CDR-H3 + Chothia CDR-H1

[0092] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315, and a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 7-25. In some aspects, the Chothia CDR-H3 sequence and the Chothia CDR-H1 sequence are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Chothia CDR-H3 and Chothia CDR-H1 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.2.6. Chothia CDR-H1 + Chothia CDR-H2

[0093] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 7-25 and a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 60-78. In some aspects, the Chothia CDR-H1 sequence and the Chothia CDR-H2 sequence are both from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Chothia CDR-H1 and Chothia CDR-H2 are both from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264.

2.2.2.7. Chothia CDR-H1 + Chothia CDR-H2 + Chothia CDR-H3

[0094] In some embodiments, the antibody comprises a V_H sequence comprising a Chothia CDR-H1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 7-25, a Chothia CDR-H2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 60-78, and a Chothia CDR-H3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 113-131 and 309-315. In some aspects, the Chothia CDR-H1 sequence, Chothia CDR-H2 sequence, and Chothia CDR-H3 sequence are all from a single illustrative V_H sequence provided in this disclosure. For example, in some aspects, the Chothia CDR-H1, Chothia CDR-H2, and Chothia CDR-H3 are all from a single illustrative V_H sequence selected from SEQ ID NOs: 246-264 and 316-322.

2.2.2.8. Variants of V_H Sequences Comprising Illustrative Chothia CDRs

[0095] In some embodiments, the V_H sequences provided herein comprise a variant of an illustrative Chothia CDR-H3, CDR-H2, and/or CDR-H1 sequence provided in this disclosure.

[0096] In some aspects, the Chothia CDR-H3 sequence comprises, consists of, or consists essentially of a variant of an illustrative Chothia CDR-H3 sequence provided in this disclosure. In some aspects, the Chothia CDR-H3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Chothia CDR-H3 sequences provided in this disclosure. In some aspects, the Chothia CDR-H3 sequence comprises, consists of, or consists essentially of any of the illustrative Chothia CDR-H3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0097] In some aspects, the Chothia CDR-H2 sequence comprises, consists of, or consists essentially of a variant of an illustrative Chothia CDR-H2 sequence provided in this disclosure. In some aspects, the Chothia CDR-H2 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Chothia CDR-H2 sequences provided in this disclosure. In some aspects, the Chothia CDR-H2 sequence comprises, consists of, or consists essentially of any of the illustrative Chothia CDR-H2 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0098] In some aspects, the Chothia CDR-H1 sequence comprises, consists of, or consists essentially of a variant of an illustrative Chothia CDR-H1 sequence provided in this disclosure. In some aspects, the Chothia CDR-H1 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative Chothia CDR-H1 sequences provided in this disclosure. In some aspects, the Chothia CDR-H1 sequence comprises, consists of, or consists essentially of any of the illustrative Chothia CDR-H1 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.2.2.9. Excluded V_H Sequences Comprising Chothia CDRs

[0099] In some embodiments, the V_H sequences provided herein do not comprise certain Chothia CDR-H3, CDR-H2, and/or CDR-H1 sequences.

[00100] In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 108-112 or 132-136. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 108. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 109. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 110. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 111. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 112. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 132. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 133. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 134. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 135. In some aspects, the Chothia CDR-H3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 136.

[00101] In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 79-83. In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 79. In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 80. In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 81. In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 82. In some aspects, the Chothia CDR-H2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 83.

[00102] In some aspects, the Chothia CDR-H1 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 26-30. In some aspects, the Chothia CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 26. In some aspects, the Chothia CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 27. In some aspects, the Chothia CDR-H1 sequence does

not comprise, consist of, or consist essentially of SEQ ID NO: 28. In some aspects, the Chothia CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 29. In some aspects, the Chothia CDR-H1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 30.

2.3. V_H Sequences

[00103] In some embodiments, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 246-264 and 316-322. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 246. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 247. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 248. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 249. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 250. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 251. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 252. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 253. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 254. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 255 (with or without a serine prepended to the sequence). In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 256. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 257. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 258. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 259. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 260. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 261. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 262. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 263. In some

aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 264. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 316. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 317. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 318. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 319. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 320. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 321. In some aspects, the antibody comprises a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 322.

2.3.1. Variants of V_H Sequences

[00104] In some embodiments, the V_H sequences provided herein comprise, consist of, or consist essentially of a variant of an illustrative V_H sequence provided in this disclosure.

[00105] In some aspects, the V_H sequence comprises, consists of, or consists essentially of a variant of an illustrative V_H sequence provided in this disclosure. In some aspects, the V_H sequence comprises, consists of, or consists essentially of a sequence having at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.5% identity with any of the illustrative V_H sequences provided in this disclosure.

[00106] In some embodiments, the V_H sequence comprises, consists of, or consists essentially of any of the illustrative V_H sequences provided in this disclosure, 20 or fewer, 19 or fewer, 18 or fewer, 17 or fewer, 16 or fewer, 15 or fewer, 14 or fewer, 13 or fewer, 12 or fewer, 11 or fewer, 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 or fewer amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.3.2. Excluded V_H Sequences

[00107] In some embodiments, the V_H sequences provided herein do not comprise certain V_H sequences.

[00108] In some aspects, the V_H sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 265-269. In some aspects, the V_H sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 265. In some

aspects, the V_H sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 266. In some aspects, the V_H sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 267. In some aspects, the V_H sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 268. In some aspects, the V_H sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 269.

2.4. CDR-L3 Sequences

[00109] In some embodiments, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 200-218. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 200. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 201. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 202. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 203. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 204. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 205. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 206. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 207. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 208. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 209. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 210. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 211. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 212. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 213. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 214. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 215. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially

of SEQ ID NO: 216. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 217. In some aspects, the antibody comprises a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 218.

[00110] In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-L3 sequence provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-L3 sequences provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-L3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[00111] In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 195-199 or 219-223. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 195. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 196. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 197. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 198. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 199. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 219. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 220. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 221. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 222. In some aspects the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 223.

2.5. V_L Sequences Comprising Illustrative CDRs

[00112] In some embodiments, the antibody comprises a V_L sequence comprising one or more CDR-L sequences comprising, consisting of, or consisting essentially of one or more illustrative CDR-L sequences provided in this disclosure, and variants thereof.

2.5.1. CDR-L3

[illegible]

some aspects, the antibody comprises a V_L sequence comprising a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 218.

2.5.2. CDR-L2

[00114] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 171-189. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 171. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 172. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 173. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 174. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 175. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 176. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 177. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 178. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 179. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 180. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 181. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 182. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 183. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 184. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 185. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of,

or consisting essentially of SEQ ID NO: 186. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 187. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 188. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L2 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 189.

2.5.3. CDR-L1

[00115] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 142-160. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 142. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 143. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 144. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 145. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 146. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 147. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 148. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 149. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 150. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 151. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 152. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 153. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 154. In some aspects, the antibody comprises a V_L sequence comprising a

CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 155. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 156. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 157. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 158. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 159. In some aspects, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 160.

2.5.4. CDR-L3 + CDR-L2

[00116] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 200-218 and a CDR-L2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 171-189. In some aspects, the CDR-L3 sequence and the CDR-L2 sequence are both from a single illustrative V_L sequence provided in this disclosure. For example, in some aspects, the CDR-L3 and CDR-L2 are both from a single illustrative V_L sequence selected from SEQ ID NOs: 270-288.

2.5.5. CDR-L3 + CDR-L1

[00117] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 200-218 and a CDR-L1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 142-160. In some aspects, the CDR-L3 sequence and the CDR-L1 sequence are both from a single illustrative V_L sequence provided in this disclosure. For example, in some aspects, the CDR-L3 and CDR-L1 are both from a single illustrative V_L sequence selected from SEQ ID NOs: 270-288.

2.5.6. CDR-L1 + CDR-L2

[00118] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 142-160 and a CDR-L2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 171-189. In some aspects, the CDR-L1 sequence and the CDR-L2 sequence are both from a single illustrative V_L sequence provided in this disclosure. For example, in some aspects, the CDR-L1 and CDR-L2 are both from a

single illustrative V_L sequence selected from SEQ ID NOs: 270-288.

2.5.7. CDR-L1 + CDR-L2 + CDR-L3

[00119] In some embodiments, the antibody comprises a V_L sequence comprising a CDR-L1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 142-160, a CDR-L2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 171-189, and a CDR-L3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L1 sequence, CDR-L2 sequence, and CDR-L3 sequence are all from a single illustrative V_L sequence provided in this disclosure. For example, in some aspects, the CDR-L1, CDR-L2, and CDR-L3 are all from a single illustrative V_L sequence selected from SEQ ID NOs: 270-288.

2.5.8. Variants of V_L Sequences Comprising Illustrative CDR-Ls

[00120] In some embodiments, the V_L sequences provided herein comprise a variant of an illustrative CDR-L3, CDR-L2, and/or CDR-L1 sequence provided in this disclosure.

[00121] In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-L3 sequence provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-L3 sequences provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-L3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[00122] In some aspects, the CDR-L2 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-L2 sequence provided in this disclosure. In some aspects, the CDR-L2 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-L2 sequences provided in this disclosure. In some aspects, the CDR-L2 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-L2 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[00123] In some aspects, the CDR-L1 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-L1 sequence provided in this disclosure. In

some aspects, the CDR-L1 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-L1 sequences provided in this disclosure. In some aspects, the CDR-L1 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-L1 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.5.9. Excluded V_L Sequences Comprising CDR-Ls

[00124] In some embodiments, the V_L sequences provided herein do not comprise certain CDR-L3, CDR-L2, and/or CDR-L1 sequences.

[00125] In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 195. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 196. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 197. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 198. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 199. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 219. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 220. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 221. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 222. In some aspects, the CDR-L3 sequence does not comprise, consist of, or consist essentially of SEQ ID NOs: 223.

[00126] In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 166-170 or 190-194. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 190. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 166. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 167. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 168. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 169. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of

SEQ ID NO: 170. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 191. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 192. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 193. In some aspects, the CDR-L2 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 194.

[00127] In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 137-141 or 161-165. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 137. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 138. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 139. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 140. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 141. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 161. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 162. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 163. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 164. In some aspects, the CDR-L1 sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 165.

2.6. V_L Sequences

[00128] In some embodiments, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 270-288. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 270. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 281. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 282. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 283. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 284. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 285. In some aspects, the antibody comprises a V_L sequence

comprising, consisting of, or consisting essentially of SEQ ID NO: 286. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 287. In some aspects, the antibody comprises a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 288.

2.6.1. Variants of V_L Sequences

[00129] In some embodiments, the V_L sequences provided herein comprise, consist of, or consist essentially of a variant of an illustrative V_L sequence provided in this disclosure.

[00130] In some aspects, the V_L sequence comprises, consists of, or consists essentially of a variant of an illustrative V_L sequence provided in this disclosure. In some aspects, the V_L sequence comprises, consists of, or consists essentially of a sequence having at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.05% identity with any of the illustrative V_L sequences provided in this disclosure.

[00131] In some embodiments, the V_L sequence comprises, consists of, or consists essentially of any of the illustrative V_L sequences provided in this disclosure, 20 or fewer, 19 or fewer, 18 or fewer, 17 or fewer, 16 or fewer, 15 or fewer, 14 or fewer, 13 or fewer, 12 or fewer, 11 or fewer, 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 or fewer amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.6.2. Excluded V_L Sequences

[00132] In some embodiments, the V_L sequences provided herein do not comprise certain V_L sequences.

[00133] In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of a sequence selected from SEQ ID NOs: 289-293. In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 289. In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 290. In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 291. In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 292. In some aspects, the V_L sequence does not comprise, consist of, or consist essentially of SEQ ID NO: 293.

2.7. Pairs

2.7.1. CDR-H3 – CDR-L3 Pairs

[00134] In some embodiments, the antibody comprises a CDR-H3 sequence and a

CDR-L3 sequence. In some aspects, the CDR-H3 sequence is part of a V_H and the CDR-L3 sequence is part of a V_L .

[00135] In some aspects, the CDR-H3 sequence is a CDR-H3 sequence comprising, consisting of, or consisting essentially of SEQ ID NOs: 113-131 and 309-315, and the CDR-L3 sequence is a CDR-L3 sequence comprising, consisting of, or consisting essentially of SEQ ID NOs: 200-218.

[00136] In some aspects, the CDR-H3 sequence is SEQ ID NO: 113, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00137] In some aspects, the CDR-H3 sequence is SEQ ID NO: 114, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is

SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00138] In some aspects, the CDR-H3 sequence is SEQ ID NO: 115, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00139] In some aspects, the CDR-H3 sequence is SEQ ID NO: 116, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00140] In some aspects, the CDR-H3 sequence is SEQ ID NO: 117, and the CDR-L3 sequence is selected from SEQ ID NOS: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00141] In some aspects, the CDR-H3 sequence is SEQ ID NO: 118, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00142] In some aspects, the CDR-H3 sequence is SEQ ID NO: 119, and the CDR-L3 sequence is selected from SEQ ID NOS: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some

aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00147] In some aspects, the CDR-H3 sequence is SEQ ID NO: 124, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00148] In some aspects, the CDR-H3 sequence is SEQ ID NO: 125, and the CDR-L3 sequence is selected from SEQ ID NOS: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is

SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00149] In some aspects, the CDR-H3 sequence is SEQ ID NO: 126, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00150] In some aspects, the CDR-H3 sequence is SEQ ID NO: 127, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00158] In some aspects, the CDR-H3 sequence is SEQ ID NO: 312, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00159] In some aspects, the CDR-H3 sequence is SEQ ID NO: 313, and the CDR-L3 sequence is selected from SEQ ID NOS: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is

SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00160] In some aspects, the CDR-H3 sequence is SEQ ID NO: 314, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

[00161] In some aspects, the CDR-H3 sequence is SEQ ID NO: 315, and the CDR-L3 sequence is selected from SEQ ID NOs: 200-218. In some aspects, the CDR-L3 sequence is SEQ ID NO: 200. In some aspects, the CDR-L3 sequence is SEQ ID NO: 201. In some aspects, the CDR-L3 sequence is SEQ ID NO: 202. In some aspects, the CDR-L3 sequence is SEQ ID NO: 203. In some aspects, the CDR-L3 sequence is SEQ ID NO: 204. In some aspects, the CDR-L3 sequence is SEQ ID NO: 205. In some aspects, the CDR-L3 sequence is SEQ ID NO: 206. In some aspects, the CDR-L3 sequence is SEQ ID NO: 207. In some aspects, the CDR-L3 sequence is SEQ ID NO: 208. In some aspects, the CDR-L3 sequence is SEQ ID NO: 209. In some aspects, the CDR-L3 sequence is SEQ ID NO: 210. In some aspects, the CDR-L3 sequence is SEQ ID NO: 211. In some aspects, the CDR-L3 sequence is SEQ ID NO: 212. In some aspects, the CDR-L3 sequence is SEQ ID NO: 213. In some aspects, the CDR-L3 sequence is SEQ ID NO: 214. In some aspects, the CDR-L3 sequence is SEQ ID NO: 215. In some aspects, the CDR-L3 sequence is SEQ ID NO: 216. In some aspects, the CDR-L3 sequence is SEQ ID NO: 217. In some aspects, the CDR-L3 sequence is SEQ ID NO: 218.

2.7.1.1. Variants of CDR-H3 – CDR-L3 Pairs

[00162] In some embodiments, the CDR-H3 – CDR-L3 pairs provided herein comprise a variant of an illustrative CDR-H3 and/or CDR-L1 sequence provided in this disclosure.

[00163] In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-H3 sequence provided in this disclosure. In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-H3 sequences provided in this disclosure. In some aspects, the CDR-H3 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-H3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[00164] In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a variant of an illustrative CDR-L3 sequence provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% identity with any of the illustrative CDR-L3 sequences provided in this disclosure. In some aspects, the CDR-L3 sequence comprises, consists of, or consists essentially of any of the illustrative CDR-L3 sequences provided in this disclosure, with 1, 2, or 3 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.7.1.2. Excluded CDR-H3 – CDR-L3 Pairs

[00165] In some embodiments, the CDR-H3 – CDR-L3 pairs provided herein do not comprise certain CDR-H3 – CDR-L3 pairs.

[00166] In some aspects, the CDR-H3 sequence is not selected from SEQ ID NOs: 108-112 or 132-136, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223.

[00167] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 108, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the

CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

[00168] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 109, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

[00169] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 110, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

[00170] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 111, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

[00171] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 112, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not

[00175] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 135, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

[00176] In some aspects, the CDR-H3 sequence is not SEQ ID NO: 136, and the CDR-L3 sequence is not selected from SEQ ID NOs: 195-199 or 219-223. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 195. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 196. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 197. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 198. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 199. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 219. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 220. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 221. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 222. In some aspects, the CDR-L3 sequence is not SEQ ID NO: 223.

2.7.2. $V_H - V_L$ Pairs

[00177] In some embodiments, the antibody comprises a V_H sequence and a V_L sequence.

[00178] In some aspects, the V_H sequence is a V_H sequence comprising, consisting of, or consisting essentially of SEQ ID NOs: 246-264 and 316-322, and the V_L sequence is a V_L sequence comprising, consisting of, or consisting essentially of SEQ ID NOs: 270-288.

[00179] In some aspects, the V_H sequence is SEQ ID NO: 246, and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some

SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some aspects, the V_L sequence is SEQ ID NO: 281. In some aspects, the V_L sequence is SEQ ID NO: 282. In some aspects, the V_L sequence is SEQ ID NO: 283. In some aspects, the V_L sequence is SEQ ID NO: 284. In some aspects, the V_L sequence is SEQ ID NO: 285. In some aspects, the V_L sequence is SEQ ID NO: 286. In some aspects, the V_L sequence is SEQ ID NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

[00188] In some aspects, the V_H sequence is SEQ ID NO: 255 (with or without a serine prepended to the sequence), and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some aspects, the V_L sequence is SEQ ID NO: 281. In some aspects, the V_L sequence is SEQ ID NO: 282. In some aspects, the V_L sequence is SEQ ID NO: 283. In some aspects, the V_L sequence is SEQ ID NO: 284. In some aspects, the V_L sequence is SEQ ID NO: 285. In some aspects, the V_L sequence is SEQ ID NO: 286. In some aspects, the V_L sequence is SEQ ID NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

[00189] In some aspects, the V_H sequence is SEQ ID NO: 256, and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some aspects, the V_L sequence is SEQ ID NO: 281. In some aspects, the V_L sequence is SEQ ID

aspects, the V_L sequence is SEQ ID NO: 286. In some aspects, the V_L sequence is SEQ ID NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

[00200] In some aspects, the V_H sequence is SEQ ID NO: 318, and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some aspects, the V_L sequence is SEQ ID NO: 281. In some aspects, the V_L sequence is SEQ ID NO: 282. In some aspects, the V_L sequence is SEQ ID NO: 283. In some aspects, the V_L sequence is SEQ ID NO: 284. In some aspects, the V_L sequence is SEQ ID NO: 285. In some aspects, the V_L sequence is SEQ ID NO: 286. In some aspects, the V_L sequence is SEQ ID NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

[00201] In some aspects, the V_H sequence is SEQ ID NO: 319, and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In some aspects, the V_L sequence is SEQ ID NO: 276. In some aspects, the V_L sequence is SEQ ID NO: 277. In some aspects, the V_L sequence is SEQ ID NO: 278. In some aspects, the V_L sequence is SEQ ID NO: 279. In some aspects, the V_L sequence is SEQ ID NO: 280. In some aspects, the V_L sequence is SEQ ID NO: 281. In some aspects, the V_L sequence is SEQ ID NO: 282. In some aspects, the V_L sequence is SEQ ID NO: 283. In some aspects, the V_L sequence is SEQ ID NO: 284. In some aspects, the V_L sequence is SEQ ID NO: 285. In some aspects, the V_L sequence is SEQ ID NO: 286. In some aspects, the V_L sequence is SEQ ID NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

[00202] In some aspects, the V_H sequence is SEQ ID NO: 320, and the V_L sequence is selected from SEQ ID NOs: 270-288. In some aspects, the V_L sequence is SEQ ID NO: 270. In some aspects, the V_L sequence is SEQ ID NO: 271. In some aspects, the V_L sequence is SEQ ID NO: 272. In some aspects, the V_L sequence is SEQ ID NO: 273. In some aspects, the V_L sequence is SEQ ID NO: 274. In some aspects, the V_L sequence is SEQ ID NO: 275. In

NO: 287. In some aspects, the V_L sequence is SEQ ID NO: 288.

2.7.2.1. Variants of $V_H - V_L$ Pairs

[00205] In some embodiments, the $V_H - V_L$ pairs provided herein comprise a variant of an illustrative V_H and/or V_L sequence provided in this disclosure.

[00206] In some aspects, the V_H sequence comprises, consists of, or consists essentially of a variant of an illustrative V_H sequence provided in this disclosure. In some aspects, the V_H sequence comprises, consists of, or consists essentially of a sequence having at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.1% identity with any of the illustrative V_H sequences provided in this disclosure.

[00207] In some embodiments, the V_H sequence comprises, consists of, or consists essentially of any of the illustrative V_H sequences provided in this disclosure, 20 or fewer, 19 or fewer, 18 or fewer, 17 or fewer, 16 or fewer, 15 or fewer, 14 or fewer, 13 or fewer, 12 or fewer, 11 or fewer, 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 or fewer amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[00208] In some aspects, the V_L sequence comprises, consists of, or consists essentially of a variant of an illustrative V_L sequence provided in this disclosure. In some aspects, the V_L sequence comprises, consists of, or consists essentially of a sequence having at least 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.05% identity with any of the illustrative V_L sequences provided in this disclosure.

[00209] In some embodiments, the V_L sequence comprises, consists of, or consists essentially of any of the illustrative V_L sequences provided in this disclosure, 20 or fewer, 19 or fewer, 18 or fewer, 17 or fewer, 16 or fewer, 15 or fewer, 14 or fewer, 13 or fewer, 12 or fewer, 11 or fewer, 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 or fewer amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

2.7.2.2. Excluded $V_H - V_L$ Pairs

[00210] In some embodiments, the $V_H - V_L$ pairs provided herein do not comprise certain $V_H - V_L$ pairs.

[00211] In some aspects, the V_H sequence is not selected from SEQ ID NOs: 265-269, and the V_L sequence is not selected from SEQ ID NOs: 289-293.

[00212] In some aspects, the V_H sequence is not SEQ ID NO: 265, and the V_L sequence is not selected from SEQ ID NO: 289-293. In some aspects, the V_L sequence is not SEQ ID NO: 289. In some aspects, the V_L sequence is not SEQ ID NO: 290. In some aspects, the V_L sequence is not SEQ ID NO: 291. In some aspects, the V_L sequence is not SEQ ID NO: 292. In some aspects, the V_L sequence is not SEQ ID NO: 293.

[00213] In some aspects, the V_H sequence is not SEQ ID NO: 266, and the V_L sequence is not selected from SEQ ID NO: 289-293. In some aspects, the V_L sequence is not SEQ ID NO: 289. In some aspects, the V_L sequence is not SEQ ID NO: 290. In some aspects, the V_L sequence is not SEQ ID NO: 291. In some aspects, the V_L sequence is not SEQ ID NO: 292. In some aspects, the V_L sequence is not SEQ ID NO: 293.

[00214] In some aspects, the V_H sequence is not SEQ ID NO: 267, and the V_L sequence is not selected from SEQ ID NO: 289-293. In some aspects, the V_L sequence is not SEQ ID NO: 289. In some aspects, the V_L sequence is not SEQ ID NO: 290. In some aspects, the V_L sequence is not SEQ ID NO: 291. In some aspects, the V_L sequence is not SEQ ID NO: 292. In some aspects, the V_L sequence is not SEQ ID NO: 293.

[00215] In some aspects, the V_H sequence is not SEQ ID NO: 268, and the V_L sequence is not selected from SEQ ID NO: 289-293. In some aspects, the V_L sequence is not SEQ ID NO: 289. In some aspects, the V_L sequence is not SEQ ID NO: 290. In some aspects, the V_L sequence is not SEQ ID NO: 291. In some aspects, the V_L sequence is not SEQ ID NO: 292. In some aspects, the V_L sequence is not SEQ ID NO: 293.

[00216] In some aspects, the V_H sequence is not SEQ ID NO: 269, and the V_L sequence is not selected from SEQ ID NO: 289-293. In some aspects, the V_L sequence is not SEQ ID NO: 289. In some aspects, the V_L sequence is not SEQ ID NO: 290. In some aspects, the V_L sequence is not SEQ ID NO: 291. In some aspects, the V_L sequence is not SEQ ID NO: 292. In some aspects, the V_L sequence is not SEQ ID NO: 293.

2.8. Consensus Sequences

[00217] In some embodiments, provided herein are anti-PD-1 antibodies comprising one or more sequences defined by consensus sequences. Each consensus sequence is based, at least in part, on one or more alignments of two or more useful anti-PD-1 CDR sequences provided in this disclosure. Based on such alignments, a person of skill in the art would recognize that different amino acid residues may be useful in certain positions of the CDRs. Accordingly, each consensus sequence encompasses two or more useful anti-PD-1 CDR

sequences.

2.8.1. CDR-H3 Consensus Sequences

[00218] In some embodiments, the antibody comprises a CDR-H3 sequence defined by the consensus sequence D- α_2 - α_3 -Y- α_5 - α_6 -G-S-G-Y, where α_2 is A, V, or S; α_3 is D or E; α_5 is S or G; and α_6 is S, L, or T. In some embodiments, α_5 is S, G, or R. Sequencing of individual clones isolated from the output of the antibody selection process revealed that R occurred at position α_5 at nearly the same frequency as G.

[00219] In some aspects, if α_2 is A, then α_3 is not D; α_5 is not S; or α_6 is not S; or combinations thereof.

[00220] In some aspects, α_2 is V or S; α_3 is E; α_5 is G; or α_6 is L or T; or combinations thereof.

[00221] In some aspects, α_2 is not A; α_3 is not D; α_5 is not S; or α_6 is not S; or combinations thereof.

[00222] In some embodiments, the antibody comprises a CDR-H3 sequence defined by the consensus sequence β_1 -G-Y- β_4 - β_5 -Y- β_7 - β_8 -F- β_{10} - β_{11} , where β_1 is not present or Q; β_4 is G or D; β_5 is N or V; β_7 is L or S; β_8 is Y or W; β_{10} is D or A; and β_{11} is V or Y.

2.8.2. Chothia CDR-H1 Consensus Sequences

[00223] In some embodiments, the antibody comprises a Chothia CDR-H1 sequence defined by the consensus sequence G- ϵ_2 - ϵ_3 - ϵ_4 - ϵ_5 - ϵ_6 - ϵ_7 , where ϵ_2 is Y or F; ϵ_3 is T, R or I; ϵ_4 is F or L; ϵ_5 is S, E, T, P, or R; ϵ_6 is T, S, H, Q, R, or W; and ϵ_7 is F, Y, or Q.

[00224] In some aspects, if ϵ_5 is T, then ϵ_6 is not S.

[00225] In some aspects, ϵ_5 is S, E, P, or R; or ϵ_6 is T, H, Q, R, or W; or combinations thereof.

[00226] In some aspects, ϵ_2 is not Y; ϵ_3 is not T or R; ϵ_5 is not T; ϵ_6 is not S; or ϵ_7 is not Y; or combinations thereof.

2.8.3. Kabat CDR-H2 Consensus Sequences

[00227] In some embodiments, the antibody comprises a Kabat CDR-H2 sequence defined by the consensus sequence W- γ_2 -S-A- γ_5 -N-G-N-T- γ_{10} -Y-A-Q-K-L-Q-G, where γ_2 is I or V; γ_5 is Y or H; and γ_{10} is K or N.

[00228] In some aspects, γ_2 is not I; γ_5 is not Y; or γ_{10} is not N; or combinations

thereof.

[00229] In some embodiments, the antibody comprises a Kabat CDR-H2 sequence defined by the consensus sequence δ_1 -I-S-G- δ_5 -G- δ_7 - δ_8 -T-Y-Y- δ_{12} -D-S-V- δ_{16} -G, where δ_1 is T or A; δ_5 is S or G; δ_7 is S or G; δ_8 is S, D or N; δ_{12} is A, P or S; and δ_{16} is K or Q.

[00230] In some aspects, if δ_1 is A, then δ_5 is not S; δ_7 is not G; δ_8 is not S; δ_{12} is not A; or δ_{16} is not K; or combinations thereof.

[00231] In some aspects, δ_1 is T; δ_5 is G; δ_7 is S; δ_8 is D or N; or δ_{12} is P or S; or combinations thereof.

[00232] In some aspects, δ_1 is not A; δ_5 is not S; δ_7 is not G; δ_8 is not S; δ_{12} is not A; or δ_{16} is not K; or combinations thereof.

2.8.4. Kabat CDR-H1 Consensus Sequences

[00233] In some embodiments, the antibody comprises a Kabat CDR-H1 sequence defined by the consensus sequence Θ_1 - Θ_2 -G- Θ_4 -S, where Θ_1 is T, R, W, Q, H, or S; Θ_2 is Y, F, or Q; and Θ_4 is M or I.

[00234] In some aspects, Θ_1 is T, R, W, Q, or H; Θ_2 is F or Q; or Θ_4 is M; or combinations thereof.

[00235] In some aspects, Θ_1 is not S; Θ_2 is not Y; or Θ_4 is not I; or combinations thereof.

2.8.5. CDR-L3 Consensus Sequences

[00236] In some embodiments, the antibody comprises a CDR-L3 sequence defined by the consensus sequence Q-Q- π_3 - π_4 - π_5 - π_6 -P- π_8 -T, where π_3 is N, S, or W; π_4 is Y, K, or I; π_5 is N, E, or S; π_6 is S, V, D, or T; and π_8 is Y or W.

[00237] In some aspects, if π_4 is Y, then π_3 is not S; π_5 is not S; π_6 is not T; or π_8 is not W; or combinations thereof.

[00238] In some aspects, π_3 is N or W; π_4 is K or I; π_5 is N or E; π_6 is S, V, or D; or π_8 is Y; or combinations thereof.

[00239] In some aspects, π_3 is not S; π_4 is not Y; π_5 is not S; π_6 is not T; or π_8 is not W; or combinations thereof.

2.8.6. CDR-L1 Consensus Sequences

[00240] In some embodiments, the antibody comprises a CDR-L1 sequence defined by

the consensus sequence S-G-D-A-L- μ_6 - μ_7 -Q-Y- μ_{10} -Y, where μ_6 is P, T, or S; μ_7 is M, T, E, or K; and μ_{10} is G or A.

[00241] In some aspects, if μ_6 is P, then μ_7 is not K, μ_{10} is not A, or combinations thereof.

[00242] In some aspects, μ_6 is T or S; μ_7 is M, T, or E; or μ_{10} is G; or combinations thereof.

[00243] In some aspects, μ_6 is not P; μ_7 is not K; or μ_{10} is not A; or combinations thereof.

[00244] In some embodiments, the antibody comprises a CDR-L1 sequence defined by the consensus sequence R-A-S-E- Σ_5 -V-D- Σ_8 - Σ_9 -G- Σ_{11} -S-F-M- Σ_{15} , where Σ_5 is S or N; Σ_8 is N or D; Σ_9 is S or Y; Σ_{11} is I or V; and Σ_{15} is S or N.

3. Germline

[00245] In some embodiments, the antibody that specifically binds PD-1 is an antibody comprising a variable region that is encoded by a particular germline gene, or a variant thereof. The illustrative antibodies provided herein comprise variable regions that are encoded by the heavy chain variable region germline genes VH1-18, VH3-21, VH3-7, and VH3-15, or variants thereof; and the light chain variable region germline genes V λ 3-25, V κ 1-9, V κ 3-11, V κ 3-20, and V κ 4-1, or variants thereof. One of skill in the art would recognize that the CDR sequences provided herein may also be useful when combined with variable regions encoded by other variable region germline genes, or variants thereof. In particular, the CDR sequences provided herein may be useful when combined with variable regions encoded by variable region germline genes, or variants thereof, that are structurally similar to the variable region germline genes recited above. For example, in some embodiments, a CDR-H sequence provided herein may be combined with a variable region encoded by a variable region germline gene selected from the VH1 or VH3 family, or a variant thereof. In some embodiments, a CDR-L sequence provided herein may be combined with a variable region encoded by a variable region germline gene selected from the V λ 3, V κ 1, V κ 3, and V κ 4 families, or a variant thereof.

4. Affinity

[00246] In some embodiments, the affinity of the antibody for PD-1, as indicated by K_D , is less than about 10^{-5} M, less than about 10^{-6} M, less than about 10^{-7} M, less than about 10^{-8} M, less than about 10^{-9} M, less than about 10^{-10} M, less than about 10^{-11} M, or less than

about 10^{-12} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-10} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-9} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-8} M. In some embodiments, the affinity of the antibody is between about 10^{-8} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-8} M and 10^{-10} M. In some embodiments, the affinity of the antibody is between about 10^{-9} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-10} M and 10^{-11} M.

[00247] In some embodiments, the affinity of the antibody for human PD-1 is between about 3.85×10^{-8} M and 2.52×10^{-10} M. In some embodiment, the affinity of the antibody for human PD-1 is about 2.55×10^{-8} M, about 1.52×10^{-8} M, about 9.52×10^{-9} M, about 1.09×10^{-8} M, about 4.50×10^{-9} M, about 1.90×10^{-9} M, about 4.76×10^{-9} M, about 4.5×10^{-9} M, about 1.04×10^{-8} M, about 9.90×10^{-9} M, about 9.13×10^{-10} M, about 2.52×10^{-10} M, about 2.58×10^{-9} M, about 3.85×10^{-8} M, about 3.66×10^{-9} M, about 3.15×10^{-9} M, about 5.14×10^{-9} M, about 2.47×10^{-9} M, about 2.79×10^{-9} M, about 1.20×10^{-9} M, or about 1.28×10^{-8} M

[00248] In some embodiments, the affinity of the antibody for human PD-1 expressed on the surface of a cell is between about 3.2 and about 0.2 nM. In some embodiment, the affinity of the antibody for human PD-1 expressed on the surface of a cell is about 0.2 nM, about 0.4 nM, about 0.9 nM, about 1 nM, about 0.3 nM, about 0.7 nM, about 0.2 nM, about 0.8 nM, about 3.2 nM, about 2.9 nM, about 1.39 nM, or about 1.34 nM.

[00249] In some embodiments, the affinity of the antibody for murine PD-1 is between about 6.09×10^{-8} M and 9.08×10^{-9} M. In some embodiment, the affinity of the antibody for murine PD-1 is about 6.09×10^{-8} M, about 6.22×10^{-8} M, or about 9.08×10^{-9} M.

[00250] In some embodiments, the affinity of the antibody for cynomolgus PD-1 is between about 2.43×10^{-8} M and 1.95×10^{-10} M. In some embodiment, the affinity of the antibody for cynomolgus PD-1 is about 2.43×10^{-8} M, about 1.55×10^{-8} M, about 2.22×10^{-8} M, about 2.56×10^{-9} M, about 2.54×10^{-9} M, about 5.61×10^{-10} M, or about 1.95×10^{-10} M

[00251] In some embodiments the antibody has a k_a of at least about $10^4 \text{ M}^{-1} \times \text{sec}^{-1}$. In some embodiments the antibody has a k_a of at least about $10^5 \text{ M}^{-1} \times \text{sec}^{-1}$. In some embodiments the antibody has a k_a of at least about $10^6 \text{ M}^{-1} \times \text{sec}^{-1}$. In some embodiments the antibody has a k_a of between about $10^4 \text{ M}^{-1} \times \text{sec}^{-1}$ and about $10^5 \text{ M}^{-1} \times \text{sec}^{-1}$. In some embodiments the antibody has a k_a of between about $10^5 \text{ M}^{-1} \times \text{sec}^{-1}$ and about $10^6 \text{ M}^{-1} \times \text{sec}^{-1}$.

[00252] In some embodiments the antibody has a k_a when associating with human PD-1 of between about $4.74 \times 10^4 \text{ M}^{-1} \times \text{sec}^{-1}$ and about $1.23 \times 10^6 \text{ M}^{-1} \times \text{sec}^{-1}$. In some embodiments the antibody has a k_a when associating with human PD-1 of about $4.88 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $1.23 \times 10^6 \text{ M}^{-1} \times \text{sec}^{-1}$, about $7.37 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $6.87 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $5.63 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $5.16 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $2.48 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $7.98 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $1.82 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $4.74 \times 10^4 \text{ M}^{-1} \times \text{sec}^{-1}$, about $1.85 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $2.00 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, about $8.12 \times 10^4 \text{ M}^{-1} \times \text{sec}^{-1}$, about $1.21 \times 10^6 \text{ M}^{-1} \times \text{sec}^{-1}$, about $1.16 \times 10^6 \text{ M}^{-1} \times \text{sec}^{-1}$, about $5.13 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$, or about $1.86 \times 10^5 \text{ M}^{-1} \times \text{sec}^{-1}$.

[00253] In some embodiments the antibody has a k_d of about 10^{-5} sec^{-1} or less. In some embodiments the antibody has a k_d of about 10^{-4} sec^{-1} or less. In some embodiments the antibody has a k_d of about 10^{-3} sec^{-1} or less. In some embodiments the antibody has a k_d of between about 10^{-2} sec^{-1} and about 10^{-5} sec^{-1} . In some embodiments the antibody has a k_d of between about 10^{-2} sec^{-1} and about 10^{-4} sec^{-1} . In some embodiments the antibody has a k_d of between about 10^{-3} sec^{-1} and about 10^{-5} sec^{-1} .

[00254] In some embodiments the antibody has a k_d when dissociating from human PD-1 of between about $1.87 \times 10^{-2} \text{ sec}^{-1}$ and about $4.17 \times 10^{-4} \text{ sec}^{-1}$. In some embodiments the antibody has a k_d when dissociating from human PD-1 of about $1.24 \times 10^{-2} \text{ sec}^{-1}$, about $1.87 \times 10^{-2} \text{ sec}^{-1}$, about $7.01 \times 10^{-3} \text{ sec}^{-1}$, about $7.74 \times 10^{-3} \text{ sec}^{-1}$, about $2.54 \times 10^{-3} \text{ sec}^{-1}$, about $9.80 \times 10^{-4} \text{ sec}^{-1}$, about $1.18 \times 10^{-3} \text{ sec}^{-1}$, about $3.59 \times 10^{-3} \text{ sec}^{-1}$, about $4.68 \times 10^{-4} \text{ sec}^{-1}$, about $1.82 \times 10^{-3} \text{ sec}^{-1}$, about $6.79 \times 10^{-4} \text{ sec}^{-1}$, about $6.28 \times 10^{-4} \text{ sec}^{-1}$, about $4.17 \times 10^{-4} \text{ sec}^{-1}$, about $2.99 \times 10^{-3} \text{ sec}^{-1}$, about $3.24 \times 10^{-3} \text{ sec}^{-1}$, about $6.17 \times 10^{-4} \text{ sec}^{-1}$, or about $2.39 \times 10^{-3} \text{ sec}^{-1}$.

[00255] In some aspects, the K_D , k_a , and k_d are determined at 25°C . In some embodiments, the K_D , k_a , and k_d are determined by surface plasmon resonance. In some embodiments, the K_D , k_a , and k_d are determined according to the methods described in Examples 4 and 6.

5. Inhibition of PD-L1 and PD-L2 Binding

[00256] In some embodiments, the antibody inhibits binding of one or more of PD-L1 and PD-L2 to PD-1.

[00257] In some embodiments, the antibody inhibits binding of PD-L1 to PD-1 with an IC_{50} of about 1 to about 7 nM. In some aspects, the antibody inhibits binding of PD-L1 to PD-1 with an IC_{50} of about 1.99, about 2.53, about 5.86, or about 5.96 nM.

[00258] In some embodiments, the antibody inhibits binding of PD-L2 to PD-1 with an

IC₅₀ of about 0.01 to about 1 nM. In some aspects, the antibody inhibits binding of PD-L2 to PD-1 with an IC₅₀ of about 0.01, about 0.18, about 0.56, or about 0.58 nM.

[00259] In some aspects, the antibody inhibits binding of PD-L1 to PD-1 with an IC₅₀ of about 5.96 nM, and inhibits binding of PD-L2 to PD-1 with an IC₅₀ of about 0.56 nM. In some aspects, the antibody inhibits binding of PD-L1 to PD-1 with an IC₅₀ of about 5.86 nM, and inhibits binding of PD-L2 to PD-1 with an IC₅₀ of about 0.58 nM. In some aspects, the antibody inhibits binding of PD-L1 to PD-1 with an IC₅₀ of about 1.99 nM, and inhibits binding of PD-L2 to PD-1 with an IC₅₀ of about 0.01 nM. In some aspects, the antibody inhibits binding of PD-L1 to PD-1 with an IC₅₀ of about 2.53 nM, and inhibits binding of PD-L2 to PD-1 with an IC₅₀ of about 0.18 nM.

6. PD-1 Assays

[00260] In some embodiments, the anti-PD-1 antibodies induce the secretion of interferon gamma when added to a peripheral blood mononuclear cell (PBMC) two-way mixed lymphocyte reaction (MLR) assay, as described in Examples 8 and 16.

[00261] In some embodiments, the anti-PD-1 antibodies induce the secretion of interferon gamma when added to a PBMC cytomegalovirus recall assay, as described in Example 16.

[00262] In some embodiments, the anti-PD-1 antibodies accelerate the onset of graft versus host disease, as shown in Example 18.

7. Glycosylation Variants

[00263] In certain embodiments, an antibody may be altered to increase, decrease or eliminate the extent to which it is glycosylated. Glycosylation of polypeptides is typically either “N-linked” or “O-linked.”

[00264] “N-linked” glycosylation refers to the attachment of a carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site.

[00265] “O-linked” glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[00266] Addition or deletion of N-linked glycosylation sites to the antibody may be accomplished by altering the amino acid sequence such that one or more of the above-described tripeptide sequences is created or removed. Addition or deletion of O-linked glycosylation sites may be accomplished by addition, deletion, or substitution of one or more serine or threonine residues in or to (as the case may be) the sequence of an antibody.

8. Fc Variants

[00267] In certain embodiments, amino acid modifications may be introduced into the Fc region of an antibody provided herein to generate an Fc region variant. In certain embodiments, the Fc region variant possesses some, but not all, effector functions. Such antibodies may be useful, for example, in applications in which the half-life of the antibody *in vivo* is important, yet certain effector functions are unnecessary or deleterious. Examples of effector functions include complement-dependent cytotoxicity (CDC) and antibody-directed complement-mediated cytotoxicity (ADCC). Numerous substitutions or deletions with altered effector function are known in the art.

[00268] An alteration in CDC and/or ADCC activity can be confirmed using *in vitro* and/or *in vivo* assays. For example, Fc receptor (FcR) binding assays can be conducted to measure FcγR binding. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Ravetch and Kinet, *Ann. Rev. Immunol.*, 1991, 9:457-492.

[00269] Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest are provided in U.S. Patent Nos. 5,500,362 and 5,821,337; Hellstrom et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1986, 83:7059-7063; Hellstrom et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1985, 82:1499-1502; and Bruggemann et al., *J. Exp. Med.*, 1987, 166:1351-1361. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, using an animal model such as that disclosed in Clynes et al. *Proc. Natl. Acad. Sci. U.S.A.*, 1998, 95:652-656.

[00270] C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. Examples of C1q binding assays include those described in WO 2006/029879 and WO 2005/100402.

[00271] Complement activation assays include those described, for example, in

Gazzano-Santoro et al., *J. Immunol. Methods*, 1996, 202:163-171; Cragg et al., *Blood*, 2003, 101:1045-1052; and Cragg and Glennie, *Blood*, 2004, 103:2738-2743.

[00272] FcRn binding and *in vivo* clearance (half-life determination) can also be measured, for example, using the methods described in Petkova et al., *Intl. Immunol.*, 2006, 18:1759-1769.

9. Preparation of Antibodies

9.1. Antigen Preparation

[00273] The PD-1 antigen to be used for production of antibodies may be intact PD-1 or a fragment of PD-1. The intact PD-1, or fragment of PD-1, may be in the form of an isolated protein or expressed by a cell. Other forms of PD-1 useful for generating antibodies will be apparent to those skilled in the art.

9.2. Monoclonal Antibodies

[00274] Monoclonal antibodies may be obtained, for example, using the hybridoma method first described by Kohler et al., *Nature*, 1975, 256:495-497, and/or by recombinant DNA methods (*see e.g.*, U.S. Patent No. 4,816,567). Monoclonal antibodies may also be obtained, for example, using phage or yeast-based libraries. *See e.g.*, U.S. Patent Nos. 8,258,082 and 8,691,730.

[00275] In the hybridoma method, a mouse or other appropriate host animal is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes are then fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. *See* Goding J.W., *Monoclonal Antibodies: Principles and Practice* 3rd ed. (1986) Academic Press, San Diego, CA.

[00276] The hybridoma cells are seeded and grown in a suitable culture medium that contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00277] Useful myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive media conditions, such as the presence or absence of HAT medium. Among these, preferred

myeloma cell lines are murine myeloma lines, such as those derived from MOP-21 and MC-11 mouse tumors (available from the Salk Institute Cell Distribution Center, San Diego, CA), and SP-2 or X63-Ag8-653 cells (available from the American Type Culture Collection, Rockville, MD). Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. *See e.g.*, Kozbor, *J. Immunol.*, 1984, 133:3001.

[00278] After the identification of hybridoma cells that produce antibodies of the desired specificity, affinity, and/or biological activity, selected clones may be subcloned by limiting dilution procedures and grown by standard methods. *See* Goding, *supra*. Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00279] DNA encoding the monoclonal antibodies may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Thus, the hybridoma cells can serve as a useful source of DNA encoding antibodies with the desired properties. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as bacteria (e.g., *E. coli*), yeast (e.g., *Saccharomyces* or *Pichia* sp.), COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody, to produce the monoclonal antibodies.

9.3. Humanized Antibodies

[00280] Humanized antibodies may be generated by replacing most, or all, of the structural portions of a monoclonal antibody with corresponding human antibody sequences. Consequently, a hybrid molecule is generated in which only the antigen-specific variable, or CDR, is composed of non-human sequence. Methods to obtain humanized antibodies include those described in, for example, Winter and Milstein, *Nature*, 1991, 349:293-299; Rader et al., *Proc. Nat. Acad. Sci. U.S.A.*, 1998, 95:8910-8915; Steinberger et al., *J. Biol. Chem.*, 2000, 275:36073-36078; Queen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86:10029-10033; and U.S. Patent Nos. 5,585,089, 5,693,761, 5,693,762, and 6,180,370.

9.4. Human Antibodies

[00281] Human antibodies can be generated by a variety of techniques known in the art, for example by using transgenic animals (e.g., humanized mice). *See, e.g.*, Jakobovits et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1993, 90:2551; Jakobovits et al., *Nature*, 1993, 362:255-

258; Bruggermann et al., *Year in Immuno.*, 1993, 7:33; and U.S. Patent Nos. 5,591,669, 5,589,369 and 5,545,807. Human antibodies can also be derived from phage-display libraries (see e.g., Hoogenboom et al., *J. Mol. Biol.*, 1991, 227:381-388; Marks et al., *J. Mol. Biol.*, 1991, 222:581-597; and U.S. Pat. Nos. 5,565,332 and 5,573,905). Human antibodies may also be generated by *in vitro* activated B cells (see e.g., U.S. Patent. Nos. 5,567,610 and 5,229,275). Human antibodies may also be derived from yeast-based libraries (see e.g., U.S. Patent No. 8,691,730).

10. Vectors, Host Cells, and Recombinant Methods

[00282] The invention also provides isolated nucleic acids encoding anti-PD-1 antibodies, vectors and host cells comprising the nucleic acids, and recombinant techniques for the production of the antibodies.

[00283] For recombinant production of the antibody, the nucleic acid encoding it may be isolated and inserted into a replicable vector for further cloning (i.e., amplification of the DNA) or expression. In some aspects, the nucleic acid may be produced by homologous recombination, for example as described in U.S. Patent No. 5,204,244.

[00284] Many different vectors are known in the art. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence, for example as described in U.S. Patent No. 5,534,615.

[00285] Illustrative examples of suitable host cells are provided below. these host cells are not meant to be limiting.

[00286] Suitable host cells include any prokaryotic (e.g., bacterial) , lower eukaryotic (e.g., yeast), or higher eukaryotic (e.g., mammalian) cells. Suitable prokaryotes include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia* (*E. coli*), *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella* (*S. typhimurium*), *Serratia* (*S. marcescans*), *Shigella*, *Bacilli* (*B. subtilis* and *B. licheniformis*), *Pseudomonas* (*P. aeruginosa*), and *Streptomyces*. One useful *E. coli* cloning host is *E. coli* 294, although other strains such as *E. coli* B, *E. coli* X1776, and *E. coli* W3110 are suitable.

[00287] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are also suitable cloning or expression hosts for anti-PD-1 antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is a commonly used lower eukaryotic

host microorganism. However, a number of other genera, species, and strains are available and useful, such as *Schizosaccharomyces pombe*, *Kluyveromyces* (*K. lactis*, *K. fragilis*, *K. bulgaricus*, *K. wickerhamii*, *K. waltii*, *K. drosophilum*, *K. thermotolerans*, and *K. marxianus*), *Yarrowia*, *Pichia pastoris*, *Candida* (*C. albicans*), *Trichoderma reesia*, *Neurospora crassa*, *Schwanniomyces* (*S. occidentalis*), and filamentous fungi such as, for example *Penicillium*, *Tolypocladium*, and *Aspergillus* (*A. nidulans* and *A. niger*).

[00288] Useful mammalian host cells include COS-7 cells, HEK293 cells; baby hamster kidney (BHK) cells; Chinese hamster ovary (CHO); mouse sertoli cells; African green monkey kidney cells (VERO-76), and the like.

[00289] The host cells used to produce the anti-PD-1 antibody of this invention may be cultured in a variety of media. Commercially available media such as, for example, Ham's F10, Minimal Essential Medium (MEM), RPMI-1640, and Dulbecco's Modified Eagle's Medium (DMEM) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., *Meth. Enz.*, 1979, 58:44; Barnes et al., *Anal. Biochem.*, 1980, 102:255; and U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, and 5,122,469, or WO 90/03430 and WO 87/00195 may be used.

[00290] Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics, trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art.

[00291] The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[00292] When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. For example, Carter et al. (*Bio/Technology*, 1992, 10:163-167) describes a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the

presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation.

[00293] In some embodiments, the antibody is produced in a cell-free system. In some aspects, the cell-free system is an *in vitro* transcription and translation system as described in Yin et al., *mAbs*, 2012, 4:217-225, incorporated by reference in its entirety. In some aspects, the cell-free system utilizes a cell-free extract from a eukaryotic cell or from a prokaryotic cell. In some aspects, the prokaryotic cell is *E. coli*. Cell-free expression of the antibody may be useful, for example, where the antibody accumulates in a cell as an insoluble aggregate, or where yields from periplasmic expression are low.

[00294] Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon[®] or Millipore[®] Pellicon[®] ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[00295] The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being a particularly useful purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human $\gamma 1$, $\gamma 2$, or $\gamma 4$ heavy chains (Lindmark et al., *J. Immunol. Meth.*, 1983, 62:1-13). Protein G is useful for all mouse isotypes and for human $\gamma 3$ (Guss et al., *EMBO J.*, 1986, 5:1567-1575).

[00296] The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_{H3} domain, the BakerBond ABX[®] resin is useful for purification.

[00297] Other techniques for protein purification, such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin Sepharose[®], chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available, and can be applied by one of skill in the art.

[00298] Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5 to about 4.5, generally performed at low salt concentrations (e.g., from about 0 to about 0.25 M salt).

11. Pharmaceutical Compositions and Methods of Administration

[00299] Any of the antibodies provided herein can be provided in any appropriate pharmaceutical composition and be administered by any suitable route of administration. Suitable routes of administration include, but are not limited to, the inhalation, intraarterial, intradermal, intramuscular, intraperitoneal, intravenous, nasal, parenteral, pulmonary, and subcutaneous routes.

[00300] The pharmaceutical composition may comprise one or more pharmaceutical excipients. Any suitable pharmaceutical excipient may be used, and one of ordinary skill in the art is capable of selecting suitable pharmaceutical excipients. Accordingly, the pharmaceutical excipients provided below are intended to be illustrative, and not limiting. Additional pharmaceutical excipients include, for example, those described in the *Handbook of Pharmaceutical Excipients*, Rowe et al. (Eds.) 6th Ed. (2009), incorporated by reference in its entirety.

[00301] In some embodiments, the pharmaceutical composition comprises an anti-foaming agent. Any suitable anti-foaming agent may be used. In some aspects, the anti-foaming agent is selected from an alcohol, an ether, an oil, a wax, a silicone, a surfactant, and combinations thereof. In some aspects, the anti-foaming agent is selected from a mineral oil, a vegetable oil, ethylene bis stearamide, a paraffin wax, an ester wax, a fatty alcohol wax, a long chain fatty alcohol, a fatty acid soap, a fatty acid ester, a silicon glycol, a fluorosilicone, a polyethylene glycol-polypropylene glycol copolymer, polydimethylsiloxane-silicon dioxide, ether, octyl alcohol, capryl alcohol, sorbitan trioleate, ethyl alcohol, 2-ethyl-hexanol, dimethicone, oleyl alcohol, simethicone, and combinations thereof.

[00302] In some embodiments, the pharmaceutical composition comprises a cosolvent. Illustrative examples of cosolvents include ethanol, poly(ethylene) glycol, butylene glycol, dimethylacetamide, glycerin, and propylene glycol.

[00303] In some embodiments, the pharmaceutical composition comprises a buffer. Illustrative examples of buffers include acetate, borate, carbonate, lactate, malate, phosphate, citrate, hydroxide, diethanolamine, monoethanolamine, glycine, methionine, guar gum, and

monosodium glutamate.

[00304] In some embodiments, the pharmaceutical composition comprises a carrier or filler. Illustrative examples of carriers or fillers include lactose, maltodextrin, mannitol, sorbitol, chitosan, stearic acid, xanthan gum, and guar gum.

[00305] In some embodiments, the pharmaceutical composition comprises a surfactant. Illustrative examples of surfactants include *d*-alpha tocopherol, benzalkonium chloride, benzethonium chloride, cetrimide, cetylpyridinium chloride, docusate sodium, glyceryl behenate, glyceryl monooleate, lauric acid, macrogol 15 hydroxystearate, myristyl alcohol, phospholipids, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxylglycerides, sodium lauryl sulfate, sorbitan esters, and vitamin E polyethylene(glycol) succinate.

[00306] In some embodiments, the pharmaceutical composition comprises an anti-caking agent. Illustrative examples of anti-caking agents include calcium phosphate (tribasic), hydroxymethyl cellulose, hydroxypropyl cellulose, and magnesium oxide.

[00307] Other excipients that may be used with the pharmaceutical compositions include, for example, albumin, antioxidants, antibacterial agents, antifungal agents, bioabsorbable polymers, chelating agents, controlled release agents, diluents, dispersing agents, dissolution enhancers, emulsifying agents, gelling agents, ointment bases, penetration enhancers, preservatives, solubilizing agents, solvents, stabilizing agents, and sugars. Specific examples of each of these agents are described, for example, in the *Handbook of Pharmaceutical Excipients*, Rowe et al. (Eds.) 6th Ed. (2009), The Pharmaceutical Press, incorporated by reference in its entirety.

[00308] In some embodiments, the pharmaceutical composition comprises a solvent. In some aspects, the solvent is saline solution, such as a sterile isotonic saline solution or dextrose solution. In some aspects, the solvent is water for injection.

[00309] In some embodiments, the pharmaceutical compositions are in a particulate form, such as a microparticle or a nanoparticle. Microparticles and nanoparticles may be formed from any suitable material, such as a polymer or a lipid. In some aspects, the microparticles or nanoparticles are micelles, liposomes, or polymersomes. In certain embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic

or therapeutic antibodies.

[00310] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising an antibody, since water can facilitate the degradation of some antibodies.

[00311] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00312] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

11.1. Parenteral Dosage Forms

[00313] In certain embodiments, provided are parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[00314] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not

limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00315] Excipients that increase the solubility of one or more of the antibodies disclosed herein can also be incorporated into the parenteral dosage forms.

11.2. Dosage and Unit Dosage Forms

[00316] In human therapeutics, the doctor will determine the posology which he considers most appropriate according to a preventive or curative treatment and according to the age, weight, condition and other factors specific to the subject to be treated.

[00317] The amount of the antibody or composition which will be effective in the prevention or treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the antibody is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00318] In certain embodiments, exemplary doses of a composition include milligram or microgram amounts of the antibody per kilogram of subject or sample weight (*e.g.*, about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to about 10 milligrams per kilogram). In certain embodiment, the dosage of the antibody provided herein, based on weight of the antibody, administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 10 mg/kg, or 15 mg/kg or more of a subject's body weight. In another embodiment, the dosage of the composition or a composition provided herein administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg to 200 mg, 0.1 mg to 100 mg, 0.1 mg to 50 mg, 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 10 mg, 0.1 mg to 7.5 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 mg to 7.5 mg, 0.25 mg to 5 mg, 0.25 mg to 2.5 mg, 0.5 mg to 20 mg, 0.5 to 15 mg, 0.5 to 12 mg, 0.5 to 10 mg, 0.5 mg to 7.5 mg, 0.5 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg

to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 7.5 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

[00319] The dose can be administered according to a suitable schedule, for example, once, two times, three times, or for times weekly. It may be necessary to use dosages of the antibody outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

[00320] Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the antibodies provided herein are also encompassed by the herein described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. For example, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[00321] In certain embodiments, treatment or prevention can be initiated with one or more loading doses of an antibody or composition provided herein followed by one or more maintenance doses.

[00322] In certain embodiments, a dose of an antibody or composition provided herein can be administered to achieve a steady-state concentration of the antibody in blood or serum of the subject. The steady-state concentration can be determined by measurement according to techniques available to those of skill or can be based on the physical characteristics of the subject such as height, weight and age.

[00323] In certain embodiments, administration of the same composition may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

12. Therapeutic Applications

[00324] For therapeutic applications, the antibodies of the invention are administered to a mammal, generally a human, in a pharmaceutically acceptable dosage form such as those known in the art and those discussed above. For example, the antibodies of the invention may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intra-cerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, or intratumoral routes. The antibodies also are suitably administered by peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route may be particularly useful, for example, in the treatment of ovarian tumors.

[00325] The antibodies provided herein may be useful for the treatment of any disease or condition involving PD-1, such as cancer, autoimmune disease, and infection.

[00326] Any suitable cancer may be treated with the antibodies provided herein. Illustrative suitable cancers include, for example, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, basal cell carcinoma, brain tumor, bile duct cancer, bladder cancer, bone cancer, breast cancer, bronchial tumor, Burkitt Lymphoma, carcinoma of unknown primary origin, cardiac tumor, cervical cancer, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasm, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, ductal carcinoma, embryonal tumor, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, fibrous histiocytoma, Ewing sarcoma, eye cancer, germ cell tumor, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic disease, glioma, head and neck cancer, hairy cell leukemia, hepatocellular cancer, histiocytosis, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, midline tract carcinoma involving *NUT* gene, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer,

oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytomas, pituitary tumor, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, renal pelvis and ureter cancer, retinoblastoma, rhabdoid tumor, salivary gland cancer, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, spinal cord tumor, stomach cancer, T-cell lymphoma, teratoid tumor, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, and Wilms tumor.

[00327] Any suitable autoimmune disease may be treated with the antibodies provided herein. Illustrative suitable autoimmune diseases, or diseases with an autoimmune component, include, for example, acute disseminated encephalomyelitis (ADEM), acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome (APS), autoimmune angioedema, autoimmune aplastic anemia, autoimmune dysautonomia, autoimmune hepatitis, autoimmune hyperlipidemia, autoimmune immunodeficiency, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune oophoritis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune thrombocytopenic purpura (ATP), autoimmune thyroid disease, autoimmune urticarial, axonal & neuronal neuropathies, Balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST disease, essential mixed cryoglobulinemia, demyelinating neuropathies, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, experimental allergic encephalomyelitis, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, herpes gestationis,

hypogammaglobulinemia, idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, immunoregulatory lipoproteins, inclusion body myositis, interstitial cystitis, juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus (SLE), Lyme disease (chronic), Meniere's disease, microscopic polyangiitis, mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neuromyelitis optica (Devic's), neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, pars planitis (peripheral uveitis), pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, type I, II, & III autoimmune polyglandular syndromes, polymyalgia rheumatic, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, progesterone dermatitis, primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, idiopathic pulmonary fibrosis, pyoderma gangrenosum, pure red cell aplasia, Raynauds phenomenon, reactive arthritis, reflex sympathetic dystrophy, Reiter's syndrome, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjogren's syndrome, sperm & testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, transverse myelitis, type 1 diabetes, ulcerative colitis, undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vesiculobullous dermatosis, vitiligo, and Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA)).

[00328] Any suitable infection may be treated with the antibodies provided herein. Illustrative suitable infections include, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and other viral infections.

13. Diagnostic Applications

[00329] In some embodiments, the antibodies provided herein are used in diagnostic applications. For example, an anti-PD-1 antibody may be useful in assays for PD-1 protein. In some aspects the antibody can be used to detect the expression of PD-1 in various cells and

tissues. These assays may be useful, for example, evaluating cancer and autoimmune disease.

[00330] In some diagnostic applications, the antibody may be labeled with a detectable moiety. Suitable detectable moieties include, but are not limited to radioisotopes, fluorescent labels, and enzyme-substrate labels. In another embodiment of the invention, the anti-PD-1 antibody need not be labeled, and the presence thereof can be detected using a labeled antibody which specifically binds to the anti-PD-1 antibody.

14. Affinity Purification Reagents

[00331] The antibodies of the invention may be used as affinity purification agents. In this process, the antibodies may be immobilized on a solid phase such as a resin or filter paper, using methods well known in the art. The immobilized antibody is contacted with a sample containing the PD-1 protein (or fragment thereof) to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PD-1 protein, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent, such as glycine buffer, pH 5.0, that will release the PD-1 protein from the antibody.

15. Kits

[00332] In some embodiments, an anti-PD-1 antibody provided herein is provided in the form of a kit, i.e., a packaged combination of reagents in predetermined amounts with instructions for performing a procedure. In some embodiments, the procedure is a diagnostic assay. In other embodiments, the procedure is a therapeutic procedure.

[00333] In some embodiments, the kit further comprises a solvent for the reconstitution of the anti-PD-1 antibody. In some embodiments, the anti-PD-1 antibody is provided in the form of a pharmaceutical composition.

EXAMPLES

Example 1: Generation and Primary Screening of anti-PD-1 Antibodies

[00334] Antibody Fab or scFv libraries were constructed using a standard overlap extension PCR protocol with mutagenic primers targeting CDRs. *See* Heckman and Pease, *Nat. Protoc.*, 2007, 2:924-932, incorporated by reference in its entirety. Selections for novel antibodies were performed using standard ribosome display protocols. *See* Dreier and Plückthun, *Methods Mol. Biol.*, 2011, Clifton, NJ, 687:283-306, incorporated by reference in its entirety. Specifically, scFv-based selection formats were performed according to

published protocols. *See* Hanes and Plückthun, *Proc. Natl. Acad. Sci. U.S.A.*, 1997, 94:4937-4942, incorporated by reference in its entirety. After multiple rounds of selection, the DNA from RT-PCR output was cloned into an optimized vector for cell-free expression using standard molecular biology techniques. *See* Yin et al., *mAbs*, 2012, 4:217-225, incorporated by reference in its entirety. All constructs were HIS- and FLAG-tagged to streamline purification and testing during screening.

[00335] Libraries of antibody variants isolated by the selections were transformed into *E. coli* and grown on agar plates with antibiotic (kanamycin). Individual colonies were picked and grown in liquid broth (TB + kanamycin), and used as a template for DNA amplification via rolling circle amplification (RCA). The variants were then expressed in a cell-free protein synthesis reaction as described in Zawada et al. (*Biotechnol. Bioeng.*, 2011, 108:1570-1578, incorporated by reference in its entirety).

[00336] Briefly, cell-free extracts were treated with 50 μ M iodoacetamide for 30 minutes at room temperature (RT; 20°C) and added to a premix containing cell-free reaction components (*see* Groff et al., *mAbs*, 2014, 6:671-678, incorporated by reference in its entirety) and 10% (v/v) RCA DNA template (approximately 10 μ g/mL DNA) for variants of interest. Cell free reactions, at a final volume of 60 μ L, were incubated at 30°C for 12h on a shaker at 650 rpm in 96-well plates. Four hundred to one-thousand-five-hundred colonies were screened, depending on the predicted diversity of the libraries used in the different selection campaigns. Following synthesis, each reaction was diluted 1:50 into PBST (PBS at pH 7.4 with 0.2% Tween-20 + 0.2% BSA) and the variants expressed in each reaction were tested for functional activity via ELISA-based binding to recombinant human PD-1 (ACROBiosystems, Inc., Catalog No. PD1-H5221 or SINO Biological Inc. Catalog No. 10377-H08H).

[00337] Standard ELISA-based methods were employed. Specifically, 384-well plates were coated with 2 μ g/mL recombinant PD-1 diluted in bicarbonate buffer, and then blocked with BSA. Antibody variants of interest were allowed to bind to the PD-1-coated plates, and detected with secondary antibodies (e.g., HRP-conjugated anti-human Fc or anti-FLAG) and then detected with chemiluminescent substrate (Pierce ELISA SuperSignalTM Substrate). Plates were analyzed on a Molecular Devices SpectraMax[®] M5 plate reader. Top hits were selected based on ELISA signal or signal/noise ratio and sequenced. Based on functional activity and sequence analysis, a subset of variants was selected for further scale-up and characterization.

Example 2: Secondary Screening of Antibody Variants

[00338] The top leads from the initial round of screening were cultured and plasmids encoding the antibody genes of interest were isolated using a QIAprep 96 Turbo[®] Miniprep Kit (Qiagen) according to the manufacturer's instructions. DNA was added to 4 mL of cell-free reaction medium to achieve a final concentration of 10 µg/mL. The cell-free reaction medium was then incubated overnight for 12 hr at 30°C, at 650 rpm.

[00339] The expressed variants from clarified cell-free reactions were purified via immobilized metal ion affinity chromatography (IMAC) using a semi-automated high throughput batch purification method. Briefly, purifications were performed in a 96-well plate format where 50 µL/well of IMAC resin (Ni Sepharose[®] High Performance, GE Healthcare) was equilibrated in IMAC binding buffer (50 mM Tris pH 8.0, 300 mM NaCl, 10 mM imidazole), incubated with 1 mL cell-free reaction for 15 minutes, followed by two washes in IMAC binding buffer. His-tagged antibody variants were then eluted using 200 µL IMAC elution buffer (50 mM Tris pH 8.0, 300mM NaCl, 500 mM imidazole), and buffer exchanged into PBS using a 96-well Zeba[™] plate (7 kDa MWCO, Thermo Fisher). Purified antibodies were quantified via high throughput capillary electrophoresis using the LabChip GXII[®] (Perkin Elmer) against a trastuzumab standard curve, according to the manufacturer's instructions.

Example 3: Hybridoma Generation

[00340] Balb/C mice were immunized with the extracellular domain of human PD-1 fused with human Fc (R&D Systems, *supra*) using standard immunization methods. The spleens and/or lymph nodes of the mice were harvested and fused with P3X cells to generate the hybridomas (Aragen Biosciences, Morgan Hill, CA), similar to what has been previously described. See Chronopoulou et al., *Methods Mol. Biol.*, 2014, 1131:47-70; and Kim et al., *Methods Mol. Biol.*, 2014, 1131:33-45, each of which is incorporated by reference in its entirety.

[00341] Total RNA was extracted from hybridoma cells using an RNeasy[®] Mini Kit (Qiagen) and converted to cDNA using a SMARTer[™] RACE cDNA Amplification Kit (Clontech). Positive clones were identified by gel electrophoresis, cloned using a TOPO[®] kit (Invitrogen), and sequenced using standard Sanger methods.

[00342] Mouse single-chain antibodies were constructed by using total gene synthesis using codons optimized for *E. coli*. The genes encoding the antibodies were cloned into a

standard cell-free expression vector. *See* Yin et al., *mAbs*, 2012, 4:217-225, incorporated by reference in its entirety.

[00343] The CDRs from m1E9 were grafted onto human antibody frameworks VH3-21, VH3-7, V κ 1-9, and V κ 3-11 by standard methodology to yield humanized antibodies h1E9-1, h1E9-2, h1E9-4, and h1E9-5. *See* Kuramochi et al., *Methods Mole. Biol.*, 2014, 1060:123-137, incorporated by reference in its entirety. The same method was used to graft the CDRs from m4B10 onto human antibody frameworks VH3-15, V κ 3-11, V κ 3-20, and V κ 4-1 to yield humanized antibodies h4B10-1, h4B10-2, and h4B10-3.

Example 4: Kinetic Analysis of Selected Antibody Variants

[00344] Human PD-1 (ACROBiosystems, Inc., Catalog No. PD1-H5221), cynomolgus PD-1 (ACROBiosystems, Inc., Catalog No. PD1-H5254), and murine PD-1 (R&D Systems Inc., Catalog No. 1021-PD-100) were used, as indicated, for kinetic analysis.

[00345] Monoclonal anti-FLAG M2 IgG (Sigma-Aldrich # F9291) was immobilized onto a CM5 chip (GE Life Sciences) using amine coupling chemistry (from Amine Coupling Kit, GE Life Sciences). The immobilization steps were carried out at a flow rate of 25 μ l/min in 1x HBS-EP+ buffer (GE Life Sciences; 10x Stock diluted before use). The sensor surfaces were activated for 7 min with a mixture of NHS (0.05 M) and EDC (0.2 M). The Anti-FLAG M2 IgG was injected over all 4 flow cells at a concentration of 25 μ g/ml in 10 mM sodium acetate, pH 4.5, for 7 min. Ethanolamine (1 M, pH 8.5) was injected for 7 min to block any remaining activated groups. An average of 12,000 response units (RU) of capture antibody was immobilized on each flow cell.

[00346] Off-rate and kinetic binding experiments were performed at 25°C using 1x HBS-EP+ buffer. Test and control antibodies were injected over the Anti-FLAG surface at concentrations of 5-10 μ g/mL for 12 seconds at a flow rate of 10 μ l/min on flow cells 2, 3 and 4, followed by a buffer wash for 30 seconds at the same flow rate. Kinetic characterization of antibody samples was carried out with a single concentration of antigen (for off-rate ranking) or a 1:2 dilution series of antigen (for kinetic characterization) and 1 injection of 0 nM antigen (i.e., buffer alone). After capturing ligand (anti-PD-1 antibody) on the anti-FLAG surface, the analyte (huPD1-His) was bound at 50, 25, 12.5, 6.25 and 0 nM for 180 seconds, followed by a 600 second dissociation phase at a flow rate of 50 μ l/min. Between each ligand capture and analyte binding cycle, regeneration was carried out using 2 injections of 10 mM glycine pH 2.0 for 30 seconds at 30 μ L/min, followed by a 30 second

buffer wash step.

[00347] The data was fit with the Biacore T200 Evaluation software, using a 1:1 Langmuir binding model. K_D (affinity, nM) was determined as a ratio of the kinetic rate constants calculated from the fits of the association and dissociation phases.

Example 5: PD-1 – PD-L1 Competition ELISA

[00348] Anti-PD1 antibodies were tested for their ability to block a PD-1/PD-L1 interaction. PD-1 (ACROBiosystems, Inc.) was adsorbed on 384-well white Maxisorp[®] plates (Nunc) at 2 µg/mL in sodium bicarbonate buffer (pH 8.9) and incubated at 30°C for 1 hour or overnight at 4°C. The plate was washed 3 times with PBS pH 7.4 with 0.05% Tween20 and blocked with 2% bovine serum albumin (BSA) in PBS pH 7.4 + 0.1% Tween20 for 1 hour at 30°C.

[00349] The blocking solution was aspirated, and a dilution series of antibody was mixed with 100 nM PD-L1-Fc (ACROBiosystems, Inc.) in 0.2% BSA in PBS pH 7.4 + 0.1% Tween20 (diluent buffer) and incubated at 30°C for 1 hour. The plate was washed, and 10 nM anti-PD-L1 antibody (BioLegend, clone 29E.2A3) in diluent buffer was added to all wells. After a 1 hour incubation at 30°C, the plate was washed and incubated with HRP-conjugated anti-mouse Fc (Jackson Laboratories), followed by detection with SuperSignal[™] Pico Chemiluminescent Substrate (Thermo Pierce). Luminescence was detected on a SpectraMax[®] M5 plate reader (Molecular Devices).

Example 6: Cell Binding Experiments

[00350] Antibodies with expression levels >250 nM and mouse IgGs from hybridomas were tested in a fluorescence-activated cell sorting (FACS) cell-binding assay. Chinese Hamster Ovary (or CHO) Cells stably expressing the human target molecule PD-1 on the cell surface (CHO-PD1) were used to screen for binding. Parental CHO cells were used as a negative control to determine background-binding levels. Parental CHO cells and CHO-PD1 cells were cultured in RPMI w/10% FCS penicillin/streptomycin (Pen/Strep) and glutamine (or Gln) and split every 3-4 days at 10^5 cells/mL.

[00351] A mix of parental CHO cells and CHO-PD1 cells was prepared as follows: Parental CHO cells were washed 2x in PBS then incubated in PBS containing 1µM CellTrace[™] Oregon Green488[®] (Life Technologies) at 37°C for 30 minutes. Cells were then washed 2x with RPMI w/10% fetal calf serum (FCS), washed 2x with FACS buffer (PBS w/2% FCS), suspended thoroughly in ice-cold FACS buffer at a final concentration of 2×10^6

cells/mL and kept on ice. CHO-PD1 cells were similarly washed with FACS buffer and kept on ice at 2×10^6 cells/mL. Parental CHO cells and CHO-PD1 cells were then mixed to obtain a 1:1 cell suspension and seeded at 100 μ L per well on 96 well polypropylene plates. Plates were spun at 1500 rpm for 5 minutes and cell pellets were suspended in 50 μ L FACS buffer containing 6-12 point dilutions of anti-PD-1 variants starting from concentrations of ~100-200 nM antibody, dispensed using BioMek FX (Beckman Coulter). Cells were then incubated on ice for 1 hr, washed with FACS buffer and incubated for 1 hr on ice with 50 μ L FACS buffer containing 2.5 μ g/ml R-phycoerythrin-conjugated goat anti-Human IgG (Jackson ImmunoResearch) or AF647-conjugated goat anti-mouse IgG (Life Technologies) dispensed using BioMek FX (Beckman Coulter). Cells were then washed 2x with FACS buffer and fixed for 10 minutes in 200 μ L PBS with 2% paraformaldehyde (PFA) prior to fluorescence detection. Samples were acquired using a Becton Dickinson LSRII FACS. Mean Fluorescence Intensity of PD-1 antibody binding was analyzed using FlowJo[®] software (Tree Star, Inc.).

Example 7: Cell-based Ligand Competition Experiments

[00352] Variants that showed cell-binding activity were tested in a fluorescence-activated cell sorting (FACS) cell-based competition assay. CHO cells stably expressing the human target molecule PD-1 on the cell surface (CHO- PD1) were used to screen for antibodies that compete with hFc-tagged recombinant human PD-L1 or PD-L2 proteins (R&D systems) for binding to PD-L1 expressed on the cell surface.

[00353] CHO-PD1 cells were cultured in RPMI with 10% FCS Pen/Strep and Gln and split every 3-4 days at 10^5 cells/ml. Cells were washed 2x with FACS buffer (PBS w/2% FCS), thoroughly in ice-cold FACS buffer at a final concentration of 1×10^6 cells/ml and seeded at 100 μ L per well on 96 well polypropylene plates. Plates were spun at 1500 rpm for 5 minutes and cell pellets were suspended in 50 μ L FACS buffer containing 8 point 1:3 dilutions (2x concentrated) of anti-PD-1 antibody variants, starting from high concentration of ~200 nM. 50 μ L FACS buffer containing a fixed amount of either 6 μ g/ml rhPDL2-Fc or 50 μ g/ml rhPDL1-Fc proteins were then added to the cells. Cell were then incubated on ice for 1 hr, washed with FACS buffer and incubated for 1hr on ice with 50 μ L FACS buffer containing 2.5 μ g/ml R-phycoerythrin-conjugated anti-human IgG (Jackson ImmunoResearch). Cells were then washed 2x with FACS buffer and fixed for 10 minutes in 200 μ L PBS with 2% PFA prior to acquisition. Samples were acquired using a Becton Dickinson LSRII FACS. Mean Fluorescence Intensity of rhPDL1 or rhPDL2 protein binding

was analyzed using FlowJo[®] software (Tree Star, Inc.).

Example 8: Evaluating the Effect of Anti-PD-1 Antibodies on Interferon Gamma Production in a Mixed Lymphocyte Reaction

[00354] Anti-PD-1 antibodies were functionally tested for potency in blocking the PD-1 pathway in a peripheral blood mononuclear cell (PBMC) two-way mixed lymphocyte reaction (MLR) assay by measuring interferon gamma (IFN-g) secretion in cell culture medium. 1×10^5 human PBMC from 2 allogeneic donors were co-cultured in RPMI media + 10% FBS in a total volume of 150 μ l in a 96-well U-bottom plate. Anti-PD-1 antibodies were added at specific concentrations to each well. Isotype control antibody, non-PD-1 targeting antibody, or nothing were used as a negative controls. Cells were cultured for 5 days at 37°C. At day 5, conditioned media was collected and levels of IFN-g were measured using DuoSet[®] ELISA kits (R&D Systems).

Example 9: Characteristics of Antibodies Isolated from Primary and Secondary Screen

[00355] Table 1 shows the characteristics of scFv-Fc antibodies (VH1-18/V λ 3-25) isolated as described in Examples 1-2, and characterized as described above.

Table 1. Characteristics of antibodies isolated as described in Examples 1-2, and characterized as described above.

Clone ID	k_a (1/Ms) Human PD-1	k_d (1/s) Human PD-1	K_D (M) Human PD-1	PD-L1 Competition	Cell Binding, K_D (nM) Human PD-1	Murine PD-1 Binding, K_D (M)	Cynomolgus PD-1 Binding, K_D (M)	MLR Activity (IFNg release)
1353-A09 (SEQ ID NO: 238)	4.88E+05	1.24E-02	2.55E-08	yes, ++	0.2	Not tested	Not tested	Not tested
1353-C07 (SEQ ID NO: 239)	1.23E+06	1.87E-02	1.52E-08	yes	0.4	Not tested	Not tested	Not tested
1353-E07 (SEQ ID NO: 240)	7.37E+05	7.01E-03	9.52E-09	yes	0.9	Not tested	Not tested	Not tested
1353-F09 (SEQ ID NO: 241)	6.87E+05	7.47E-03	1.09E-08	yes	1	Not tested	Not tested	Not tested
1353-G08 (SEQ ID NO: 242)	5.63E+05	2.54E-03	4.50E-09	yes, +++	0.3	6.09E- 08	2.43E-08	Not tested
1353-G10 (SEQ ID NO: 243)	5.16E+05	9.80E-04	1.90E-09	yes, ++	0.7	6.22E- 08	1.55E-08	positive
1353-H08 (SEQ ID NO: 244)	2.48E+05	1.18E-03	4.76E-09	yes, +++	0.2	Not tested	Not tested	Not tested
1353-H09 (SEQ ID NO: 245)	7.98E+05	3.59E-03	4.50E-09	yes, ++	0.8	9.08E- 09	2.22E-08	positive

Example 10: Characteristics of Murine Hybridoma Antibodies

[00356] Table 2 shows the characteristics of IgG antibodies isolated as described in Example 3, and characterized as described above.

Table 2. Characteristics of murine hybridoma antibodies, characterized as described above.

Clone ID	EC50 ¹ (nM)	IC50 ² (nM)	Cell Binding, K_D ³ (nM)	PD-L1 Competit ion, IC ₅₀ ⁴ (nM)	PD-L2 Competit ion, IC ₅₀ ⁴ (nM)	Biacore Human PD1 K_D (M)	Biacore Cynomol gus K_D (M)	MLR, IFNg secretion
1B10 VH: SEQ ID NO: 255, with serine prepended to the sequence VL: SEQ ID NO: 279	1.71	9.47	3.2	5.96	0.56	1.04E-08	2.56E-09	positive
1E9	0.33	0.89	2.9	5.86	0.58	9.90E-09	2.54E-09	positive

Clone ID	EC50 ¹ (nM)	IC50 ² (nM)	Cell Binding, K _D ³ (nM)	PD-L1 Competit ion, IC ₅₀ ⁴ (nM)	PD-L2 Competit ion, IC ₅₀ ⁴ (nM)	Biacore Human PD1 K _D (M)	Biacore Cynomol gus K _D (M)	MLR, IFN γ secretion
VH: SEQ ID NO: 256 VL: SEQ ID NO: 280								
4B10 VH: SEQ ID NO: 257 VL: SEQ ID NO: 281	0.47	1.43	1.39	1.99	0.01	9.13E-10	5.61E-10	positive
10B4 VH: SEQ ID NO: 258 VL: SEQ ID NO: 282	0.59	1.32	1.34	2.53	0.18	2.52E-10	1.95E-10	positive

¹ Binding of human PD-1 (ACROBiosystems, Inc., Cat. No. PD1-H5221) via ELISA.

² Competition against PD-L1 (ACROBiosystems, Inc., Cat No. PD1-H5258) via ELISA.

³ CHO cell line overexpressing human PD-1.

⁴ Cell-based competition. i.e., Inhibition of PD-L1 or PD-L2 binding to CHO cells overexpressing human PD-1 is inhibited by IgG.

Example 11: Characteristics of Humanized Antibodies

[00357] Table 3 shows the characteristics of humanized scFv antibodies derived from the murine hybridoma antibodies of Example 10, and characterized as described above.

Table 3. Characteristics of humanized antibodies, characterized as described above.

Clone	k_a (1/Ms) Human PD-1	k_d (1/s) Human PD-1	K_D (M) Human PD-1
h1E9-1 (VH3-21-V κ 1-9) scFv (SEQ ID NO: 227)	1.82E+05	4.68E-04	2.58E-09
h1E9-2 (VH3-21-V κ 3-11) scFv (SEQ ID NO: 228)	4.74E+04	1.82E-03	3.85E-08
h1E9-4 (VH3-7-V κ 1-9) scFv (SEQ ID NO: 229)	1.85E+05	6.79E-04	3.66E-09
h1E9-5 (VH3-7-V κ 3-11) scFv (SEQ ID NO: 230)	2.00E+05	6.28E-04	3.15E-09
m4B10 scFv (SEQ ID NO: 237)	8.12E+04	4.17E-04	5.14E-09
h4B10-1 (VH3-15-V κ 3-11) scFv (SEQ ID NO: 231)	1.21E+06	2.99E-03	2.47E-09
h4B10-2 (VH3-15-V κ 3-20) scFv (SEQ ID NO: 232)	1.16E+06	3.24E-03	2.79E-09
h4B10-3 (VH3-15-V κ 4-1) scFv (SEQ ID NO: 233)	5.13E+05	6.17E-04	1.20E-09
m1B10 scFv (SEQ ID NO: 235)	1.86E+05	2.39E-03	1.28E-08

Example 12: Thermal Stability Data

[00358] Table 4 provides thermal stability of selected antibodies, as determined by differential scanning fluorimetry (DSF).

Table 4. Thermal stability of selected antibodies, as determined by DSF.

Variant ID	Target	Scaffold	T _{m1} (°C)	T _{m2} (°C)
1353-G12	PD1	scFv-Fc	48.2	

Variant ID	Target	Scaffold	Tm1 (°C)	Tm2 (°C)
1353-G08	PD1	scFv-Fc	45.3	
1353-G10	PD1	scFv-Fc	48.6	
1353-H09	PD1	scFv-Fc	49.4	
m1B10	PD1	scFv	55.3	
h1E9-1	PD1	scFv	52.5	
h1E9-2	PD1	scFv	50.9	
h1E9-4	PD1	scFv	55.2	
h1E9-5	PD1	scFv	51.7	
h4b10-1	PD1	scFv	45.5	59.4
h4b10-2	PD1	scFv	45	61.7
h4b10-3	PD1	scFv	52.1	59.3

Example 13: Construction and Evaluation of h1E9-4 and h1E9-5 IgGs

[00359] Variable domains from h1E9-4 scFv (V_H: SEQ ID NO: 260; V_L: SEQ ID NO: 284), and h1E9-5 scFv (V_H: SEQ ID NO: 261; V_L: SEQ ID NO: 285) were grafted onto human antibody constant domains to generate human IgG1 antibodies based on these scFvs.

[00360] Specifically, the V_H sequences were grafted onto C_{H1}-C_{H2}-C_{H3} constant domains to yield full-length IgG HCs with C-terminal FlagHis tags (GSGDYKDDDDKSGSGHHHHHH; SEQ ID NO: 294) for ease of purification and assay development. The V_L sequences were grafted onto C_L domains to yield full-length IgG LCs. The sequence for both the h1E9-4 and h1E9-5 HCs, with C-terminal FlagHis tag, is provided in SEQ ID NO: 302. The sequence for the h1E9-4 LC is provided in SEQ ID NO: 304. The sequence for the h1E9-5 LC is provided in SEQ ID NO: 303.

[00361] The IgGs were expressed in a cell-free reaction, as described in Example 1, and purified using the FlagHis tags. The affinity of the IgGs for PD-1 was measured by surface plasmon resonance (Biacore®) and determined to be essentially equivalent to that of the parent scFvs. Affinity data is provided in Table 5.

Table 5. Affinity of h1E9-4 and h1E9-5 IgGs for PD-1 antigen.

Sample	Ligand	k_a (1/Ms)	k_d (1/s)	K_D (M)
PD-1-his	h1E9-4 IgG	3.56E+04	4.42E-04	1.24E-08
PD-1-his	h1E9-5 IgG	2.43E+04	4.71E-04	1.94E-08

Example 14: Construction and Evaluation of h1E9 Humanized IgGs

[00362] The CDRs for m1E9 were grafted onto human antibody frameworks VH3-23, VH3-30, Vk4-1, Vk3-20, Vk2-28, and Vk1-33 by standard methodology (T. Kuramochi, T. Igawa, H. Tsunoda, and K. Hattori, Method in Molecular Biology, Human Monoclonal Antibodies: Methods and Protocols, 1060, 123-137) to yield humanized antibodies h1E9-HC1, h1E9-HC2, h1E9-HC3, h1E9-LC1, h1E9-LC2, h1E9-LC3, and h1E9-LC4. The HC constructs included C-terminal FlagHis tags (GSGDYKDDDDKSGSGHHHHHH; SEQ ID NO: 294) for ease of purification and assay development. The resulting h1E9 heavy chains were: h1E9-HC3 (SEQ ID NO:324), h1E9-HC2 (SEQ ID NO:325), and h1E9-HC3 (SEQ ID NO:326). The resulting light chains were: h1E9-LC4 (SEQ ID NO:327), h1E9-LC3 (SEQ ID NO:328), h1E9-LC2 (SEQ ID NO:329), and h1E9-LC1 (SEQ ID NO:330).

[00363] The humanized heavy chains h1E9-HC1, h1E9-HC2, h1E9-HC3, and h1E9-5 were paired with humanized IgG light chains h1E9-LC1, h1E9-LC2, h1E9-LC3, and h1E9-LC4. These 16 combinations were then assessed for binding to human PD1 in vitro by surface plasmon resonance (Biacore®) and subsequently human and cynomolgus PD1 binding on CHO cells using FACS as described below.

[00364] Surface plasmon resonance (Biacore®) data is provided in Table 6.

Table 6. Affinity of h1E9 humanized IgGs for PD-1 antigen.

Sample	Ligand	SEQ ID NOS		K_D (M)
PD-1-his	h1E9-HC1 x h1E9-LC1	326	330	5.08E-09
PD-1-his	h1E9-HC1 x h1E9-LC2	326	329	1.90E-08
PD-1-his	h1E9-HC1 x h1E9-LC3	326	328	6.38E-09
PD-1-his	h1E9-HC1 x h1E9-LC4	326	327	6.33E-09
PD-1-his	h1E9-HC2 x h1E9-LC1	325	330	3.11E-09

Sample	Ligand	SEQ ID NOS		K _D (M)
PD-1-his	h1E9-HC2 x h1E9-LC2	325	329	1.23E-08
PD-1-his	h1E9-HC2 x h1E9-LC3	325	328	1.09E-08
PD-1-his	h1E9-HC2 x h1E9-LC4	325	327	4.96E-09
PD-1-his	h1E9-HC3 x h1E9-LC1	324	330	3.60E-09
PD-1-his	h1E9-HC3 x h1E9-LC2	324	329	3.19E-09
PD-1-his	h1E9-HC3 x h1E9-LC3	324	328	1.69E-08
PD-1-his	h1E9-HC3 x h1E9-LC4	324	327	9.40E-09
PD-1-his	h1E9-5-IgG-HC-FLAG-HIS x h1E9-LC1	261	330	3.70E-09
PD-1-his	h1E9-5-IgG-HC-FLAG-HIS x h1E9-LC2	261	329	1.62E-08
PD-1-his	h1E9-5-IgG-HC-FLAG-HIS x h1E9-LC3	261	328	1.63E-08
PD-1-his	h1E9-5-IgG-HC-FLAG-HIS x h1E9-LC4	261	327	7.31E-09

[00365] The affinity of the IgGs for cell-surface expressed human PD-1 were measured according to Example 6, above. Affinity data is provided in Table 7.

Table 7. Affinity of h1E9 humanized IgGs for Cell-Surface Human PD-1 antigen (nM).

		h1E9-HC1	h1E9-HC2	h1E9-HC3	h1E9-5 HC
		SEQ ID NO: 326	SEQ ID NO:325	SEQ ID NO:324	SEQ ID NO:261
h1E9-LC1	SEQ ID NO:330	6	7	8	9
h1E9-LC2	SEQ ID NO:329	12	11	19	16
h1E9-LC3	SEQ ID NO:328	12	9	12	11
h1E9-LC4	SEQ ID NO:327	8	4	9	14

[00366] The affinity of the IgGs for cell-surface expressed cynomolgus PD-1 were measured according to Example 6, above. Affinity data is provided in Table 8.

Table 8. Affinity of h1E9 humanized IgGs for Cell-Surface Cynomolgus PD-1 antigen (nM).

		h1E9-HC1	h1E9-HC2	h1E9-HC3	h1E9-5 HC
		SEQ ID NO: 326	SEQ ID NO:325	SEQ ID NO:324	SEQ ID NO:261
h1E9-LC1	SEQ ID NO:330	7	6	4	4
h1E9-LC2	SEQ ID NO:329	19	9	11	11
h1E9-LC3	SEQ ID NO:328	15	9	8	9
h1E9-LC4	SEQ ID NO:327	11	6	5	12

Example 15: In Vivo Efficacy of Anti-PD-1 Antibodies on Tumor Establishment and Growth

[00367] MC38 colorectal cancer cells (2×10^6 cells in 0.1 mL PBS) were implanted subcutaneously on the right flank of C57BL/6 mice (Charles River Laboratories). On day 2 post-cell implantation (day 0), mice were treated with anti-PD-1 or control antibody at a dose of 5 mg/kg intraperitoneally. Animals were dosed on dosing days 0, 4, 8, 11, and 14.

[00368] The treatment groups were as follows:

- (1) PBS vehicle;
- (2) control rat IgG2a, clone 2A3;
- (3) anti-PD-1 rat IgG2a, clone RMP1-14;
- (4) anti-PD-1 human scFv-Fc, clone PD1-F2 (*see* SEQ ID NOs: 306 and 293 for V_H and V_L sequences, respectively, and SEQ ID NO: 305 for the scFv-Fc);
- (5) anti-PD-1 human scFv-Fc, clone 1353-G08 (*see* SEQ ID NOs: 251 and 275 for V_H and V_L sequences, respectively, and SEQ ID NO: 242 for the scFv-Fc);
- (6) anti-PD-1 human scFv-Fc, clone 1353-G10 (*see* SEQ ID NOs: 252 and 276 for V_H and V_L sequences, respectively, and SEQ ID NO: 243 for the scFv-Fc); and
- (7) anti-PD-1 human IgG, clone PD1-F2v (*see* SEQ ID NOs: 603 and 293 for V_H and V_L sequences, respectively, SEQ ID NO: 307 for the HC sequence, and SEQ ID NO: 308 for the LC sequence).

[00369] Antibodies (2) and (3) were obtained commercially from Bio X Cell. Antibodies (4) – (6) were produced using the cell-free expression methods described in

Example 1. Antibody 7 was produced by mammalian cell expression using HEK293 cells and standard techniques.

[00370] Tumors were measured using an electronic caliper and tumor volumes were calculated using the formula, $\text{volume} = (\text{width}^2 \times \text{length})/2$. Statistical analysis was performed via a two-tailed Mann-Whitney test at day 17 post-treatment.

[00371] At day 17 post-treatment, all anti-PD-1 antibodies with strong mouse PD-1 reactivity (i.e., antibodies RMP1-14, PD1-F2, and 1353-G08) resulted in a significant delay in tumor establishment and growth ($p < 0.01$) compared to the PBS and control rat IgG2a treatment groups. In contrast, antibody 1353-G10, which binds human PD-1 but has weaker reactivity with mouse PD-1, showed no significant effect on tumor establishment and growth ($p > 0.05$).

[00372] FIG. 2 provides a chart of the tumor volume over the 17-days of treatment with the various antibodies.

Example 16: Cytomegalovirus (CMV) Recall Assay

[00373] Anti-PD-1 antibodies were functionally tested for potency in blocking the PD-1 pathway in restimulating peripheral blood mononuclear cells (PBMC) from cytomegalovirus-positive (CMV+) human donors by measuring IFN-g secretion in cell culture medium.

[00374] CD14+ monocytes and CD3+ T cells were obtained from peripheral blood mononuclear cells (PBMC) isolated from CMV+ human donors (AllCells, Alameda, CA) using MACS Cell Separation kits (Miltenyi Biotec).

[00375] CD14+ monocytes were differentiated into immature dendritic cells (DC) by culturing cells at 1×10^6 cells/ml for 7 days in presence of GM-CSF and IL-4 (Peprotech) in X-Vivo 15 media (Lonza) containing 2% human AB serum (Sigma-Aldrich), penicillin-streptomycin (Corning Mediatech) and GlutaMAX (Life Technologies). Following differentiation, DCs were matured by culturing in X-Vivo 15 + 2% human AB serum media at 1×10^6 cells/ml for 2 days in the presence of GM-CSF, IL-4, TNF- α , IL-1b, IL-6 (Peprotech) and prostaglandin E2 (Sigma-Aldrich).

[00376] To set-up the CMV recall assay, mature DCs were collected and washed. 10,000 DCs and 100,000 pan CD3+ T cells were plated per well in a 96-well U-bottom plate in a total volume of 100 μ l media containing peptide pools for the CMV IE-1 and CMV pp65

proteins (Miltenyi Biotec).

[00377] Anti-PD-1 or control human IgG antibody (50 μ l, final volume of 150 μ l per well) were added starting at a final concentration of 400 nM with 5-fold serial dilutions. Cells were co-cultured with peptides and antibodies for 5-6 days. Conditioned media was collected and tested for human IFN-g levels by ELISA (BD Biosciences).

[00378] As shown in FIG. 3, anti-PD-1 human IgG 1353-G10 (SEQ ID NOs: 252 and 276) showed significant fold-increase in IFN-g levels (closed circles). The IFN-g levels were substantial compared to Nivolumab IgG (open circles).

Example 17: DC/CD4+ T cell Mixed Lymphocyte Reaction (MLR) Assay

[00379] Anti-PD-1 antibodies were functionally tested for potency in blocking the PD-1 pathway in a peripheral blood mononuclear cell (PBMC) two-way mixed lymphocyte reaction (MLR) assay by measuring interferon gamma (IFN-g) secretion in cell culture medium.

[00380] CD14+ monocytes and CD4+ T cells were obtained from PBMC isolated from human donors using MACS Cell Separation kits. CD14+ monocytes were differentiated into immature DC by culturing cells at 1×10^6 cells/ml cell density for 7 days in presence of GM-CSF and IL-4 in RPMI media containing 10% fetal bovine serum, penicillin-streptomycin and GlutaMAX.

[00381] Following differentiation, DCs were matured by culturing in RPMI + 10% FBS media at 1×10^6 cells/ml cell density for 2 days in the presence of GM-CSF, IL-4, TNF- α , IL-1b, IL-6 and prostaglandin E2.

[00382] To set-up the DC/CD4+ T cell MLR, mature DCs were collected and washed. 10,000 DCs and 100,000 CD4+ T cells were plated per well in a 96-well U-bottom plate in a total volume of 100 μ l media. Anti-PD-1 or control human IgG antibody (50 μ l, final volume of 150 μ l per well) were added starting at a final concentration of 400 nM with 5-fold serial dilutions. Cells were co-cultured with peptides and antibodies for 5-6 days. Conditioned media was collected and tested for human IFN-g levels by ELISA.

[00383] As shown in FIG. 4, anti-PD-1 human IgG 1353-G10 (SEQ ID NOs: 252 and 276) showed significant fold-increase in IFN-g levels (closed circles). The IFN-g levels were substantial compared to Nivolumab IgG (open circles).

Example 18: Effect of PD-1 Blockade on Graft Versus Host Disease (GVHD)

Response

[00384] Anti-PD-1 antibodies described herein were evaluated for acceleration of graft versus host disease (GVHD) in a mouse model. Since PD-1 negatively regulates immune response, blockade of PD-1 by an effective antibody should accelerate the immune and GVHD response.

[00385] 40 female NSG mice aged 7 weeks and weighing approximately 19-22 g were used as human PBMC recipients. Groups were randomized into four groups of ten. On day 0, all animals received 2×10^7 human PBMC injected via the tail vein. Prior to PBMC injection, animals were dosed intraperitoneally (IP) with either control anti-GFP, Nivolumab anti-PD-1 antibody, or 1353-G10 anti-PD1 antibody (SEQ ID NOs: 252 and 276) as detailed in Table 9. Treatment was administered 2x per week until study conclusion.

Table 9. Treatment groups

Group	huPBMC concentration	Test article	Dose	Dosing frequency	Total number of doses	Route	N
1	2×10^7	Control Anti-GFP	10 mg/kg	2x/week	10	IP	10
2	2×10^7	Anti-PD1 Nivolumab	10 mg/kg	2x/week	10	IP	10
3	2×10^7	Anti-PD1 1353-G10	10 mg/kg	2x/week	10	IP	10
4	2×10^7	Anti-PD1 1353-G10	3 mg/kg	2x/week	10	IP	10

[00386] Animals were weighed and observed at least two times per week for 5 weeks. Monitoring increased to daily when 10% body weight loss (compared to initial mouse weight) occurred. Animals were euthanized with CO₂ at the end of five weeks (end of study), when they exhibited weight loss greater than 20%, or were unable to right themselves, cold to the touch, and moribund (severe hair ruffling, body weight loss, hunched posture, or decreased activity).

[00387] Upon sacrifice (after 5 weeks) or pre-mature euthanasia (due to body weight loss or moribundity), the spleen, liver, and serum were collected for further analyses. The liver and spleen were placed in formalin for 24 hours then transferred to 70% ethanol for storage. The serum was flash frozen and stored at -80°C. All procedures were conducted according to the guidelines of the Sutro Institutional Animal Care and Use Committee

(IACUC) and Sutro IACUC protocol SU-001-2013

[00388] As shown in FIG. 5, anti-PD-1 treatment with human IgG 1353-G10 (SEQ ID NOs: 252 and 276) showed accelerated mouse morbidity by approximately two weeks (median survival of 13 days for 10 mg/kg 1353-G10 versus 27 days for anti-GFP control). The onset of GVHD severity was similar in mice treated with high (10 mg/kg) and low (3 mg/kg) 1353-G10. Body weight loss was also faster with both doses of 1353-G10 compared to control and Nivolumab (data not shown). Median survival with both doses of 1353-G10 was less compared to Nivolumab, indicating greater PD-1 blockade potency for 1353-G10 *in vivo*.

Example 19: Sequences

[00389] Table 10 provides sequences referred to herein.

Table 10. Sequences.

SEQ ID NO	Molecule	Region	Scheme	Sequence
1	hPD-1			MQIPQAPWPVWVAVLQLGWRPGWFLDSPDRP WNPPTFSPALLVVTEGDNATFTCSFSNTS ESFVLNWYRMSPSNQTDKLAAPEDRSQPGQ DCRFRVTQLPNGRDFHMSVVRARRNDSGT YLCGAISLAPKAQIKESLRAELRVTERRAEV PTAHPSPSPRPAGQFQTLVVGVGGLLGS LVLLVWVLAVICSRAARGTIGARRTGQPLKE DPSAVPVFSVDYGELDFQWREKTPEPPVP CVPEQTEYATIVFPSGMGTSSPARRGSADGP RSAQPLRPEDGHCSWPL
2	PD1-17	CDR-H1		SGGSIRSTRWWS
3	PD1-28	CDR-H1		SYGIS
4	PD1-33	CDR-H1		SYYIH
5	PD1-35	CDR-H1		SGAYYWS
6	PD1-F2	CDR-H1		SSYWMS
7	10B4	CDR-H1	Chothia	GYIFSSY
8	1353-A09	CDR-H1	Chothia	GYRFTWY
9	1353-C07	CDR-H1	Chothia	GYRFSTF
10	1353-E07	CDR-H1	Chothia	GYRFETY
11	1353-F09	CDR-H1	Chothia	GYRFRQY
12	1353-G08	CDR-H1	Chothia	GYRFTRY
13	1353-G10	CDR-H1	Chothia	GYRFPHY
14	1353-H08	CDR-H1	Chothia	GYRFTRQ
15	1353-H09	CDR-H1	Chothia	GYRFPHY
16	1B10	CDR-H1	Chothia	GHSITS DY

SEQ ID NO	Molecule	Region	Scheme	Sequence
17	1E9	CDR-H1	Chothia	GFTFSTF
18	4B10	CDR-H1	Chothia	GFTFSTY
19	h1E9-1	CDR-H1	Chothia	GFTFSTF
20	h1E9-2	CDR-H1	Chothia	GFTFSTF
21	h1E9-4	CDR-H1	Chothia	GFTFSTF
22	h1E9-5	CDR-H1	Chothia	GFTFSTF
23	h4B10-1	CDR-H1	Chothia	GFTFSTY
24	h4B10-2	CDR-H1	Chothia	GFTFSTY
25	h4B10-3	CDR-H1	Chothia	GFTFSTY
26	PD1-17	CDR-H1	Chothia	GGSIGSGGSIRSTR
27	PD1-28	CDR-H1	Chothia	GYRFTSY
28	PD1-33	CDR-H1	Chothia	GYTLTSY
29	PD1-35	CDR-H1	Chothia	GGSISSGAY
30	PD1-F2	CDR-H1	Chothia	GFTFSSYWCD
31	10B4	CDR-H1	Kabat	SYWIG
32	1353-A09	CDR-H1	Kabat	WYGIS
33	1353-C07	CDR-H1	Kabat	TFGIS
34	1353-E07	CDR-H1	Kabat	TYGIS
35	1353-F09	CDR-H1	Kabat	QYGIS
36	1353-G08	CDR-H1	Kabat	RYGIS
37	1353-G10	CDR-H1	Kabat	HYGIS
38	1353-H08	CDR-H1	Kabat	RQGIS
39	1353-H09	CDR-H1	Kabat	HYGIS
40	1B10	CDR-H1	Kabat	SDYAWN
41	1E9	CDR-H1	Kabat	TFGMS
42	4B10	CDR-H1	Kabat	TYGMS
43	h1E9-1	CDR-H1	Kabat	TFGMS
44	h1E9-2	CDR-H1	Kabat	TFGMS
45	h1E9-4	CDR-H1	Kabat	TFGMS
46	h1E9-5	CDR-H1	Kabat	TFGMS
47	h4B10-1	CDR-H1	Kabat	TYGMS
48	h4B10-2	CDR-H1	Kabat	TYGMS
49	h4B10-3	CDR-H1	Kabat	TYGMS
50	PD1-17	CDR-H1	Kabat	SGGSIRSTRWWS
51	PD1-28	CDR-H1	Kabat	SYGIS
52	PD1-33	CDR-H1	Kabat	SYYIH
53	PD1-35	CDR-H1	Kabat	SGAYYWS
54	PD1-F2	CDR-H1	Kabat	SYWCDRMS
55	PD1-17	CDR-H2		EIYHSGSTNYNPSLKS
56	PD1-28	CDR-H2		WISAYNGNTNYAQKLQG
57	PD1-33	CDR-H2		IINPRGATISYAQKFQG
58	PD1-35	CDR-H2		YIYYNGNTYYNPSLRS
59	PD1-F2	CDR-H2		AISGSGGSTYYADSVKG
60	10B4	CDR-H2	Chothia	FPGSGS

SEQ ID NO	Molecule	Region	Scheme	Sequence
61	1353-A09	CDR-H2	Chothia	SAYNGN
62	1353-C07	CDR-H2	Chothia	SAYNGN
63	1353-E07	CDR-H2	Chothia	SAYNGN
64	1353-F09	CDR-H2	Chothia	SAYNGN
65	1353-G08	CDR-H2	Chothia	SAHNGN
66	1353-G10	CDR-H2	Chothia	SAYNGN
67	1353-H08	CDR-H2	Chothia	SAYNGN
68	1353-H09	CDR-H2	Chothia	SAYNGN
69	1B10	CDR-H2	Chothia	SYSGR
70	1E9	CDR-H2	Chothia	SGGGSD
71	4B10	CDR-H2	Chothia	SGGGSN
72	h1E9-1	CDR-H2	Chothia	SGGGSD
73	h1E9-2	CDR-H2	Chothia	SGGGSD
74	h1E9-4	CDR-H2	Chothia	SGGGSD
75	h1E9-5	CDR-H2	Chothia	SGGGSD
76	h4B10-1	CDR-H2	Chothia	SGGGSN
77	h4B10-2	CDR-H2	Chothia	SGGGSN
78	h4B10-3	CDR-H2	Chothia	SGGGSN
79	PD1-17	CDR-H2	Chothia	YHSGS
80	PD1-28	CDR-H2	Chothia	SAYNGN
81	PD1-33	CDR-H2	Chothia	NPRGAT
82	PD1-35	CDR-H2	Chothia	YYNGN
83	PD1-F2	CDR-H2	Chothia	SGSGGS
84	10B4	CDR-H2	Kabat	KIFPGSGSADYNENFKG
85	1353-A09	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
86	1353-C07	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
87	1353-E07	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
88	1353-F09	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
89	1353-G08	CDR-H2	Kabat	WVSAHNGNTNYAQKLQG
90	1353-G10	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
91	1353-H08	CDR-H2	Kabat	WISAYNGNTKYAQKLQG
92	1353-H09	CDR-H2	Kabat	WISAYNGNTNYAQKLQG
93	1B10	CDR-H2	Kabat	YISYSGRTSYNPSLTS
94	1E9	CDR-H2	Kabat	TISGGGSDTYYPDSVQG
95	4B10	CDR-H2	Kabat	TISGGGSNTYYSDSVKG
96	h1E9-1	CDR-H2	Kabat	TISGGGSDTYYPDSVQG
97	h1E9-2	CDR-H2	Kabat	TISGGGSDTYYPDSVQG
98	h1E9-4	CDR-H2	Kabat	TISGGGSDTYYPDSVQG
99	h1E9-5	CDR-H2	Kabat	TISGGGSDTYYPDSVQG
100	h4B10-1	CDR-H2	Kabat	TISGGGSNTYYSDSVKG
101	h4B10-2	CDR-H2	Kabat	TISGGGSNTYYSDSVKG
102	h4B10-3	CDR-H2	Kabat	TISGGGSNTYYSDSVKG
103	PD1-17	CDR-H2	Kabat	EIYHSGSTNYNPSLKS
104	PD1-28	CDR-H2	Kabat	WISAYNGNTNYAQKLQG

SEQ ID NO	Molecule	Region	Scheme	Sequence
105	PD1-33	CDR-H2	Kabat	IINPRGATISYAQKFQG
106	PD1-35	CDR-H2	Kabat	YIYYNGNTYYNPSLRS
107	PD1-F2	CDR-H2	Kabat	AISGSGGSTYYADSVKG
108	PD1-17	CDR-H3		QDYGDSGDWYFDL
109	PD1-28	CDR-H3		DADYSSGSGY
110	PD1-33	CDR-H3		AGIYGFDY
111	PD1-35	CDR-H3		ASDYVWGGYRYMDAFDI
112	PD1-F2	CDR-H3		ENWGSYFDL
113	10B4	CDR-H3		GYGNYLYFDV
114	1353-A09	CDR-H3		DSEYSSGSGY
115	1353-C07	CDR-H3		DVDYSSGSGY
116	1353-E07	CDR-H3		DAEYSLGSGY
117	1353-F09	CDR-H3		DAEYSGSGY
118	1353-G08	CDR-H3		DADYSGSGY
119	1353-G10	CDR-H3		DVDYGTGSGY
120	1353-H08	CDR-H3		DVDYSGSGY
121	1353-H09	CDR-H3		DAEYSGSGY
122	1B10	CDR-H3		GYALDY
123	1E9	CDR-H3		QGYDVYSWFAY
124	4B10	CDR-H3		QRDSAWFAS
125	h1E9-1	CDR-H3		QGYDVYSWFAY
126	h1E9-2	CDR-H3		QGYDVYSWFAY
127	h1E9-4	CDR-H3		QGYDVYSWFAY
128	h1E9-5	CDR-H3		QGYDVYSWFAY
129	h4B10-1	CDR-H3		QRDSAWFAS
130	h4B10-2	CDR-H3		QRDSAWFAS
131	h4B10-3	CDR-H3		QRDSAWFAS
132	PD1-17	CDR-H3		QDYGDSGDWYFDL
133	PD1-28	CDR-H3		DADYSSGSGY
134	PD1-33	CDR-H3		AGIYGFDY
135	PD1-35	CDR-H3		ASDYVWGGYRYMDAFDI
136	PD1-F2	CDR-H3		ENWGSYFDL
137	PD1-17	CDR-L1		TRSSGSIASNSVQ
138	PD1-28	CDR-L1		SGDALPKQYAY
139	PD1-33	CDR-L1		TGTSNDVGGYNYVS
140	PD1-35	CDR-L1		SGSNSNIGNSNVN
141	PD1-F2	CDR-L1		RASQGISSWLA
142	10B4	CDR-L1		KASQSVSDDVA
143	1353-A09	CDR-L1		SGDALTTQYAY
144	1353-C07	CDR-L1		SGDALSEQYAY
145	1353-E07	CDR-L1		SGDALPKQYAY
146	1353-F09	CDR-L1		SGDALPKQYAY
147	1353-G08	CDR-L1		SGDALPMQYGY
148	1353-G10	CDR-L1		SGDALPKQYAY

SEQ ID NO	Molecule	Region	Scheme	Sequence
149	1353-H08	CDR-L1		SGDALPKQYAY
150	1353-H09	CDR-L1		SGDALPKQYAY
151	1B10	CDR-L1		RTSSSVNYMH
152	1E9	CDR-L1		RASESVDNSGISFMS
153	4B10	CDR-L1		RASENVDDYGVSFMN
154	h1E9-1	CDR-L1		RASESVDNSGISFMS
155	h1E9-2	CDR-L1		RASESVDNSGISFMS
156	h1E9-4	CDR-L1		RASESVDNSGISFMS
157	h1E9-5	CDR-L1		RASESVDNSGISFMS
158	h4B10-1	CDR-L1		RASENVDDYGVSFMN
159	h4B10-2	CDR-L1		RASENVDDYGVSFMN
160	h4B10-3	CDR-L1		RASENVDDYGVSFMN
161	PD1-17	CDR-L1		TRSSGSIASNSVQ
162	PD1-28	CDR-L1		SGDALPKQYAY
163	PD1-33	CDR-L1		TGTSNDVGGYNYVS
164	PD1-35	CDR-L1		SGSNSNIGNSNVN
165	PD1-F2	CDR-L1		RASQGISSWLA
166	PD1-17	CDR-L2		EDNQRP
167	PD1-28	CDR-L2		KDTERPS
168	PD1-33	CDR-L2		DVTNRPS
169	PD1-35	CDR-L2		GNNQRPS
170	PD1-F2	CDR-L2		KASTLES
171	10B4	CDR-L2		YAFKRYI
172	1353-A09	CDR-L2		KDTERPS
173	1353-C07	CDR-L2		KDTERPS
174	1353-E07	CDR-L2		KDTERPS
175	1353-F09	CDR-L2		KDTERPS
176	1353-G08	CDR-L2		KDTERPS
177	1353-G10	CDR-L2		KDTERPS
178	1353-H08	CDR-L2		KDTERPS
179	1353-H09	CDR-L2		KDTERPS
180	1B10	CDR-L2		ATSKLAS
181	1E9	CDR-L2		TASNQGS
182	4B10	CDR-L2		PASNQGS
183	h1E9-1	CDR-L2		TASNQGS
184	h1E9-2	CDR-L2		TASNQGS
185	h1E9-4	CDR-L2		TASNQGS
186	h1E9-5	CDR-L2		TASNQGS
187	h4B10-1	CDR-L2		PASNQGS
188	h4B10-2	CDR-L2		PASNQGS
189	h4B10-3	CDR-L2		PASNQGS
190	PD1-17	CDR-L2		EDNQRP
191	PD1-28	CDR-L2		KDTERPS
192	PD1-33	CDR-L2		DVTNRPS

SEQ ID NO	Molecule	Region	Scheme	Sequence
193	PD1-35	CDR-L2		GNNQRPS
194	PD1-F2	CDR-L2		KASTLES
195	PD1-17	CDR-L3		QSSDSSAVV
196	PD1-28	CDR-L3		QSADNSITYRV
197	PD1-33	CDR-L3		SSYTIVTNFEVL
198	PD1-35	CDR-L3		AAWDDSLNGPV
199	PD1-F2	CDR-L3		QQSYSTPWT
200	10B4	CDR-L3		QQNYNSPYT
201	1353-A09	CDR-L3		QSADNSITYRV
202	1353-C07	CDR-L3		QSADNSITYRV
203	1353-E07	CDR-L3		QSADNSITYRV
204	1353-F09	CDR-L3		QSADNSITYRV
205	1353-G08	CDR-L3		QSADNSITYRV
206	1353-G10	CDR-L3		QSADNSITYRV
207	1353-H08	CDR-L3		QSADNSITYRV
208	1353-H09	CDR-L3		QSADNSITYRV
209	1B10	CDR-L3		QQWISDPWT
210	1E9	CDR-L3		QQSKEVPWT
211	4B10	CDR-L3		QQSKEVPWT
212	h1E9-1	CDR-L3		QQSKEVPWT
213	h1E9-2	CDR-L3		QQSKEVPWT
214	h1E9-4	CDR-L3		QQSKEVPWT
215	h1E9-5	CDR-L3		QQSKEVPWT
216	h4B10-1	CDR-L3		QQSKEVPWT
217	h4B10-2	CDR-L3		QQSKEVPWT
218	h4B10-3	CDR-L3		QQSKEVPWT
219	PD1-17	CDR-L3		QSSDSSAVV
220	PD1-28	CDR-L3		QSADNSITYRV
221	PD1-33	CDR-L3		SSYTIVTNFEVL
222	PD1-35	CDR-L3		AAWDDSLNGPV
223	PD1-F2	CDR-L3		QQSYSTPWT
224	HC Constant			ASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO	Molecule	Region	Scheme	Sequence
225	Kappa LC			HMTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
226	Lambda LD			GQPKAAPSVTLFPPSSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS
227	h1E9-1	scFv		MEVQLVESGGGLVKPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVSTISGGGSDTY YPDSVQGRFTISRDNANKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGTLLTVTS SGGGGSGGGGSGGGGSDIQLTQSPSFLSASV GDRVITITCRASESDNSGISFMSWYQQKP GKAPKLLIYTASNQSGVPSRFSGSGSGTEF TLTISSLQPEDFATYYCQQSKEVPWTFGQ GTKVEIKGSGDYKDDDDKSGHHHHHH
228	h1E9-2	scFv		MEVQLVESGGGLVKPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVSTISGGGSDTY YPDSVQGRFTISRDNANKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGTLLTVTS SGGGGSGGGGSGGGGSEIVLTQSPATLSLSP GERATLSCRASESDNSGISFMSWYQQKP GQAPRLLIYTASNQSGIPARFSGSGSGTDF TLTISSLEPEDFAVYYCQQSKEVPWTFGQ GTKVEIKGSGDYKDDDDKSGHHHHHH
229	h1E9-4	scFv		MEVQLVESGGGLVQPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGGSDTY YPDSVQGRFTISRDNANKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGTLLTVTS SGGGGSGGGGSGGGGSDIQLTQSPSFLSASV GDRVITITCRASESDNSGISFMSWYQQKP GKAPKLLIYTASNQSGVPSRFSGSGSGTEF TLTISSLQPEDFATYYCQQSKEVPWTFGQ GTKVEIKGSGDYKDDDDKSGHHHHHH
230	h1E9-5	scFv		MEVQLVESGGGLVQPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGGSDTY YPDSVQGRFTISRDNANKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGTLLTVTS SGGGGSGGGGSGGGGSEIVLTQSPATLSLSP GERATLSCRASESDNSGISFMSWYQQKP GQAPRLLIYTASNQSGIPARFSGSGSGTDF TLTISSLEPEDFAVYYCQQSKEVPWTFGQ GTKVEIKGSGDYKDDDDKSGHHHHHH

SEQ ID NO	Molecule	Region	Scheme	Sequence
231	h4B10-1	scFv		MEVQLVESGGGLVKPGGSLRLSCAASGFTFS TYGMSWVRQAPGKGLEWVATISGGGSNTY YDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGLTVTVSSG GGSGGGGSGGGGSEIVLTQSPATLSLSPGE RATLSCRASENVDDYGVSEFMNWIYQQKPGQ APRLLIYPASNQSGGIPARFSGSGSGTDFTL TISSELEPEDFAVYYCQQSKEVPWTFGQGT KVEIKGSGDYKDDDDKSGSGHHHHH
232	h4B10-2	scFv		MEVQLVESGGGLVKPGGSLRLSCAASGFTFS TYGMSWVRQAPGKGLEWVATISGGGSNTY YDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGLTVTVSSG GGSGGGGSGGGGSEIVLTQSPGTLSSLSPGE RATLSCRASENVDDYGVSEFMNWIYQQKPGQ APRLLIYPASNQSGGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQSKEVPWTFGQGT KVEIKGSGDYKDDDDKSGSGHHHHH
233	h4B10-3	scFv		MEVQLVESGGGLVKPGGSLRLSCAASGFTFS TYGMSWVRQAPGKGLEWVATISGGGSNTY YDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGLTVTVSSG GGSGGGGSGGGGSDIVMTQSPDSLAVSLGE RATINCRASENVDDYGVSEFMNWIYQQKPGQ PPKLLIYPASNQSGVDPDRFSGSGSGTDFTL TISSLQAEDVAVYYCQQSKEVPWTFGGGT KLEIKGSGDYKDDDDKSGSGHHHHH
234	m10B4	scFv		MQVQLQQSGAELMKPGASVKMSCKTTGYIFS SYWIGWVKQRPGHGLEWIGKIFPGSGSADYN ENFKGKATFTVDTSSNTAYMQLSSLTSEDSA VYYCARGYGNLYFDVWGAGTTVTVSSGGGG SGGGGSGGGGSNIVMTQTPKFLVLSAGDRIT ITCKASQSVSDDVAWYQQKPGQSPKLLISYA FKRYIGVPDRFTGSGYGTDFTFITISTVQAED LAVYFCQQNYNSPYTFGGGKLELKGSGDYK DDDDKSGSGHHHHH
235	m1B10	scFv		MSDVQLQESGPGLVKPSQSLSLTCTVTGHSI TSDYAWNWIWIRQFPGNKLEWMGYISYSGRTSY NPSLTSRISITRDTSKNQFFLQLNSVTTEDT ATYYCARGYALDYWGQTSVTVSSGGGGSGG GGSGGGGSIIVLSQSPAILSASPGEKVTMTC RTSSSVNYMHWFQQKPGSSPKPIYATSKLA SGVPARFSGSGSGTSYSLTISRVEAEDAATY FCQQWISDPWTFGGGKLEIKGSGDYKDDDD KSGSGHHHHH

SEQ ID NO	Molecule	Region	Scheme	Sequence
236	m1E9	scFv		MEVKLVESGGGLVSPGGSLKLSCAASGFTFS TFGMSWVRQTPEKRLEWVATISGGGSDTYYP DSVQGRFIIISRYNAKNNLYLQMNSLRPEDTA LYYCARQGYDVYSWFAYWGQGLVTVSAGGG GSGGGSGGGGSDIILTQSPASLAVSLGQRA AISCRASESVDNSGISFMSWFQQKPGQPPKLLI YITASNQSGVPARFSGSGSGTEFSLNIHP MEEDDTAMYFCQQSKEVPWTFGGGTKLEIRG SGDYKDDDDKSGSHHHHHH
237	m4B10	scFv		MEVKLVESGGGLVKPGGSLKLSCAASGFTFS TYGMSWVRQTPEKRLQWVATISGGGSENTYY DSVKGRFTISRDNKNNLYLQMSSLRSEDTA LYYCARQRDSAWFASWGQGLVTVSAGGGGS GGGGSGGGSDIVLTQSPASLAVSLGQRATI SCRASENVDDYGVSMNWFQQKPGQPPKLLI YPASNQSGVPARFSGSGSGTDFSLNIHPME EDDTAMYFCQQSKEVPWTFGGGTKLEIKGSG DYKDDDDKSGSHHHHHH
238	1353-A09	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFT WYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDSEYSSSGSYWGQGLVTVSS GGGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALTQYAYWYQQKPGQAPVM VIYKDTERPSPGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVLAAGSDQEPKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFCSCVMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSHHHHHH H

SEQ ID NO	Molecule	Region	Scheme	Sequence
239	1353-C07	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCASGYRFS TFGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARDVDYSSSGSYWGQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALSEQYAYWYQQKPGQAPVM VIYK DTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSA DNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFS CSVMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSGHHHHH H
240	1353-E07	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCASGYRFE TYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARDAEYSLGSGYWQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPKQYAYWYQQKPGQAPVM VIYK DTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSA DNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFS CSVMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSGHHHHH H

SEQ ID NO	Molecule	Region	Scheme	Sequence
241	1353-F09	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFR QYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYSGSGYWGQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPKQYAYWYQQKPGQAPVM VLYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFSQVMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSGHHHHH H
242	1353-G08	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFT RYGISWVRQAPGQGLEWMGWVSAHNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDADYSGSGYWGQGLVTVSS GGGVSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPMQYGYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFSQVMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSGHHHHH H

SEQ ID NO	Molecule	Region	Scheme	Sequence
243	1353-G10	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFP HYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYGTGSGYWGQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPKQYAYWYQQKPGQAPVM VIYKDTERP SGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQ SADNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFS CSVMHEALHNNH YTQKSLSLSPGKSGSDYKDDDDKSGSHHHHH H
244	1353-H08	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFT RQGISWVRQAPGQGLEWMGWISAYNGNTK YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYGS GSGYWGQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPKQYAYWYQQKPGQAPVM VIYKDTERP SGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQ SADNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFS CSVMHEALHNNH YTQKSLSLSPGKSGSDYKDDDDKSGSHHHHH H

SEQ ID NO	Molecule	Region	Scheme	Sequence
245	1353-H09	scFv-Fc		MEVQLVQSGAEVKKPGASVKVSCKASGYRFP HYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYSGSGYWGQGLVTVSS GGGSGGGSGGGSSYELTQPPSVSVSPGQ TARITCSGDALPKQYAYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSA DNSITYRVFGGGTKV TVLAAGSDQEPKKLAAGSDQEPKSSDKTHTC PPCSAPELLGGSSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFL YSKLTVDKSRWQQGNVFS CSMHEALHNNH YTQKSLSLSPGKSGDYKDDDDKSGSGHHHHH H
246	10B4	VH		QVQLQQSGAELMKPGASVKMSCKTTGYIFSS YWIGWVKQRPGHGLEWIGKIFPGSGSADYNE NFKGKATFTVDTSSNTAYMQLSLTSEDSAV YYCARGYGNLYFDVWGAGTTTVTVSS
247	1353-A09	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFTW YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDSEYSSSGSGYWGQGLVTVSS
248	1353-C07	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFST FGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYSSSGSGYWGQGLVTVSS
249	1353-E07	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFET YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYSLGSGYWGQGLVTVSS
250	1353-F09	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFRQ YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYSGSGYWGQGLVTVSS
251	1353-G08	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFR YGISWVRQAPGQGLEWMGWVSAHNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDADYSGSGYWGQGLVTVSS
252	1353-G10	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFP YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYGTGSGYWGQGLVTVSS

SEQ ID NO	Molecule	Region	Scheme	Sequence
253	1353-H08	VH		EVQLVQSGAEVKKPGASVKVSCASGYRFRTR QGISWVRQAPGQGLEWMGWISAYNGNTK YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYGS GSGYWGQGT LVTVSS
254	1353-H09	VH		EVQLVQSGAEVKKPGASVKVSCASGYRFPH YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYGS GSGYWGQGT LVTVSS
255	1B10	VH		DVQLQESGPGGLVKPSQSLSLTCTVTGHSITS DYAWNWI RQFPGNKLEWMGYISYGRTSYNP SLTSRISITRDTSKNQFFLQLNSVTTEDTAT YYCARGYALDYWGQGT SVTVSS
256	1E9	VH		EVKLVESGGGLVSPGGSLKLSCAASGFTFST FGMSWVRQTPEKRLEWVATISGGGSDTYYPD SVQGRFIIISRYNAKNNLYLQMNSLRPEDTAL YYCARQGYDVYSWFAYWGQGT LVTVSA
257	4B10	VH		EVKLVESGGGLVKPGGSLKLSCAASGFTFST YGMWVRQTPEKRLQWVATISGGGSNTYYSD SVKGRFTISRDNKNNLYLQMSSLRSEDAL YYCARQRDSAWFASWGQGT LVTVSA
258	h1E9-1	VH		EVQLVESGGGLVKPGGSLRLSCAASGFTFST FGMSWVRQAPGKGLEWVSTISGGGSDTY YPDSVQGRFTISRDNKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGT LVTVS S
259	h1E9-2	VH		EVQLVESGGGLVKPGGSLRLSCAASGFTFST FGMSWVRQAPGKGLEWVSTISGGGSDTY YPDSVQGRFTISRDNKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGT LVTVS S
260	h1E9-4	VH		EVQLVESGGGLVQPGGSLRLSCAASGFTFST FGMSWVRQAPGKGLEWVATISGGGSDTY YPDSVQGRFTISRDNKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGT LVTVS S
261	h1E9-5	VH		EVQLVESGGGLVQPGGSLRLSCAASGFTFST FGMSWVRQAPGKGLEWVATISGGGSDTY YPDSVQGRFTISRDNKNSLYLQMNSLRAED TAVYYCARQGYDVYSWFAYWGQGT LVTVS S
262	h4B10-1	VH		EVQLVESGGGLVKPGGSLRLSCAASGFTFST YGMWVRQAPGKGLEWVATISGGGSNTY YSDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGT LVTVSS
263	h4B10-2	VH		EVQLVESGGGLVKPGGSLRLSCAASGFTFST YGMWVRQAPGKGLEWVATISGGGSNTY YSDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGT LVTVSS

SEQ ID NO	Molecule	Region	Scheme	Sequence
264	h4B10-3	VH		EVQLVESGGGLVVKPGGSLRLSCAASGFTFST YGMSWVRQAPGKGLEWVATISGGGSNTY YSDSVKGRFTISRDDSKNTLYLQMNSLKTED TAVYYCARQRDSAWFASWGQGLTVTVSS
265	PD1-17	VH		QVQLQESGPGVVKPSGTLTLCAISGGSIGSG GGSIRSTRWWSWVRQSPGKGLEWIGEIYH SGSTNYNPSLKSRTVITSLDKSRNHFSRLNS VTAADTAVYYCARQDYGDSGDWYFDLWKG GTMVTVSS
266	PD1-28	VH		EVQLVQSGAEVKKPGASVKVSKASGYRFTS YGISWVRQAPGQGLEWMGWISAYNGNTNY AQKLQGRVTMTTDTSTNTAYMELRSLRSDDT AVYYCARDADYSSSGSGYWGQGLTVTVSS
267	PD1-33	VH		QVQLVQSGAEVKKPGASVRVSKASGYTLTS YYIHWVRQAPGQGLEWMGIINPRGATISY AQKFQGRVTMTTRDTSTSTVYMELRNLSKEDT ALYYCATAGIYGFDYWGRTLVTVSS
268	PD1-35	VH		QVQLQESGPGLVKPSQTLTLCTVSGGSISS GAYYWSWIRQHPGKGLEWIGYIYNGNTY YNPSLRSLVTISVDASKNQFSLKLSSVTAAD TAVYYCARASDYVWGGYRYMDAFDIWGRG TLITVSS
269	PD1-F2	VH		EVQLVQSGGGVQVQGRSLRLSCAASGFTFSS YWCDRMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCAKENWGSYFDLWGQGT TVTVSS
270	10B4	VL		NIVMTQTPKFLLVSAGDRITITCKASQSVSD DVAWYQQKPGQSPKLLISYAFKRYIGVPDFR TSGSYGTDFTFTISTVQAEDLAVYFCQQNYN SPYTFGGGTKLELKR
271	1353-A09	VL		SYELTQPPSVSVSPGQTARITCSGDALTTQY AYWYQQKPGQAPVM VIYKDTERPSPGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVL
272	1353-C07	VL		SYELTQPPSVSVSPGQTARITCSGDALSEQY AYWYQQKPGQAPVM VIYKDTERPSPGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVL
273	1353-E07	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVM VIYKDTERPSPGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQADNSITYRVFGGGTKV TVL

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274	1353-F09	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVM VLYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSADNSITYRVFGGGTVL
275	1353-G08	VL		SYELTQPPSVSVSPGQTARITCSGDALPMQY GYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSADNSITYRVFGGGTVL
276	1353-G10	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSADNSITYRVFGGGTVL
277	1353-H08	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSADNSITYRVFGGGTVL
278	1353-H09	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVM VIYKDTERPSGIPERFSGSSSGTKVTLTISG VQAEDEADYYCQSADNSITYRVFGGGTVL
279	1B10	VL		QIVLSQSPAILSASPGEKVTMTCRTSSSVNY MHWYQQKPGSSPKPWIYATSKLASGVPARFS GSGSGTSYSLTISRVEAEDAATYFCQQWISD PWTFGGGTKLEIK
280	1E9	VL		DIILTQSPASLAVSLGQRAAISCRASESVDN SGISFMSWFQQKPGQPPKLLIYTASNQSGV PARFSGSGSGTEFSLNIHPMEEDDTAMYFCQ QSKEVPWTFGGGTKLEIR
281	4B10	VL		DIVLTQSPASLAVSLGQRATISCRASENVDD YGVSFMNWFQQKPGQPPKLLIYPASNQSGV PARFSGSGSGTDFSLNIHPMEEDDTAMYFCQ QSKEVPWTFGGGTKLEIK
282	h1E9-1	VL		DIQLTQSPSFLSASVGDRVITICRASESVDN SGISFMSWYQQKP GKAPKLLIYTASNQSGVPSRFSGSGSGTEF TLTISSLQPEDFATYYCQQSKEVPWTFGQ GTKVEIK
283	h1E9-2	VL		EIVLTQSPATLSLSPGERATLSCRASESVDN SGISFMSWYQQKP GQAPRLLIYTASNQSGIPARFSGSGSGTDF TLTISSLEPEDFAVYYCQQSKEVPWTFGQ GTKVEIK

SEQ ID NO	Molecule	Region	Scheme	Sequence
284	h1E9-4	VL		DIQLTQSPSFLSASVGDRTITCRASESVDN SGISFMSWYQQKPGKAPKLLIYTASNQSGV PSRFGSGSGTEFTLTISLQPEDFATYYCQ QSKEVPWTFGQ GTKVEIK
285	h1E9-5	VL		EIVLTQSPATLSLSPGERATLSCRASESVDN SGISFMSWYQQK GQAPRLLIYTASNQSGIPARFSGSGSGTDF TLTISLQPEDFAVYYCQQSKEVPWTFGQ GTKVEIK
286	h4B10-1	VL		EIVLTQSPATLSLSPGERATLSCRASENVDD YGVSFMNWYQQKPGQ APRLLIYPASNQSGIPARFSGSGSGTDFTL TISLQPEDFAVYYCQQSKEVPWTFGQGT KVEIK
287	h4B10-2	VL		EIVLTQSPGTLTLSPGERATLSCRASENVDD YGVSFMNWYQQKPGQ APRLLIYPASNQSGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQSKEVPWTFGQGT KVEIK
288	h4B10-3	VL		DIVMTQSPDSLAVSLGERATINCRASENVDD YGVSFMNWYQQKPGQ PPKLLIYPASNQSGVPDRFSGSGSGTDFTL TISLQAEADVAVYYCQQSKEVPWTFGGGT KLEIK
289	PD1-17	VL		NFMLTQPHSVSESPGKTVTISCTRSSGSIAS NSVQWYQQRPGSSPTTVIYEDNQRPSGVP DRFSGSIDSSNSASLTVSGLKTEDEADYYC QSSDSSAVVFGSGTKLTVL
290	PD1-28	VL		SYELTQPPSVSVSPGQTARITCSGDALPKQY AYWYQQKPGQAPVMVIYKDTERPSGIPER FSGSSSGTKVTLTISGVQAEDEADYYCQSD NSITYRVFGGGTKVTVL
291	PD1-33	VL		QSALTQPASVSGSPGQSITISCTGTSNDVGG YNYVSWYQHHPGKAPKLLIYDVTNRPSGV SDRFSGSKSGNTASLTISGLLAEDEGDYYCS SYTIVTNFEVLFGGGTKLTV
292	PD1-35	VL		QSVLTQPPSASGTPGQRVTISCSGSNSNIGS NSVNWYQQLPGTAPKLLIYGNQRPSGVP DRFSGSKSGTSASLAISGLQSENEADYYCAA WDDSLNGPVFGRGTVL
293	PD1-F2	VL		DIVMTQSPSTLSASVGDRTITCRASQGISS WLAWYQQKPGRAPKVLIIYKASTLES GVPSRFGSGSGTDFTLTISLQPEDFATYY CQQSYSTPWTFGQGTKLEIK
294	FlagHis Tag			GSGDYKDDDDKSGSHHHHHH
295	IgG1 Fc from scFv-			AAGSDQEPKSSDKTHTCPPCSAPELLGGSSV FLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRV

SEQ ID NO	Molecule	Region	Scheme	Sequence
	Fc			VSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTP PVLDSGDSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGKSGSDYKDDDD KGSG
296	HC Constant			ASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSKLTVDKSRW QQGNVFS CSVMHEALHNHYTQKSLSLSPGK
297	LC Constant			RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
298	Linker			GGGGSGGGSGGGGS
299	murine PD-1			MWVRQVPWSFTWAVLQLSWQSGWLLEVPNGP WRSLTFYPAWLTVSEGANATFTCSLSNWS EDLMLNWNRLSPSNQTEKQAAFCNGLSQPVQDA RFQIIQLPNRHDFHMNILDTRRNDSGIYLCG AISLHPKAKIEESPGAELVVTERILETSTRY PSPSPKPEGRFQGMVIGIMSALVGIPVLLLL AWALAVFCSTSMSEARGAGSKDDTLKEEPSA APVPSVAYEELDFQGREKTPELPTACVHTEY ATIVFTEGLGASAMGRRGSADGLQGPRPPRH EDGHCSWPL
300	cyno PD-1			MWVRQVPWSFTWAVLQLSWQSGWLLEVPNGP WRSLTFYPAWLTVSEGANATFTCSLSNWS EDLMLNWNRLSPSNQTEKQAAFCNGLSQPVQDA RFQIIQLPNRHDFHMNILDTRRNDSGIYLCG AISLHPKAKIEESPGAELVVTERILETSTRY PSPSPKPEGRFQGMVIGIMSALVGIPVLLLL AWALAVFCSTSMSEARGAGSKDDTLKEEPSA APVPSVAYEELDFQGREKTPELPTACVHTEY ATIVFTEGLGASAMGRRGSADGLQGPRPPRH EDGHCSWPL
301	Linker			AAGSDQEPK
302	h1E9-4 & h1E9-5	HC-FlagHis		MEVQLVESGGGLVQPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGSDTYYP DSVQGRFTISRDNKNSL YLQMNSLR AEDTAVYYCARQGYDVYSWFAYW GQGTLLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTV

SEQ ID NO	Molecule	Region	Scheme	Sequence
				SWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPP VLDSGDSFFLYSKLTVDKSRWQQGNVFCSSV MHEALHNHYTQKSLSLSPGKSGSDYKDDDDK GSGHHHHHH
303	h1E9-5	LC		MEIVLTQSPATLSLSPGERATLSCRASESVD NSGISFMSWYQQKPGQAPRLLIYTASNQGS IPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQSKEVPWTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYSLSTLTLSKADY EKHKVYACEVTHQGLSPVTKSFNRGEC
304	h1E9-4	LC		MDIQLTQSPSFLSASVGDRVTITCRASESVD NSGISFMSWYQQKPGKAPKLLIYTASNQGS VPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQQSKEVPWTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQ SGNSQESVTEQDSKSTYSLSTLTLSKADY EKHKVYACEVTHQGLSPVTKSFNRGEC
305	PD1-F2v- scFvFcFlag His	scFv-Fc		MGAHSEVQLVQSGGGVVPGRSLRLSCAASG FTFSSYWMSWVRQAPGKGLEWVSAISGSGGS TYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCAKENWGSYFD LWGQGTITVTVSSGGGGSGGGSGGGSGVHS DIVMTQSPSTLSASVGDR VTITCRASQGISSWLAWYQQKPGRAPKVLII KASTLESGVPSRFSGSGSGTDFTLTITSSLP EDFATYYCQQSYSTPWTF GQGTKLEIKAAGSDQEPKSSDKTHTCPPCSA PELLGGSSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSMHEALHNHYTQKS LSLSPGKSGSDYKDDDDKSGHHHHHH
306	PD1-F2v	VH		EVQLVQSGGGVVPGRSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCAKENWGSYFDLWGQGT TVSS
307	PD1-F2v	HC		GAHSEVQLVQSGGGVVPGRSLRLSCAASGF

SEQ ID NO	Molecule	Region	Scheme	Sequence
				TFSSYWMSWVRQAPGKGLEWVSAISGSGGST YYADSVKGRFTISRDN SKNTLYLQMNSLRAE DTAVYYCAKENWGSYFDLWGQGT TVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHCTPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFCSSVMH EALHNHYTQKSLSLSPGK
308	PD1-F2v	LC		GVHSDIVMTQSPSTLSASVGDRTITCRASQ GISSWLAWYQQKPGRAPKVLIYKASTLESQV PSRFSGSGSGTDFTLTISLQPEDFATYYCQ QSYSTPWTFGQGTKLEIKRHMTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKSTYSLSSLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
309	1353-E07-R5	CDR-H3		DAEYRLGSGY
310	1353-A09-R5	CDR-H3		DSEYRSGSGY
311	1353-F09-R5	CDR-H3		DAEYRSGSGY
312	1353-G08-R5	CDR-H3		DADYRSGSGY
313	1353-G10-R5	CDR-H3		DVDYRTGSGY
314	1353-C07-R5	CDR-H3		DVDYRSGSGY
315	1353-H08-R5	CDR-H3		DVDYRSGSGY
316	1353-E07-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFT YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARD AEYRLGSGYWGQGLTVTVSS
317	1353-A09-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFT YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARD SEYRSGSGYWGQGLTVTVSS
318	1353-F09-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFR YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARD AEYRSGSGYWGQGLTVTVSS
319	1353-G08-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFR YGISWVRQAPGQGLEWMGWISAHNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSD TAVYYCARD ADYRSGSGYWGQGLTVTVSS

SEQ ID NO	Molecule	Region	Scheme	Sequence
320	1353-G10-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFPH YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYRTGSGYWGQGTLLTVSS
321	1353-C07-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFTS FGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYRSGSGYWGQGTLLTVSS
322	1353-H08-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFTS QGISWVRQAPGQGLEWMGWISAYNGNTK YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDVDYRSGSGYWGQGTLLTVSS
323	1353-H09-R5	VH		EVQLVQSGAEVKKPGASVKVSCKASGYRFPH YGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTNTAYMELRSLRSDD TAVYYCARDAEYRSGSGYWGQGTLLTVSS
324	H1E9-HC3	HC-FlagHis		MEVQLVESGGGLVQPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGGSDTYYP DSVKGRFTISRDNKNSLYLQMNSLRAEDTA VYYCARQGYDVYSWFAYWGQGTLLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSKLTVDKSRWQQGNVFSFSVMHE ALHNHYTQKSLSLSPGKSGDYKDDDDKSGS HHHHH
325	H1E9-HC2	HC-FlagHis		MQVQLVESGGGVVQPGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGGSDTYYP DSVKGRFTISRDNKNTLYLQMNSLRAEDTA VYYCARQGYDVYSWFAYWGQGTLLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSKLTVDKSRWQQGNVFSFSVMHE ALHNHYTQKSLSLSPGKSGDYKDDDDKSGS HHHHH
326	H1E9-HC1	HC-FlagHis		MEVQLLESGGGLVQPGGSLRLSCAASGFTFS TFGMSWVRQAPGKGLEWVATISGGGSDTYYP DSVKGRFTISRDNKNTLYLQMNSLRAEDTA VYYCARQGYDVYSWFAYWGQGTLLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

SEQ ID NO	Molecule	Region	Scheme	Sequence
				EPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSKLTVDKSRWQQGNVFSQSVMHE ALHNHYTQKSLSLSPGKSGDYKDDDDKSGS HHHHH
327	H1E9-LC4	LC		MDIVLTQSPDSLAVSLGERATINCRASESVD NSGISFMSWYQQKPGQPPKLLIYTASNQGS VPDRFSGSGSGTDFTLTISLQAEDVAVYYC QQSKEVPWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRG EC
328	H1E9-LC3	LC		MEIVLTQSPGTLSSLSPGERATLSCRASESVD NSGISFMSWYQQKPGQAPRLLIYTASNQGS IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC QQSKEVPWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRG EC
329	H1E9-LC2	LC		MDIVLTQSPSLPVTGPGEPAISCRASESVD NSGISFMSWYLQKPGQSPQLLIYTASNQGS VPDRFSGSGSGTDFTLTKISRVEADVGVYYC QQSKEVPWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRG EC
330	H1E9-LC1	LC		MDIQLTQSPSSLSASVGDRVTITCRASESVD NSGISFMSWYQQKPGKAPKLLIYTASNQGS VPSRFSGSGSGTDFTFTISLQPEDIATYYC QQSKEVPWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTTL SKADYEEKHKVYACEVTHQGLSPVTKSFNRG EC
331		CDR-H2	Kabat	TISGGGSDTYYPDSVQG

Equivalents

[00390] The disclosure set forth above may encompass multiple distinct inventions with independent utility. Although each of these inventions has been disclosed in its preferred form(s), the specific embodiments thereof as disclosed and illustrated herein are not to be

considered in a limiting sense, because numerous variations are possible. The subject matter of the inventions includes all novel and nonobvious combinations and subcombinations of the various elements, features, functions, and/or properties disclosed herein. The following claims particularly point out certain combinations and subcombinations regarded as novel and nonobvious. Inventions embodied in other combinations and subcombinations of features, functions, elements, and/or properties may be claimed in this application, in applications claiming priority from this application, or in related applications. Such claims, whether directed to a different invention or to the same invention, and whether broader, narrower, equal, or different in scope in comparison to the original claims, also are regarded as included within the subject matter of the inventions of the present disclosure.

WHAT IS CLAIMED IS:

1. An isolated antibody that specifically binds to PD-1, wherein the antibody comprises a CDR-H3 sequence selected from:
 - a. a sequence defined by the consensus sequence β_1 -G-Y- β_4 - β_5 -Y- β_7 - β_8 -F- β_{10} - β_{11} , wherein β_1 is not present or Q; β_4 is G or D; β_5 is N or V; β_7 is L or S; β_8 is Y or W; β_{10} is D or A; and β_{11} is V or Y;
 - b. a sequence defined by the consensus sequence D- α_2 - α_3 -Y- α_5 - α_6 -G-S-G-Y, wherein α_2 is A, V, or S; α_3 is D or E; α_5 is S, G, or R; and α_6 is S, L, or T; and wherein if α_2 is A, then α_3 is not D; α_5 is not S; or α_6 is not S; or combinations thereof; and
 - c. a sequence selected from SEQ ID NOs: 122 and 124, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
2. The antibody of claim 1, wherein α_2 is V or S; α_3 is E; α_5 is G; or α_6 is L or T; or combinations thereof.
3. The antibody of claim 1, wherein the CDR-H3 sequence is selected from SEQ ID NOs: 113-131 and 309-315.
4. The antibody of claim 1, further comprising a CDR-H2 sequence selected from SEQ ID NOs: 60-83, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
5. The antibody of claim 4, wherein the CDR-H2 sequence is selected from SEQ ID NOs: 60-78.
6. The antibody of any of claims 4-5, wherein the CDR-H2 sequence is a Chothia CDR-H2 sequence.
7. The antibody of any of claims 1-3, wherein the antibody comprises a CDR-H2 sequence selected from:
 - a. a sequence defined by the consensus sequence W- γ_2 -S-A- γ_5 -N-G-N-T- γ_{10} -Y-A-Q-K-L-Q-G, wherein γ_2 is I or V; γ_5 is Y or H; and γ_{10} is K or N;
 - b. a sequence defined by the consensus sequence δ_1 -I-S-G- δ_5 -G- δ_7 - δ_8 -T-Y-Y- δ_{12} -D-S-V- δ_{16} -G, wherein δ_1 is T or A; δ_5 is S or G; δ_7 is S or G; δ_8 is S, D or N; δ_{12} is A, P or S; and δ_{16} is K or Q; and

- c. a sequence selected from SEQ ID NOs: 84, 93, 103, 105, and 106, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
8. The antibody of claim 7, wherein γ_2 is not I; γ_5 is not Y; or γ_{10} is not N; or combinations thereof.
9. The antibody of claim 7, wherein if δ_1 is A, then δ_5 is not S; δ_7 is not G; δ_8 is not S; δ_{12} is not A; or δ_{16} is not K; or combinations thereof.
10. The antibody of any of claims 7-9, wherein the CDR-H2 sequence is a Kabat CDR-H2 sequence.
11. The antibody of claim 10, wherein the Kabat CDR-H2 sequence is selected from SEQ ID NOs: 84-102 or 331.
12. The antibody of any of the preceding claims, further comprising a CDR-H1 sequence selected from:
 - a. a sequence defined by the consensus sequence G- ϵ_2 - ϵ_3 - ϵ_4 - ϵ_5 - ϵ_6 - ϵ_7 , wherein ϵ_2 is Y or F; ϵ_3 is T, R or I; ϵ_4 is F or L; ϵ_5 is S, E, T, P, or R; ϵ_6 is T, S, H, Q, R, or W; and ϵ_7 is F, Y, or Q; and
 - b. a sequence selected from SEQ ID NOs: 16, 26, 29, and 30, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
13. The antibody of any claim 12, wherein if ϵ_5 is T, then ϵ_6 is not S.
14. The antibody of any of claims 12-13, wherein the CDR-H1 sequence is a Chothia CDR-H1 sequence.
15. The antibody of claim 14, wherein the Chothia CDR-H1 sequence is selected from SEQ ID NOs: 7-25.
16. The antibody of any of claims 1-11, wherein the antibody comprises a CDR-H1 sequence selected from:
 - a. a sequence defined by the consensus sequence Θ_1 - Θ_2 -G- Θ_4 -S, wherein Θ_1 is T, R, W, Q, H, or S; Θ_2 is Y, F, or Q; and Θ_4 is M or I; and
 - b. a sequence selected from SEQ ID NOs: 31, 40, 50, 52, 53, and 54, or a variant thereof having 3, 2, or 1 amino acid substitution(s).

17. The antibody of claim 16, wherein Θ_1 is T, R, W, Q, or H; Θ_2 is F or Q; or Θ_4 is M; or combinations thereof.
18. The antibody of any of claims 16-17, wherein the CDR-H1 sequence is a Kabat CDR-H1 sequence.
19. The antibody of claim 18, wherein the Kabat CDR-H1 sequence is selected from SEQ ID NOs: 31-49.
20. The antibody of any of the preceding claims, further comprising a CDR-L3 sequence selected from:
 - a. a sequence defined by the consensus sequence Q-Q- π_3 - π_4 - π_5 - π_6 -P- π_8 -T, wherein π_3 is N, S, or W; π_4 is Y, K, or I; π_5 is N, E, or S; π_6 is S, V, D, or T; and π_8 is Y or W; and
 - b. a sequence selected from SEQ ID NOs: 206, 219, 221, and 222, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
21. The antibody of claim 20, wherein if π_4 is Y, then π_3 is not S; π_5 is not S; π_6 is not T; or π_8 is not W; or combinations thereof.
22. The antibody of any of claims 20-21, wherein the CDR-L3 sequence is selected from SEQ ID NOs: 200-218.
23. The antibody of any of the preceding claims, further comprising a CDR-L2 sequence selected from SEQ ID NOs: 171-194, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
24. The antibody of claim 23, wherein the CDR-L2 sequence is selected from SEQ ID NOs: 171-189.
25. The antibody of any of the preceding claims, further comprising a CDR-L1 sequence selected from:
 - a. a sequence defined by the consensus sequence S-G-D-A-L- μ_6 - μ_7 -Q-Y- μ_{10} -Y, wherein μ_6 is P, T, or S; μ_7 is M, T, E, or K; and μ_{10} is G or A;
 - b. a sequence defined by the consensus sequence R-A-S-E- Σ_5 -V-D- Σ_8 - Σ_9 -G- Σ_{11} -S-F-M- Σ_{15} , wherein Σ_5 is S or N; Σ_8 is N or D; Σ_9 is S or Y; Σ_{11} is I or V; and Σ_{15} is S or N; and

- c. a sequence selected from SEQ ID NOs: 142, 151, 161, 163, 164, and 165, or a variant thereof having 3, 2, or 1 amino acid substitution(s).
26. The antibody of claim 25, wherein if μ_6 is P, then μ_7 is not K; or μ_{10} is not A; or combinations thereof.
27. The antibody of any of claims 25-26, wherein the CDR-L1 sequence is selected from SEQ ID NOs: 142-160.
28. An isolated antibody that specifically binds to PD-1, wherein the antibody comprises:
- a. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 7 and 31; a CDR-H2 comprising one or more of SEQ ID NOs: 60 and 84; and a CDR-H3 comprising SEQ ID NO: 113;
 - b. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 8 and 32; a CDR-H2 comprising one or more of SEQ ID NOs: 61 and 85; and a CDR-H3 comprising SEQ ID NO: 114;
 - c. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 9 and 33; a CDR-H2 comprising one or more of SEQ ID NOs: 62 and 86; and a CDR-H3 comprising SEQ ID NO: 115;
 - d. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 10 and 34; a CDR-H2 comprising one or more of SEQ ID NOs: 63 and 87; and a CDR-H3 comprising SEQ ID NO: 116;
 - e. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 11 and 35; a CDR-H2 comprising one or more of SEQ ID NOs: 64 and 88; and a CDR-H3 comprising SEQ ID NO: 117;
 - f. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 12 and 36; a CDR-H2 comprising one or more of SEQ ID NOs: 65 and 89; and a CDR-H3 comprising SEQ ID NO: 118;
 - g. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 13 and 37; a CDR-H2 comprising one or more of SEQ ID NOs: 66 and 90; and a CDR-H3 comprising SEQ ID NO: 119;

- h. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 14 and 38; a CDR-H2 comprising one or more of SEQ ID NOs: 67 and 91; and a CDR-H3 comprising SEQ ID NO: 120;
- i. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 15 and 39; a CDR-H2 comprising one or more of SEQ ID NOs: 68 and 92; and a CDR-H3 comprising SEQ ID NO: 121;
- j. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 16 and 40; a CDR-H2 comprising one or more of SEQ ID NOs: 69 and 93; and a CDR-H3 comprising SEQ ID NO: 122;
- k. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 17 and 41; a CDR-H2 comprising one or more of SEQ ID NOs: 70 and 94; and a CDR-H3 comprising SEQ ID NO: 123;
- l. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 18 and 42; a CDR-H2 comprising one or more of SEQ ID NOs: 71 and 95; and a CDR-H3 comprising SEQ ID NO: 124;
- m. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 8 and 32; a CDR-H2 comprising one or more of SEQ ID NOs: 61 and 85; and a CDR-H3 comprising SEQ ID NO: 310;
- n. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 9 and 33; a CDR-H2 comprising one or more of SEQ ID NOs: 62 and 86; and a CDR-H3 comprising SEQ ID NO: 314;
- o. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 10 and 34; a CDR-H2 comprising one or more of SEQ ID NOs: 63 and 87; and a CDR-H3 comprising SEQ ID NO: 309;
- p. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 11 and 35; a CDR-H2 comprising one or more of SEQ ID NOs: 64 and 88; and a CDR-H3 comprising SEQ ID NO: 311;
- q. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 12 and 36; a CDR-H2 comprising one or more of SEQ ID NOs: 65 and 89; and a CDR-H3 comprising SEQ ID NO: 312;

- r. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 13 and 37; a CDR-H2 comprising one or more of SEQ ID NOs: 66 and 90; and a CDR-H3 comprising SEQ ID NO: 313;
 - s. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 14 and 38; a CDR-H2 comprising one or more of SEQ ID NOs: 67 and 91; and a CDR-H3 comprising SEQ ID NO: 315; or
 - t. a V_H comprising: a CDR-H1 comprising one or more of SEQ ID NOs: 15 and 39; a CDR-H2 comprising one or more of SEQ ID NOs: 68 and 92; and a CDR-H3 comprising SEQ ID NO: 311.
29. An isolated antibody that specifically binds to PD-1, wherein the antibody comprises:
- a. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 142; a CDR-L2 comprising SEQ ID NO: 171; and a CDR-L3 comprising SEQ ID NO: 200;
 - b. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 143; a CDR-L2 comprising SEQ ID NO: 172; and a CDR-L3 comprising SEQ ID NO: 201;
 - c. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 144; a CDR-L2 comprising SEQ ID NO: 173; and a CDR-L3 comprising SEQ ID NO: 202;
 - d. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 145; a CDR-L2 comprising SEQ ID NO: 174; and a CDR-L3 comprising SEQ ID NO: 203;
 - e. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 146; a CDR-L2 comprising SEQ ID NO: 175; and a CDR-L3 comprising SEQ ID NO: 204;
 - f. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 147; a CDR-L2 comprising SEQ ID NO: 176; and a CDR-L3 comprising SEQ ID NO: 205;
 - g. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 148; a CDR-L2 comprising SEQ ID NO: 177; and a CDR-L3 comprising SEQ ID NO: 206;
 - h. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 149; a CDR-L2 comprising SEQ ID NO: 178; and a CDR-L3 comprising SEQ ID NO: 207;
 - i. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 150; a CDR-L2 comprising SEQ ID NO: 179; and a CDR-L3 comprising SEQ ID NO: 208;

- j. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 151; a CDR-L2 comprising SEQ ID NO: 180; and a CDR-L3 comprising SEQ ID NO: 209; or
 - k. a V_L comprising: a CDR-L1 comprising SEQ ID NO: 152; a CDR-L2 comprising SEQ ID NO: 181; and a CDR-L3 comprising SEQ ID NO: 210.
30. An isolated antibody that specifically binds to PD-1, wherein the antibody comprises a V_H region selected from:
- a. SEQ ID NOs: 246 and 255-264, or a variant thereof having 20 or fewer amino acid substitutions;
 - b. SEQ ID NOs: 252-253, or a variant thereof having 4 or fewer amino acid substitutions;
 - c. SEQ ID NOs: 248, 251, and 254, or a variant thereof having 3 or fewer amino acid substitutions; and
 - d. SEQ ID NOs: 247, 249, and 250, or a variant thereof having 2 or fewer amino acid substitutions.
31. An isolated antibody that specifically binds to PD-1, wherein the antibody comprises a V_L region selected from:
- a. SEQ ID NOs: 270 and 279-288, or a variant thereof having 20 or fewer amino acid substitutions; and
 - b. SEQ ID NOs: 271, 272, and 275, or a variant thereof having 1 or fewer amino acid substitutions.
32. An antibody comprising the V_H region or variant thereof of claim 30 and the V_L region or variant thereof of claim 31.
33. The antibody of claim 32, wherein:
- a. the V_H region is SEQ ID NO: 246, or the variant thereof, and the V_L region is SEQ ID NO: 270, or the variant thereof;
 - b. the V_H region is SEQ ID NO: 247, or the variant thereof, and the V_L region is SEQ ID NO: 271, or the variant thereof;

- c. the V_H region is SEQ ID NO: 248, or the variant thereof, and the V_L region is SEQ ID NO: 272, or the variant thereof;
- d. the V_H region is SEQ ID NO: 249, or the variant thereof, and the V_L region is SEQ ID NO: 273;
- e. the V_H region is SEQ ID NO: 250, or the variant thereof, and the V_L region is SEQ ID NO: 274;
- f. the V_H region is SEQ ID NO: 251, or the variant thereof, and the V_L region is SEQ ID NO: 275, or the variant thereof;
- g. the V_H region is SEQ ID NO: 252, or the variant thereof, and the V_L region is SEQ ID NO: 276;
- h. the V_H region is SEQ ID NO: 253, or the variant thereof, and the V_L region is SEQ ID NO: 277;
- i. the V_H region is SEQ ID NO: 254, or the variant thereof, and the V_L region is SEQ ID NO: 278;
- j. the V_H region is SEQ ID NO: 255, or the variant thereof, and the V_L region is SEQ ID NO: 279, or the variant thereof;
- k. the V_H region is SEQ ID NO: 256, or the variant thereof, and the V_L region is SEQ ID NO: 280, or the variant thereof;
- l. the V_H region is SEQ ID NO: 257, or the variant thereof, and the V_L region is SEQ ID NO: 281, or the variant thereof;
- m. the V_H region is SEQ ID NO: 258, or the variant thereof, and the V_L region is SEQ ID NO: 282, or the variant thereof;
- n. the V_H region is SEQ ID NO: 259, or the variant thereof, and the V_L region is SEQ ID NO: 283, or the variant thereof;
- o. the V_H region is SEQ ID NO: 260, or the variant thereof, and the V_L region is SEQ ID NO: 284, or the variant thereof;
- p. the V_H region is SEQ ID NO: 261, or the variant thereof, and the V_L region is SEQ ID NO: 285, or the variant thereof;

- q. the V_H region is SEQ ID NO: 262, or the variant thereof, and the V_L region is SEQ ID NO: 286, or the variant thereof;
 - r. the V_H region is SEQ ID NO: 263, or the variant thereof, and the V_L region is SEQ ID NO: 287, or the variant thereof;
 - s. the V_H region is SEQ ID NO: 264, or the variant thereof, and the V_L region is SEQ ID NO: 288, or the variant thereof;
 - t. the V_H region is SEQ ID NO: 317, or the variant thereof, and the V_L region is SEQ ID NO: 271, or the variant thereof;
 - u. the V_H region is SEQ ID NO: 321, or the variant thereof, and the V_L region is SEQ ID NO: 272, or the variant thereof;
 - v. the V_H region is SEQ ID NO: 316, or the variant thereof, and the V_L region is SEQ ID NO: 273;
 - w. the V_H region is SEQ ID NO: 318, or the variant thereof, and the V_L region is SEQ ID NO: 274;
 - x. the V_H region is SEQ ID NO: 319, or the variant thereof, and the V_L region is SEQ ID NO: 275, or the variant thereof;
 - y. the V_H region is SEQ ID NO: 320, or the variant thereof, and the V_L region is SEQ ID NO: 276;
 - z. the V_H region is SEQ ID NO: 322, or the variant thereof, and the V_L region is SEQ ID NO: 277; or
 - aa. the V_H region is SEQ ID NO: 323, or the variant thereof, and the V_L region is SEQ ID NO: 278.
34. The antibody of any of claims 1, 4, 7, 12, 16, 20, 23, 25, and 30-33, wherein the amino acid substitution is a conservative amino acid substitution.
35. An isolated antibody that specifically binds to PD-1, wherein the antibody binds to the same epitope as a second antibody selected from:
- a. an antibody with a V_H of SEQ ID NO: 246 and a V_L of SEQ ID NO: 270;
 - b. an antibody with a V_H of SEQ ID NO: 255 and a V_L of SEQ ID NO: 279;

- c. an antibody with a V_H of SEQ ID NO: 256 and a V_L of SEQ ID NO: 280;
 - d. an antibody with a V_H of SEQ ID NO: 257 and a V_L of SEQ ID NO: 281;
 - e. an antibody with a V_H of SEQ ID NO: 258 and a V_L of SEQ ID NO: 282;
 - f. an antibody with a V_H of SEQ ID NO: 259 and a V_L of SEQ ID NO: 283;
 - g. an antibody with a V_H of SEQ ID NO: 260 and a V_L of SEQ ID NO: 284;
 - h. an antibody with a V_H of SEQ ID NO: 261 and a V_L of SEQ ID NO: 285;
 - i. an antibody with a V_H of SEQ ID NO: 262 and a V_L of SEQ ID NO: 286;
 - j. an antibody with a V_H of SEQ ID NO: 263 and a V_L of SEQ ID NO: 287; and
 - k. an antibody with a V_H of SEQ ID NO: 264 and a V_L of SEQ ID NO: 288.
36. The antibody of claim 35, wherein the isolated inhibits binding of the second antibody to the PD-1 by at least 50%, or wherein the second antibody inhibits binding of the isolated antibody to the PD-1 by at least 50%.
37. The antibody of any of the preceding claims, further comprising at least one constant region domain.
38. The antibody of claim 37, wherein the constant region comprises a sequence selected from SEQ ID NOs: 224-226 and 297.
39. The antibody of any of the preceding claims, wherein the antibody is a monoclonal antibody.
40. The antibody of any of the preceding claims, wherein the antibody is an IgA, an IgD, an IgE, an IgG, or an IgM.
41. The antibody of any of the preceding claims, wherein the antibody is humanized or human.
42. The antibody of any of the preceding claims, wherein the antibody is aglycosylated.
43. The antibody of any of the preceding claims, wherein the antibody is an antibody fragment.

44. The antibody of claim 43, wherein the antibody fragment is selected from an Fv fragment, a Fab fragment, a $F(ab')_2$ fragment, a Fab' fragment, an scFv (sFv) fragment, and an scFv-Fc fragment.
45. The antibody of claim 44, wherein the antibody is an scFv fragment.
46. The antibody of claim 45, wherein the scFv fragment comprises a sequence selected from SEQ ID NOs: 227-237.
47. The antibody of claim 44, wherein the antibody is an scFv-Fc fragment.
48. The antibody of claim 47, wherein the scFv-Fc fragment comprises a sequence selected from SEQ ID NOs: 238-245 or SEQ ID NOs 238-245 with AAGSDQEPK (SEQ ID NO: 301) removed from the sequence.
49. The antibody of any of the preceding claims comprising a heavy chain selected from the heavy chains of SEQ ID NOS:302 and 324-326.
50. The antibody of any of the preceding claims comprising a light chain selected from SEQ ID NOS:303, 304, and 327-330.
51. The antibody of any of the preceding claims, wherein the antibody has a k_a of about $4.74 \times 10^4 \text{ M}^{-1} \times \text{sec}^{-1}$ to about $1.23 \times 10^6 \text{ M}^{-1} \times \text{sec}^{-1}$ when associating with human PD-1 at a temperature of 25°C.
52. The antibody of any of the preceding claims, wherein the antibody has a k_d of about $1.87 \times 10^{-2} \text{ sec}^{-1}$ to about $4.17 \times 10^{-4} \text{ sec}^{-1}$ when dissociating from human PD-1 at a temperature of 25°C.
53. The antibody of any of the preceding claims, wherein the antibody has a K_D of about $3.85 \times 10^{-8} \text{ M}$ to about $2.52 \times 10^{-10} \text{ M}$ when bound to human PD-1 at a temperature of 25°C.
54. The antibody of any of the preceding claims, wherein the antibody specifically binds one or more of murine PD-1 and cynomolgus PD-1.
55. A kit comprising an antibody of any of the preceding claims, and instructions for use of the antibody.
56. The kit of claim 55, wherein the antibody is lyophilized.

57. The kit of claim 56, further comprising a fluid for reconstitution of the lyophilized antibody.
58. A polynucleotide encoding an antibody of any of claims 1 to 54.
59. A vector comprising the polynucleotide of claim 58.
60. A host cell comprising the vector of claim 59.
61. The host cell of claim 60, wherein the host cell is selected from a bacterial cell, a fungal cell, and a mammalian cell.
62. The host cell of claim 60, wherein the host cell is selected from an *E. coli* cell, a *Saccharomyces cerevisiae* cell, and a CHO cell.
63. A cell-free expression reaction comprising the vector of claim 59.
64. A pharmaceutical composition comprising the antibody of any of claims 1 to 54 and a pharmaceutically acceptable carrier.
65. A method of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of an antibody of any of claims 1 to 54, or a pharmaceutical composition of claim 64.
66. A method of diagnosing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of an antibody of any of claims 1 to 54, or a pharmaceutical composition of claim 64.
67. The method of any of claims 65 to 66, wherein the disease or condition is selected from a cancer and an autoimmune disease.

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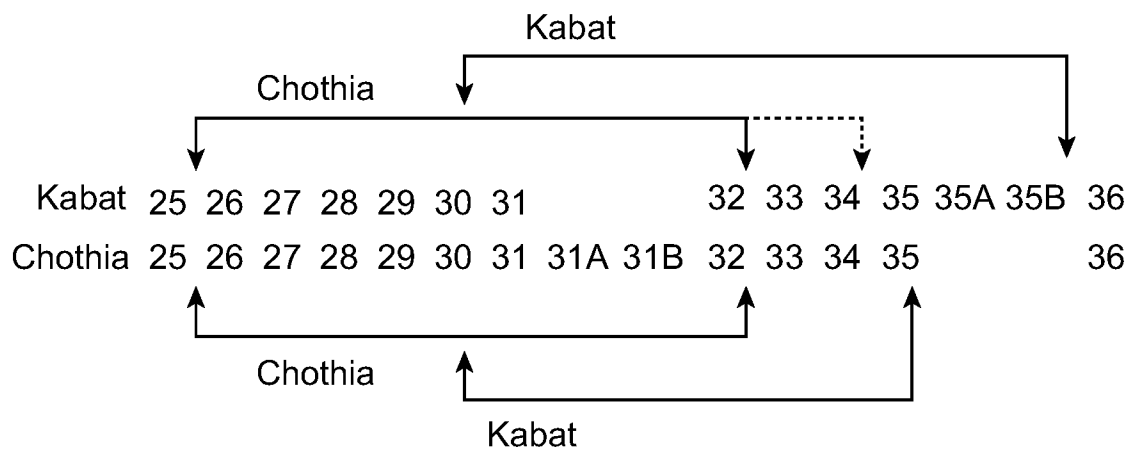


FIG. 1

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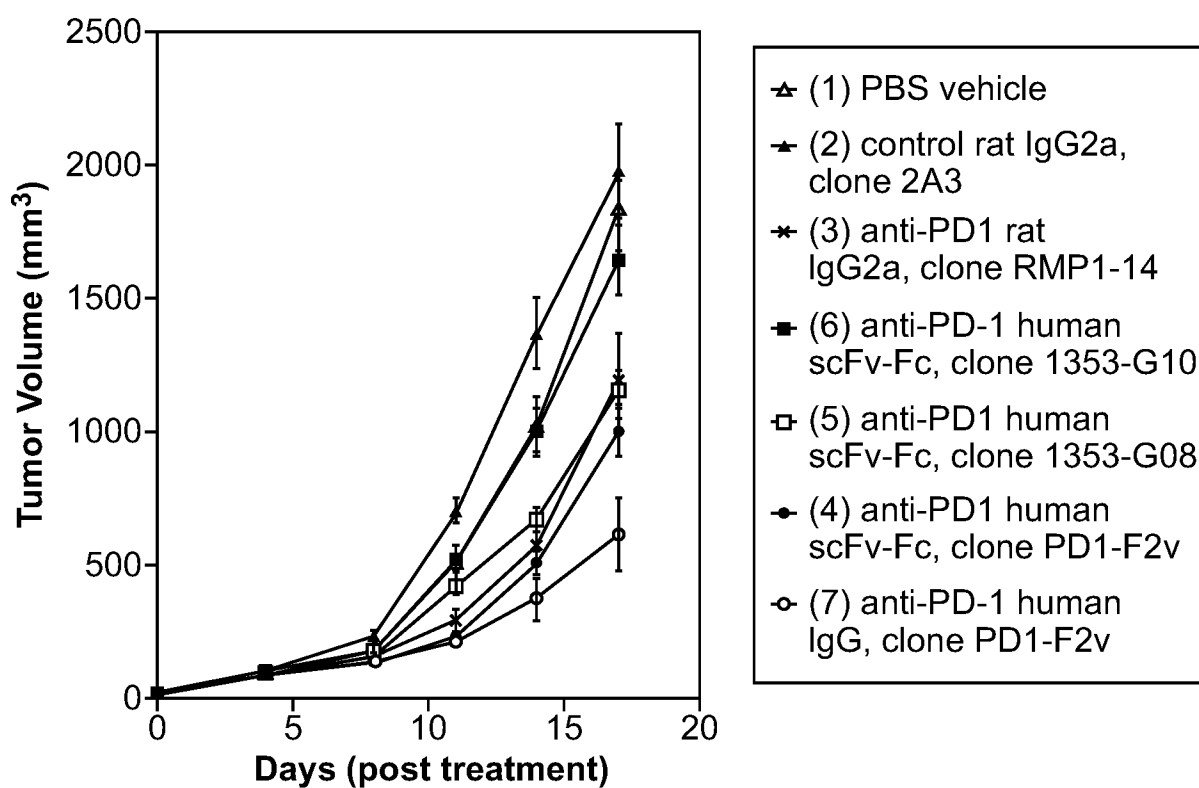


FIG. 2

FIG. 3 CMV Recall Assay

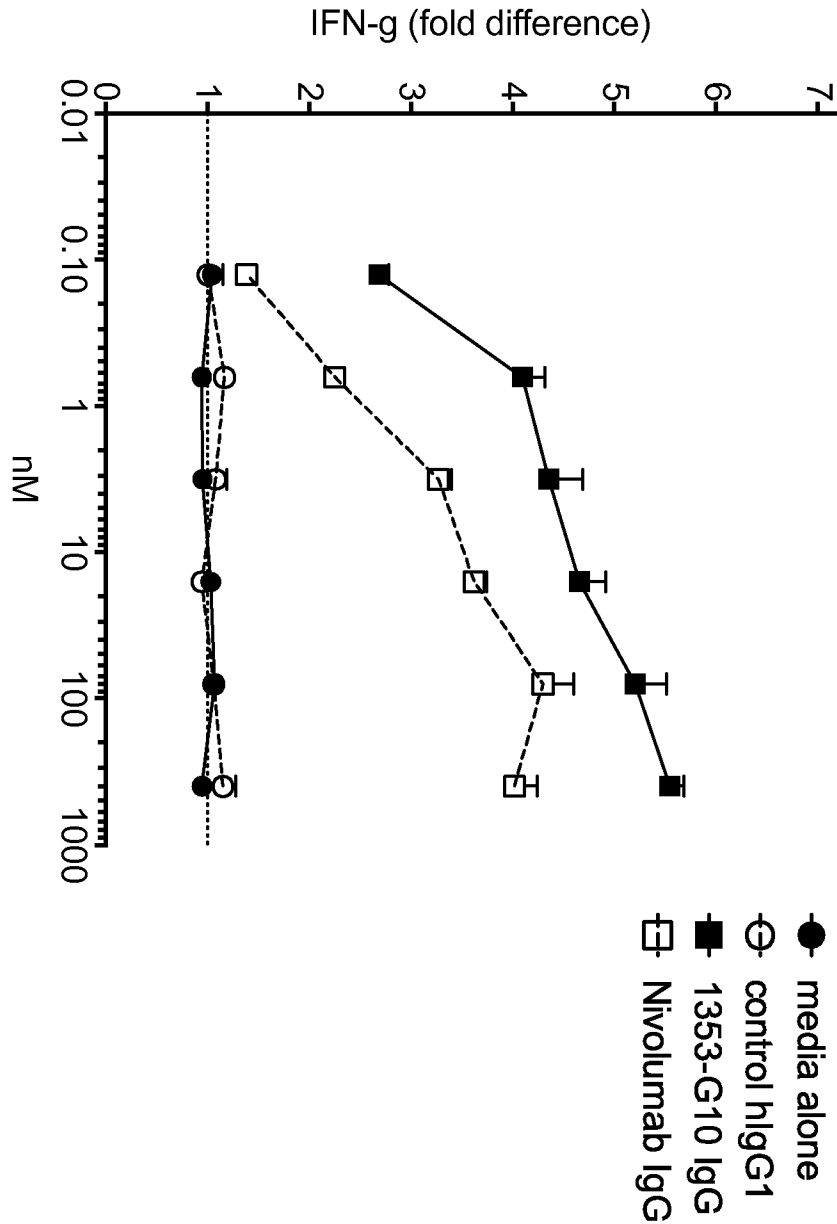


FIG. 4 MLR Assay

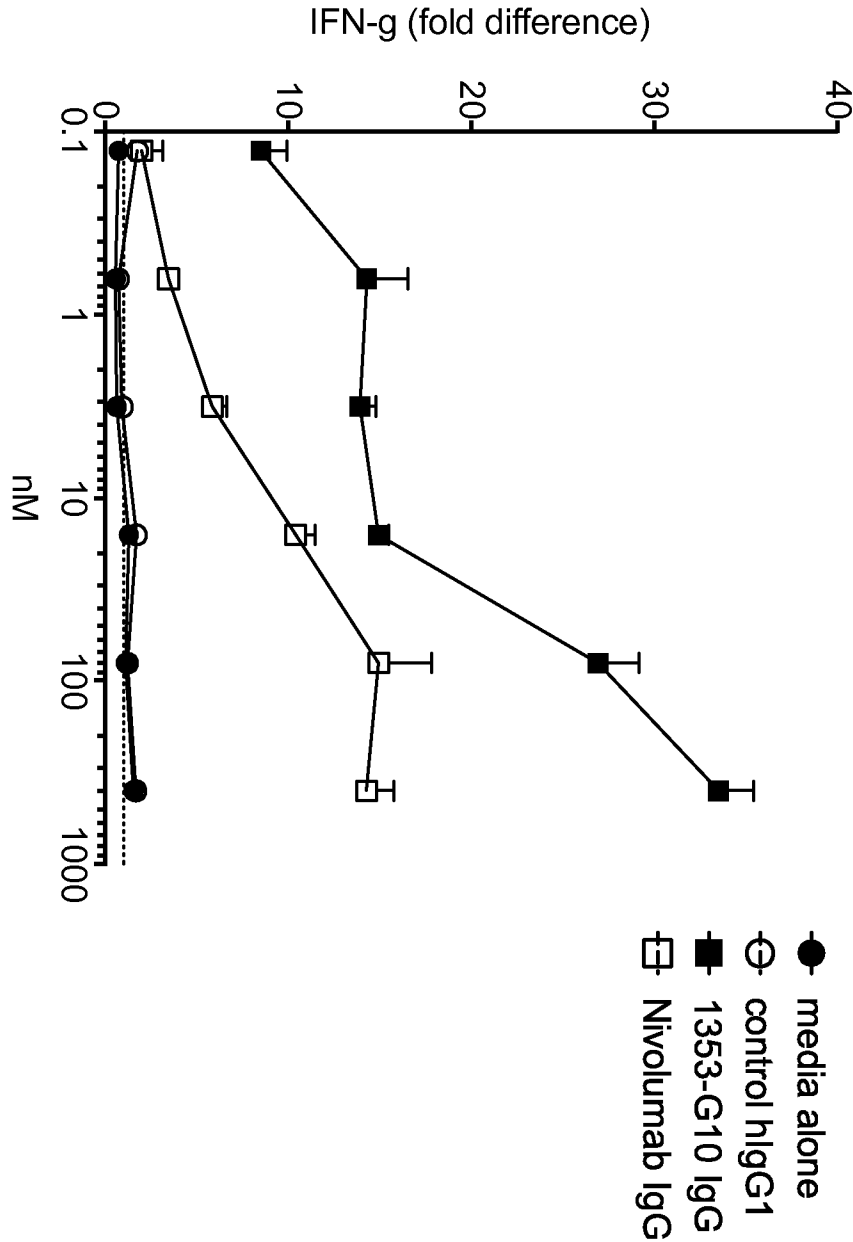


FIG. 5 GVHD Response

