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Anti-PD-L1 cancer immunotherapy antibodies

Abstract

Provided are compositions and methods relating to or derived from anti-PD-L1 antibodies with ADCC and/or CDC activities. More specifically, provided are fully human antibodies that bind PD-L1, PD-L1-binding antibody fragments, derivatives of such antibodies, and PD-L1-binding polypeptides comprising such fragments.

Inventors: **Li; Chiang J. (Cambridge, MA), Unniraman; Shyam (Newton, MA), Bader; Hannah (Waltham, MA), Jha; Mithilesh (Sharon, MA)**

Applicant: **1GLOBE BIOMEDICAL CO., LTD.** (Beijing, CN); **1GLOBE HEALTH INSTITUTE LLC** (Norwood, MA)

Family ID: **1000008767395**

Assignee: **1GLOBE BIOMEDICAL CO., LTD. (Beijing, CN); 1GLOBE HEALTH INSTITUTE LLC (Norwood, MA)**

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Primary Examiner: Canella; Karen A.

Attorney, Agent or Firm: Milstein Zhang & Wu LLC

Background/Summary

CROSS REFERENCE TO RELATED APPLICATIONS (1) This application is a national phase application under 35 U.S.C. 371 of international application PCT/CN2019/101659, filed Aug. 20, 2019 which claims priority to and the benefit of U.S. Provisional Patent Application Ser. No. 62/720,015 filed Aug. 20, 2018, the entire content of which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING
(1) Sequence listings and related materials in the ASCII text file named “Seq-007PCT.txt” and created on Feb. 16, 2021 with a size of about 91 kilobytes, is hereby incorporated by reference.
FIELD OF THE INVENTION
(2) The present invention relates to antigen-binding polypeptides that bind human PD-L1, pharmaceutical compositions and uses thereof. Aspects of the invention also relate to expression system producing such antigen-binding polypeptides or antibodies. The described antigen-binding polypeptides or pharmaceutical compositions of the invention are useful for treating a subject in need thereof for a pathological condition, such as a mammalian cancer, an infection, and so on.
BACKGROUND OF INVENTION
(3) Immune cells have costimulatory and inhibitory receptors on their cell surfaces that interact with membrane-bound and soluble ligands. These receptors serve to regulate the potency, duration, and type of the immune response by altering thresholds and the durations of immune cell activation or inhibition. These are often referred collectively to as immune checkpoints. Many of these checkpoint molecules are members of either the B7 superfamily or tumor necrosis factor (TNF) superfamily of molecules.
(4) The B7 family includes both inhibitory and stimulatory co-receptors. For example, on the one hand, ligation of Programmed (Cell) Death Protein 1 (PD-1) and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) with their respective ligands (PD-L1, PD-L2 and B7-1, B7-2, respectively) leads to suppression of the activation or generation of regulatory T cells, anergy, exhaustion and apoptosis. On the other hand, ligation of Cluster of Differentiation (CD28) and Inducible T-cell COStimulator (ICOS) receptors with their respective ligands results in increased

proliferation and production of cytokine. In contrast, the TNF family of costimulatory receptors includes only stimulatory molecules such as OX40, 4-1BB, CD40, CD27 and their ligands that favor proliferation and effector function differentiation. In addition, there are other co-receptors that do belong to either of these families e.g., Tim-3, LAG-3, Ceacam-1, etc.

(5) For the past couple of decades, it has become clear that many types of cancer generate an immunosuppressive environment within the tumor through a variety of mechanisms. A recurrent theme is the ectopic expression of an inhibitory immune checkpoint ligand (especially PDL1) that suppresses intratumoral T cells. There is also increasing evidence that blocking this tumor mediated immunity suppression can de-repress intratumoral T cells and allow them to kill the tumor (Adachi K, Tamada K. *Cancer Sci.* 2015; 106(8):945-50; Rafiq S, et al., *Nat Biotechnol.* 2018 Aug. 13; Hargadon K M, et al., *Int Immunopharmacol.* 2018; 62:29-39). Blocking can be done through an antibody or a variety of other methods. This is different from traditional anti-cancer antibody therapy where the antibody binds to the cancer cell and recruits complement dependent cytotoxicity (CDC) as well as antibody-dependent cellular cytotoxicity (ADCC) to directly kill the tumor cells.

(6) CTLA-4 antibodies were the first of a class of immunotherapeutics based on immune checkpoint blockade to win FDA approval. Other blockade targets, such as PD1 and its associated molecules, offer more and different opportunities for enhancing the antitumor immunity in a clinical setting.

BRIEF SUMMARY OF THE INVENTION

(7) The present invention provides antigen-binding polypeptides that bind PD-L1 (or, interchangeably, “anti-PD-L1 polypeptide(s),” “PD-L1-binding polypeptides”), preferably, the human PD-L1; the polypeptide has one or both of the following features: (a) binds to PD-L1 and inhibits its ability to interact with PD1; and (b) has an isotype or constant region that can trigger ADCC and/or CDC. The resulting antibody can kill tumor cells through two synergistic pathways —T cell de-repression and direct cytotoxicity. The polypeptides of the present invention can be used to treat tumors by itself or in combination with (a) antibodies targeting other immunosuppressive pathways; (b) chemotherapy or radiation therapy; (c) other mechanisms of blocking immunosuppressive pathways, e.g., aptamers or RNAi; or (d) other immunotherapy agents, e.g. cytokines, targeted therapeutics, etc.

(8) In one aspect, the present invention provides an antigen-binding polypeptide, e.g., an antibody, fragment, derivative or analog thereof, that is of the IgG1 isotype and binds to a PD-L1 epitope, preferably with a binding affinity of at least 10.sup.−6M, and having a heavy chain variable domain sequence “consisting essentially of,” meaning herein, that is at least 80%, or, more preferably, 85%, 90%, 95%, or even 100%, identical to the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:54, SEQ ID NO:58, SEQ ID NO:62, SEQ ID NO:66, SEQ ID NO:70, SEQ ID NO:74, SEQ ID NO:78, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:90, SEQ ID NO:94, SEQ ID NO:98, SEQ ID NO:102, SEQ ID NO:106, and combinations thereof, and that having a light chain variable domain sequence consisting essentially of, meaning, that is at least 80%, or, more preferably, 85%, 90%, 95%, or even 100%, identical to the amino acid sequences selected from the group consisting of SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO: 76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, and combinations thereof.

(9) In preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:18 and SEQ ID NO:20; (b)

SEQ ID NO:42 and SEQ ID NO:44; or (c) SEQ ID NO:34 and SEQ ID NO:36.
(10) In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:22 and SEQ ID NO:24; (b) SEQ ID NO:2 and SEQ ID NO:4; (c) SEQ ID NO:62 and SEQ ID NO:64; or (d) SEQ ID NO:82 and SEQ ID NO:84.
(11) In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:70 and SEQ ID NO:72; (b) SEQ ID NO:50 and SEQ ID NO:52; (c) SEQ ID NO:102 and SEQ ID NO:104; or (d) SEQ ID NO:30 and SEQ ID NO:32.
(12) In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective variable region sequences consist essentially of the following pairing: (a) SEQ ID NO:6 and SEQ ID NO:8; (b) SEQ ID NO:10 and SEQ ID NO:12; (c) SEQ ID NO:14 and SEQ ID NO:16; (d) SEQ ID NO:26 and SEQ ID NO:28; (e) SEQ ID NO:38 and SEQ ID NO:40; (f) SEQ ID NO:46 and SEQ ID NO:48; (g) SEQ ID NO:54 and SEQ ID NO:56; or (h) SEQ ID NO:58 and SEQ ID NO:60.
(13) In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective variable region sequences consist essentially of the following pairing: (a) SEQ ID NO:66 and SEQ ID NO:68; (b) SEQ ID NO:74 and SEQ ID NO:76; (c) SEQ ID NO:78 and SEQ ID NO:80; (d) SEQ ID NO:86 and SEQ ID NO:88; (e) SEQ ID NO:90 and SEQ ID NO:92; (f) SEQ ID NO:94 and SEQ ID NO:96; (g) SEQ ID NO:98 and SEQ ID NO:100; or (h) SEQ ID NO:106 and SEQ ID NO:108.
(14) Preferably, the antigen-binding polypeptide is fully human or otherwise humanized. In a preferred embodiment, the antigen-binding polypeptide further comprising a human constant region. In one feature, the human constant region is IgG1. In some embodiments, the antibody of the invention further includes a second pair of heavy and light chain variable regions that are, e.g., substantially identical to the first pair.
(15) In a preferred version, the binding of the anti-PD-L1 polypeptide to PD-L1 blocks PD-L1's interaction with PD1. This could be either because the epitope for the binding on PD-L1 is at or near the PD1 interaction interface or because there is an allosteric change in the conformation of the PD1 interaction interface.
(16) In another aspect, the present invention provides nucleic acid molecules that encode the above mentioned polypeptides. The nucleic acid molecule can be a DNA molecule or RNA molecule. In a preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:17 and SEQ ID NO:19; (b) SEQ ID NO:33 and SEQ ID NO:35; (c) SEQ ID NO:41 and SEQ ID NO:43.
(17) In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:21 and SEQ ID NO:23; (b) SEQ ID NO:1 and SEQ ID NO:3; (c) SEQ ID NO:61 and SEQ ID NO:63; or (d) SEQ ID NO:81 and SEQ ID NO:83.
(18) In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:69 and SEQ ID NO:71; (b) SEQ ID NO:49 and SEQ ID NO:51;

(c) SEQ ID NO:101 and SEQ ID NO:103; or (d) SEQ ID NO:29 and SEQ ID NO:31.
(19) In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:5 and SEQ ID NO:7; (b) SEQ ID NO:9 and SEQ ID NO:11; (c) SEQ ID NO:13 and SEQ ID NO:15; (d) SEQ ID NO:25 and SEQ ID NO:27; (e) SEQ ID NO:37 and SEQ ID NO:39; (f) SEQ ID NO:45 and SEQ ID NO:47; (g) SEQ ID NO:53 and SEQ ID NO:55; or (h) SEQ ID NO:57 and SEQ ID NO:59.
(20) In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:65 and SEQ ID NO:67; (b) SEQ ID NO:73 and SEQ ID NO:75; (c) SEQ ID NO:77 and SEQ ID NO:79; (d) SEQ ID NO:85 and SEQ ID NO:87; (e) SEQ ID NO:89 and SEQ ID NO:91; (f) SEQ ID NO:93 and SEQ ID NO:95; (g) SEQ ID NO:97 and SEQ ID NO:99; or (h) SEQ ID NO:105 and SEQ ID NO:107.
(21) In another aspect, the present invention provides a pharmaceutical composition that includes an antigen-binding polypeptide, e.g., the anti-PD-L1 antibody, fragment, derivative or analog, as disclosed herein. The pharmaceutical composition further includes a pharmaceutically acceptable excipient, carrier, or diluent.
(22) In a related aspect, the present invention provides a method of treating a subject in need thereof for a pathological condition therapeutically, said method comprising administering to said subject a therapeutically effective amount of the anti-PD-L1 polypeptide or antibody disclosed herein. The method may further include a step of administering a second and different therapeutic antibody against at least one cell-surface antigen indicative of said condition. The condition being treated may be a mammalian cancer, an infection, and so on. In various embodiments, the anti-PD-L1 polypeptide may be an antibody, an antibody fragment, an antibody derivative or an antibody analog.
(23) Preferably, the spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck cancer, pancreatic cancer, and combinations thereof. More broadly, any cancer where at least a significant fraction of the tumor cells express detectable amount of PD-L1 is contemplated as targets to be treated by the composition of the present invention.
(24) In yet another aspect, the invention provides a method of treating a subject in need thereof for similar conditions prophylactically, said method comprising administering to said subject a prophylactically effective amount of the pharmaceutical composition of the invention. The method may further include a step of administering a vaccine against said condition. In one embodiment, the condition is a cancer.
(25) In a further aspect, the invention provides a mammalian expression system that produces the antigen-binding polypeptide, e.g., an antibody, fragment, derivative or analog thereof, that binds to a PD-L1 epitope described herein.

Description

BRIEF DESCRIPTION OF FIGURES
(1) FIG. **1** schematically depicts screening for antigen-binding polypeptides with solid phase phage panning technologies, specifically, using indirect coating of test proteins to the immunotubes,

according to an embodiment of the present invention.
(2) FIG. **2** schematically depicts screening for antigen-binding polypeptides with solid phase phage panning technologies, specifically, using direct coating of test proteins to the immunotubes, according to an embodiment of the present invention.
(3) FIG. **3** is a chart listing data that characterize the ability to bind hPDL1 of representative single chain variable fragments (scfv) obtained through an embodiment of present invention in indirect ELISA binding assay. “NC” represents negative control.
(4) FIG. **4** is a chart listing data that characterize the ability to bind hPDL1 of representative single chain variable fragments (scfv) obtained through an embodiment of present invention in FACS binding assay. “PC” represents positive control using hPDL1/293T cells stained with anti-hPDL1-APC (10 μg/ml). “NC” represents negative control with unstained hPDL1/293T cells.
(5) FIG. **5** is a chart listing data that characterize the ability to block the interaction between hPD1 and hPDL1 of various single chain variable fragments (scfv) obtained through an embodiment of present invention in receptor blocking assay (plates coated by hPDL1). “PC” represents positive control with added biotin-hPD1-Fc. “NC” represents negative control where only buffer was added.
(6) FIG. **6** is a chart listing data that characterize the ability to block the interaction between hPD1 and hPDL1 of various single chain variable fragments (scfv) obtained through an embodiment of present invention in receptor blocking assay (plates coated by hPD1). “PC” represents positive control with added biotin-hPDL1-Fc. “NC” represents negative control where only buffer was added.
(7) FIG. **7** depicts ability to bind hPDL1-Fc, mPDL1-Fc (mouse PDL1) and hIgG1 of the single chain variable fragments (scfv) obtained through embodiments of the present invention in direct ELISA assays.
(8) FIGS. **8**A and **8**B show full-length antibody 4-1E8 characterized by SDS-PAGE (FIG. **8**A) and size exclusion chromatography (FIG. **8**B).
(9) FIGS. **9**A and **9**B show full-length antibody 3-1B11 characterized by SDS-PAGE (FIG. **9**A) and size exclusion chromatography (FIG. **9**B).
(10) FIGS. **10**A and **10**B show full-length antibody 3-1E4 characterized by SDS-PAGE (FIG. **10**A) and size exclusion chromatography (FIG. **10**B).
(11) FIGS. **11**B and **11**C show results of quantitative binding analysis of some of the full-length antibody embodiments according to the present invention to hPDL1 in an ELISA format according to FIG. **11**A.
(12) FIGS. **12**A and **12**B show results of quantitative FACS for some of the full-length antibody embodiments according to the present invention where binding to hPDL1-expressing 293T cells (top graph), and hPDL1-negative 293T cells (bottom graph).
(13) FIG. **13**B shows results in receptor blocking assay of the lead antibody candidates in the present invention in RBA Format 1 (FIG. **13**A): coated with hPDL1-Fc and added with Biotin-hPD1-Fc.
(14) FIG. **14**B shows results in receptor blocking assay of the lead antibody candidates in the present invention in RBA Format 2 (FIG. **14**A): coated with hPD1-Fc and added with Biotin-hPDL1-Fc.
(15) FIG. **15** is a chart listing data that characterizes various full-length antibodies obtained through an embodiment of the present invention.
(16) FIGS. **16**A-**16**D depict affinities to PD-L1 of lead antibody candidates using BIAcore: FIG. **16**A schematically depicts the BIAcore format utilized according to an example of the present invention; FIG. **16**B lists results from testing lead antibody candidates≤ affinity to PD-L1 using BIAcore; FIG. **16**C depicts the response curve of antibody coded 4-1E8 of BIAcore affinity testing; and FIG. **16**D depicts the response curve of antibody coded 3-1B11 of BIAcore affinity testing.
(17) FIG. **17**A schematically depicts an epitope-binning format utilized according to an example of the present invention. FIG. **17**B schematically depicts an epitope bins for lead antibody candidates

according to an embodiment of the present invention. FIG. **17**C lists epitope-binning matrix for lead antibody candidates using the format represented in FIG. **17**A.
(18) FIGS. **18**A-**18**D show binding abilities of: controls (FIG. **18**A), antibodies of the invention coded "4-1E8" (FIG. **18**B), "3-1E4" (FIG. **18**C), and "3-1B11" (FIG. **18**D) to Rhesus PDL1-GFP expressing construct transfected 293T cell (top) and parental 293T (bottom) cells through FACS assays.
(19) FIGS. **19**A-**19**D show binding abilities of: controls (FIG. **19**A), antibodies of the invention coded "4-1E8" (FIG. **19**B), "3-1E4" (FIG. **19**C), and "3-1B11" (FIG. **19**D) to Rhesus PDL1 expressing construct transfected 293T cell (top) and parental 293T (bottom) cells through FACS assays.
(20) FIG. **20** shows representative EC50 results of IL-2 production experiment according to embodiments of the invention.
(21) FIG. **21** shows ADCC activity of the polypeptide embodiment coded "4-1E8" in comparison to commercially available anti-PDL1 antibody Atezolizumab.
(22) FIGS. **22**A-**22**C show ADCC activity of the polypeptide embodiment coded "4-1E8" in comparison to embodiments coded "3-1B11" (FIG. **22**A) and "3-1E4" (FIG. **22**B), with key data points summarized in a chart (FIG. **22**C).
(23) FIGS. **23**A, **23**B and **23**C provide three sets of experimental data of IL-2 production ability of PBMCs co-cultured with PDL1+ MDA-MB-231 tumor cells in the presence of lead antibodies according to the invention in comparison to commercially available anti-PDL1 antibodies.
(24) FIG. **24** provides results of IFNγ production ability of CD8 T cells co-cultured with PDL1+ MDA-MB-231 tumor cells in the presence of lead antibodies according to the invention in comparison to commercially available anti-PDL1 antibodies.
(25) FIGS. **25**A and **25**B show mixed lymphocyte reaction results of lead antibodies according to embodiments of the invention.
(26) FIGS. **26**A and **26**B show the specificity of binding by antibodies of the invention coded "4-1E8" (FIG. **26**A) and "3-1B11" (FIG. **26**B).
(27) FIGS. **27**A and **27**B show ability of the antibodies of the invention E8 (FIG. **27**A) and B11 (FIG. **27**B) to block CD80 from binding PD-L1-expressing cells (grey silled curves) compared to CD80 alone (solid line) and secondary alone (dashed line).
(28) FIG. **28** shows half-life measurement of the antibody embodiments of the invention using Tg32 mice.

DETAILED DESCRIPTION OF INVENTION

(29) Unless otherwise noted, technical terms are used according to conventional usage.
(30) As used herein, "a" or "an" may mean one or more. As used herein when used in conjunction with the word "comprising," the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more. Furthermore, unless otherwise required by context, singular terms include pluralities and plural terms include the singular.
(31) As used herein, "about" refers to a numeric value, including, for example, whole numbers, fractions, and percentages, whether or not explicitly indicated. The term "about" generally refers to a range of numerical values (e.g., +/−5 to 10% of the recited value) that one of ordinary skill in the art would consider equivalent to the recited value (e.g., having the same function or result). In some instances, the term "about" may include numerical values that are rounded to the nearest significant figure. Unless indicated otherwise, "about" is +/−10% of the recited value(s).
(32) An "antigen-binding polypeptide" is a polypeptide comprising a portion that binds to an antigen. Examples of antigen-binding polypeptides include antibodies, antibody fragments (e.g., an antigen binding portion of an antibody), antibody derivatives, and antibody analogs.
(33) An antigen binding polypeptide or protein can have, for example, the structure of a naturally occurring antibody (also known as "immunoglobulin". Each naturally occurring antibody is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa)

and one “heavy” chain (about 50-70 kDa). The variable regions of each light/heavy chain pair form the antibody-binding site such that an intact antibody has two binding sites.

(34) The variable regions of naturally occurring antibody chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper-variable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in *Sequences of Proteins of Immunological Interest,* 5.sup.th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. Other numbering systems for the amino acids in immunoglobulin chains include IMGT (international ImMunoGeneTics information system; Lefranc et al., *Dev. Comp. Immunol.* 29:185-203; 2005) and AHo (Honegger and Pluckthun, *J. Mol. Biol.* 309(3):657-670; 2001).

(35) Antibodies can be obtained from sources such as serum or plasma that contain immunoglobulins having varied antigenic specificity. If such antibodies are subjected to affinity purification, they can be enriched for a particular antigenic specificity. Such enriched preparations of antibodies usually are made of less than about 10% antibody having specific binding activity for the particular antigen. Subjecting these preparations to several rounds of affinity purification can increase the proportion of antibody having specific binding activity for the antigen. Antibodies prepared in this manner are often referred to as “monospecific.” Monospecific antibody preparations can be made up of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 99.9% antibody having specific binding activity for the particular antigen.

(36) The term “antibody” or “Ab” (and their plural forms), as used herein, broadly refers to any immunoglobulin (Ig) molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment(s), mutant(s), variant(s), derivative(s) or analog(s) thereof, which retains the essential and specific epitope-binding features of an Ig molecule. Such fragment, mutant, variant, derivative or analog antibody formats are known in the art, and include, inter alia, Fab, F(ab′), F(ab′).sub.2, Fv, single-chain antibodies (scFv), single-domain antibodies (sdAbs), complementarity determining region (CDR) fragments, chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. Antibody fragments, derivatives and analogs may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

(37) A Fab fragment is a monovalent fragment having the V.sub.L, V.sub.H, C.sub.L and C.sub.H1 domains; a F(ab′).sub.2 fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V.sub.H and C.sub.H1 domains; an Fv fragment has the V.sub.L and V.sub.H domains of a single arm of an antibody; and a dAb fragment has a V.sub.H domain, a V.sub.L domain, or an antigen-binding fragment of a V.sub.H or V.sub.L domain (see, e.g., U.S. Pat. Nos. 6,846,634; 6,696,245, US App. Pub. 20/0202512; 2004/0202995; 2004/0038291; 2004/0009507; 2003/0039958, and Ward et al., *Nature* 341:544-546, 1989).

(38) A single-chain antibody (scFv) is an antibody in which a V.sub.L and a V.sub.H region are joined via a linker (e.g., a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., 1988, *Science* 242:423-26 and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83). Diabodies are bivalent antibodies comprising two polypeptide chains, where each polypeptide chain comprises V.sub.H and V.sub.L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48, and Poljak et al., 1994, *Structure* 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from

their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen-binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.
(39) Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat et al. supra; Lefranc et al., supra and/or Honegger and Pluckthun, supra. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding polypeptide may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.
(40) An antigen binding polypeptide may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a “bispecific” or “bifunctional” antibody has two different binding sites.
(41) The term “human antibody” or “humanized antibody” as used herein includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human or humanized antibody). These antibodies may be prepared in a variety of ways, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes. A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.
(42) The term “chimeric antibody” as used herein refers to an antibody that contains one or more regions from one antibody and one or more regions from at least another antibody. In an embodiment, the CDRs from more than one human anti-PD-L1 antibodies are mixed and matched in a chimeric antibody.
(43) Activated T cells express PD1 on their cell surface. Binding of PD-L1 to PD1 activates PD1 and suppresses the PD1.sup.+ T cells. A “neutralizing antibody” or an “inhibitory antibody” as used herein refers to an antibody that blocks the activation of PD1 when an excess of the anti-PD-L1 antibody reduces the amount of said activation by at least about 20% using an assay such as those described herein in the Examples. In various embodiments, the antigen binding protein reduces the amount of activation of PD1 by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.
(44) Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques known in the art. Preferred

amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, Bowie et al., 1991, *Science* 253:164.

(45) As used herein, an antigen-binding polypeptide "specifically binds" to an antigen (e.g., human PD-L1) if it binds to the antigen with a dissociation constant of 100 nanomolar or less.

(46) An "antigen binding domain," "antigen binding region," or "antigen binding site," as used herein, is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody to specifically bind to its antigen, it will include at least part of at least one of its CDR domains.

(47) An "epitope" as used herein is the portion of a molecule that is bound by an antigen binding protein (e.g., by an antibody). An epitope can comprise non-contiguous portions of the molecule (e.g., in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

(48) As used herein, the terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably throughout and include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs (e.g., peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutant, or variant thereof.

(49) A "vector" as used herein is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

(50) As used herein, a nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (e.g., the level, timing, or location of expression) of the nucleotide sequence. A "regulatory sequence" is a nucleic acid that affects the expression (e.g., the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (e.g., polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: *Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

(51) Preferably, the broad spectrum of mammalian cancers to be treated by compositions of the present invention is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell

derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck cancer, pancreatic cancer, and combinations thereof. More broadly, any cancer where at least a fraction of the tumor cells express detectable amount of PD-L1 can potentially be treated by the composition of the invention.

(52) Polypeptides of the present disclosure can be produced using any standard methods known in the art. In one example, the polypeptides are produced by recombinant DNA methods by inserting a nucleic acid sequence (e.g., a cDNA) encoding the polypeptide into a recombinant expression vector and expressing the DNA sequence under conditions promoting expression.

(53) Nucleic acids encoding any of the various polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for E. coli and other bacteria, as well as mammalian cells, plant cells, yeast cells and insect cells. See for example: Mayfield et al., *Proc. Natl. Acad. Sci. USA.* 2003 100(2):438-42; Sinclair et al. *Protein Expr. Purif.* 2002 (1):96-105; Connell N D. *Curr. Opin. Biotechnol.* 2001 12(5):446-9; Makrides et al. *Microbiol. Rev.* 1996 60(3):512-38; and Sharp et al. *Yeast.* 1991 7(7):657-78.

(54) General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., *Current Protocols in Molecular Biology* (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

(55) The recombinant DNA of the present invention can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, N.Y., 1985).

(56) The expression construct of the present invention is introduced into the host cell using a method appropriate to the host cell. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent). Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells.

(57) Proteins disclosed herein can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial cell-free translation system.

(58) PD-L1-binding polypeptides can also be produced by chemical synthesis (e.g., by the methods described in *Solid Phase Peptide Synthesis,* 2nd ed., 1984, The Pierce Chemical Co., Rockford, Ill.). Modifications to the protein can also be produced by chemical synthesis.

(59) The polypeptides of the present disclosure can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (e.g., with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography,

hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification, polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

(60) The purified polypeptide is preferably at least 85% pure, more preferably at least 90% or 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently purified for use as a pharmaceutical product.

(61) Post-Translational Modifications of Polypeptides

(62) In certain embodiments, the binding polypeptides of the invention may further comprise post-translational modifications. Exemplary post-translational protein modifications include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while also reducing the possible immunogeneticity of the protein. See Raju et al. *Biochemistry.* 2001 31; 40(30):8868-76. Effects of such non-amino acid elements on the functionality of a polypeptide may be tested for its antagonizing role in PD-L1 or PD-1 function, e.g., its inhibitory effect on angiogenesis or on tumor growth.

(63) In one embodiment, modified forms of the subject polypeptides comprise linking the subject soluble polypeptides to nonproteinaceous polymers. In one specific embodiment, the polymer is polyethylene glycol (“PEG”), polypropylene glycol, or polyoxyalkylenes, in the manner as set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

(64) In one feature, the pegylated embodiments of binding polypeptides of the invention preferably retain at least 25%, 50%, 60%, 70%, 80%, 90%, 95% or 100% of the biological activity associated with the unmodified protein. In one embodiment, biological activity refers to its ability to bind to PD-L1, as assessed by KD, k.sub.on or k.sub.off rates. In one specific embodiment, the pegylated binding polypeptide protein shows an increase in binding to human PD-L1 relative to the unpegylated counterpart. In another embodiment, the biological activity refers to blockage of PD-L1/PD1 interaction.

(65) Therapeutics, Vaccines & Administration

(66) The present disclosure further features methods for treating conditions or preventing pre-conditions which respond to inhibition of an PD-L1 biological activity. Preferred examples are conditions that are characterized by cellular hyperproliferation and sustained infection. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated. Because regulatory agencies require that a protein reagent to be used as a therapeutic be formulated with acceptably low levels of pyrogens, therapeutic formulations of the present invention can be distinguished from other formulations for being substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (e.g., U.S. FDA).

(67) Pharmaceutical formulations of the present invention may include at least one pharmaceutically acceptable diluent, carrier, or excipient. Excipients included in the formulations will have different purposes depending, for example, on the kind of gene construct or effector cells used, and the mode of administration. Examples of generally used excipients include, without limitation: saline, buffered saline, dextrose, water-for-infection, glycerol, ethanol, and combinations thereof, stabilizing agents, solubilizing agents and surfactants, buffers and preservatives, tonicity agents, bulking agents, and lubricating agents.

(68) In another embodiment of the invention, a pharmaceutical formulation of the invention is

administered into the patient. Exemplary administration modes include, but are not limited to, intravenous injection. Other modes include, without limitation, intratumoral, intradermal, subcutaneous (s.c., s.q., sub-Q, Hypo), intramuscular (i.m.), intraperitoneal (i.p.), intra-arterial, intramedullary, intracardiac, intra-articular (joint), intrasynovial (joint fluid area), intracranial, intraspinal, and intrathecal (spinal fluids). Any known device useful for parenteral injection or infusion of the formulations can be used to effect such administration. As used herein, the terms "treat", "treating", and "treatment" have their ordinary and customary meanings, and include one or more of: blocking, ameliorating, or decreasing in severity and/or frequency a symptom of a disease (e.g., cancer) in a subject, and/or inhibiting the growth, division, spread, or proliferation of cancer cells, or progression of cancer (e.g., emergence of new tumors) in a subject. Treatment means blocking, ameliorating, decreasing, or inhibiting by about 5% to about 100% versus a subject in which the methods of the present invention have not been practiced. Preferably, the blocking, ameliorating, decreasing, or inhibiting is about 100%, 99%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% versus a subject in which the methods of the present invention have not been practiced.

(69) The invention also provides a kit comprising one or more containers filled with quantities of gene constructs encoding the polypeptides of the invention, with pharmaceutically acceptable excipients. The kit may also include instructions for use. Associated with the kit may further be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

EXAMPLES

(70) Screening of Antigen-Binding Polypeptide Employing Phage Display Techniques:

(71) Indirect coating: Referring to FIG. **1**, PDL1-binding single chain variable fragments (scFv) were identified by standard phage display technique. Human naïve scFv libraries were generated through PCR-based reconstruction from B cells from 50 healthy donors. Solid phase immunotube-based panning was performed using hPDL1-Fc fusion protein and irrelevant Fc fusion protein indirectly immobilized onto immunotube coated with anti-human IgG Fc antibody. To pan for strong binders, Fc-binding scFvs were first depleted using the irrelevant Fc fusion proteins and then the unbound phages were selected for binding with the hPDL1-Fc fusion protein. Eluted phages were amplified in bacteria. These rounds were repeated 3-4 times and the phage titers and complexity was determined after the second round onwards. Once, convergence in sequence was seen (rounds 3 and 4), individual phage clones were tested for their ability to bind hPDL1 in ELISA assays.

(72) Direct coating: This was conducted by directly coating the Fc proteins onto the immunotube without the use of the anti-human Fc antibody (FIG. **2**).

(73) Phage Binding ELISAs:

(74) ELISAs were performed using the same strategy as the panning. For clones from the indirect panning, plates were first coated with anti-human Fc antibody and then the Fc protein. For clones from the direct panning, plates were directly coated with the Fc protein. In indirect ELISA assays, phages were tested for their ability to bind hPDL1-Fc and an irrelevant Fc protein (or hIgG1) in parallel assays. Phages that showed low binding to the irrelevant Fc protein and high binding to the hPDL1 were selected for further sequencing and secondary screening. Data were shown in FIG. **3**. Non-specific binding of most clones is low (signal value against Fc protein (1:10 dilution) is less than 0.2). In direct ELISA assays, phages were tested for their ability to bind hPDL1-Fc, mPDL1-Fc (mouse PDL1) and hIgG1 in parallel assays. Phages showed that there was no significant binding to mouse PDL1 by any of the lead molecules in the present invention, namely, none of the lead molecules show significant cross-reactivity with mouse PDLL. Data are shown in FIG. **7**.

(75) Sequencing:

(76) Unique clones were identified by initially sequencing the CDR3 region of the heavy chain.

This was later confirmed by the complete sequence as well. A small subset of clones shared the same CDR3 but had significant divergence in other parts of their sequences.
(77) Secondary Screening by FACS:
(78) Phages, phage lysates or lysates from bacteria expressing scFvs were tested for their ability to preferentially bind to 293T cells expressing hPDL1 but not parental 293T cells. The ratio of the mean fluorescence intensity (MFI) was used as the basis for identifying positive clones. Data were shown in FIG. **4**. Most clones showed high ratio that could be identified as positive clones.
(79) Blocker Identification:
(80) Phages, phage lysates or lysates from bacteria expressing scFvs were tested for their ability to block the interaction between hPD1 and hPDLL The binding assays were set up by either coating the plates with hPD1-Fc or hPDL1-Fc. Binding of the biotinylated ligand (hPDL1 or hPD1) was detected using streptavidin-HRP using standard methods. The loss of binding in the presence of the scFv was used to identify potential blockers. Results are shown in FIGS. **5** and **6**.
(81) Generation and Characterization of Fc Fusion Proteins:
(82) Since scFvs are relatively unstable, some scFvs were converted to Fc fusions and expressed in mammalian cells. These were purified using Protein A columns and tested for their ability to block PD1-PDL1 interaction as well as their ability to bind PDL1-expressing 293T cells.
(83) Generation of Full-Length Antibodies:
(84) Full-length antibody genes were constructed by PCR-amplifying the VH and VL regions from individual scFv clones and cloned into appropriate expression vectors using standard methods familiar to one skilled in the art. Full-length antibody proteins were generated by transiently transfecting suspension-grown 293T cells and purified using a Protein A column by standard methods familiar to one skilled in the art.
(85) Characterization of Full-Length Antibodies:
(86) Exemplary full length antibodies were characterized by SDS-PAGE and size exclusion chromatography (result was shown in FIGS. **8**A, **8**B, **9**A, **9**B, **10**A, and **10**B), as well as quantification of their potency in (a) specifically binding hPDL1 by ELISA (result was shown in FIGS. **11**B and **11**C); (b) specifically binding hPDL1-expressing 293T cells and unstrained 293T cells (results were shown in FIGS. **12**A and **12**B); and (c) blocking PD1-PDL1 interaction in both versions of the blocking assay. Resulting data for exemplary lead antibody candidates in Format 1 and Format 2 are shown in FIGS. **13**B and **14**B. Resulting data for 27 antibody embodiments in the present invention are shown in FIG. **15**.
(87) Affinity of PD-L1 Interaction by BIAcore:
(88) The lead antibody candidates were tested for their affinities to PD-L1 using BIAcore (FIGS. **16**B-**16**D). Briefly, biotinylated hPDL1 was captured through streptavidin onto the sensor chip surface. Antibody was made to flow over the chip and the reaction parameters were calculated using a single cycle kinetics method based on the stability of the interaction. KD values were evaluated using BIAcore X100 evaluation software 2.0 with bivalent analyte binding model.
(89) Rhesus PD-L1 Binding by FACS
(90) (A) 293T cells were transiently transfected with Rhesus PDL1-GFP expression construct. Embodiments 4-1E8, 3-1E4 and 3-1B11 were tested and compared to control. Results are shown in FIGS. **18**A-**18**D: all three antibodies bound rhesus PDL1
(91) (B) 293T cells were transiently transfected with Rhesus PDL1 expression construct. Embodiments 4-1E8, 3-1E4 and 3-1B11 were tested and compared to control. Results are shown in FIGS. **19**A-**19**D: all three antibody embodiments bound rhesus PDL1.
(92) IL2 Induction and EC50 Determination
(93) Peripheral Blood Mononuclear Cells (PBMCs) were isolated from human blood with a Ficoll gradient, followed by red blood cell lysis, using standard protocols. For the assay, RPMI+ medium was prepared as follows: 10% FBS, 1% anti-anti (Gibco) and 1% non-essential amino acids (Gibco) were added to RPMI medium with ATCC modification (Gibco). After isolation from blood,

PBMCs were resuspended in 10-20 ml RPMI and were cultured overnight at 37° C. with 5% CO.sub.2. Next, PBMCs were seeded into 96 well tissue culture plates (Corning) at a concentration of 100 000 PBMCs/96 well; the final volume per well was 200 ul. Staphylococcal Enterotoxin B (SEB) was added at a concentration of 1 ng/ml, and lead antibodies were added at 20 ug/ml (for screening) or at a range of concentrations from 50 ug/ml to 0.003 ug/ml. As controls, cells without SEB (e.g. no stimulation); with SEB alone or with SEB and isotype control (e.g., baseline).
(94) After a 76-hour incubation at 37° C. with 5% CO.sub.2, PBMCs were spun down at 1200 rpm for 15 minutes at room temperature, and supernatants were collected and stored at −20° C. IL2 ELISA was performed using a commercially available IL2-ELISA kit (Biolegend or Thermofisher), following instructions from the manufacturer. Supernatants were diluted 1/20-1/80 for the ELISA. The absorbance was measured using a Spectramax3 M3 microplate reader (Molecular Devices), and data were analyzed using Graphpad software. The lead antibody candidates were compared to commercially available anti-PD1 antibodies. Results are shown in FIG. **20**. In the tumor co-culture experiments with MDA-MB-231 cells (see FIGS. **23**A-**23**C), the 4-1E8 was consistently better than 3-1B11 and 3-1E4 in de-repressing IL2 (see FIGS. **23**A-**23**C) and IFNγ (see FIG. **24**). However, all three antibodies were as good or better than commercial PDL1 antibodies such as atezolizumab (Atezo) and durvalumab (Durva) production in similar co-culture experiments with T cells and MDA-MB-231 cells.
(95) ADCC Activity
(96) As shown in FIGS. **21** and **22**, all three lead antibodies showed robust ADCC activity while atezolizumab (which is engineered to be ADCC-negative) showed no activity. Among the three embodiments of the invention, 4-1E8 showed the most amount of ADCC activity.
(97) Mixed Lymphocyte Reaction
(98) Peripheral Blood Mononuclear Cells (PBMCs) were isolated from human blood with a Ficoll gradient, followed by red blood cell lysis, using standard protocols. Cells were cultured in serum-free RPMI 1640 for 1 hour at 37° C. Non-adherent cells were removed, and remaining monocytes were cultured in RPMI 1640 supplemented with 5% human AB serum, 2 ng/mL GM-CSF, and 10 ng/mL IL4 (BD Biosciences). Fresh media with cytokine supplements were added every 2 to 3 days. Mature dendritic cells were induced by addition of 20 ng/mL TNFa (BD Biosciences) on day 6 and cultured for 24 hours.
(99) Dendritic cells were harvested, phenotyped, and frozen for later use. CD4 T cells were isolated from PBMCs using magnetic beads (Dynal) as per manufacturer's instructions. CD4 T cells were cultured in 96 well-flat bottom plates (Costar) together with allogeneic dendritic cells at a ratio of 1:2.5, using RPMI 1640 supplemented with 10% human AB serum. Dendritic cells were treated with 100 mg/mL of mitomycin C (Sigma) before addition. Proliferation was measured by CFSE (or similar dye) dilution in T cells. IFNg release was measured using a commercially available IFNg-ELISA kit, following instructions of the manufacturer. The absorbance was measured using a Spectramax3 M3 microplate reader (Molecular Devices), and data were analyzed using graphpad software. In these studies, the lead antibody candidates according to embodiments of the present invention performed comparably to other commercially available anti-PD1 and anti-PDL1 antibodies. Exemplary results are shown in FIGS. **25**A and **25**B.
(100) Binding Specificity
(101) Lines of Expi293 cells were generated that stably expressed a variety of B7 family members and their receptors. The ability of anti-PDL1 antibodies was tested by FACS using fluorescent anti-human IgG. Resulting data for exemplary lead antibody candidates are shown in FIGS. **26**A and **26**B.
(102) Blocking CD80-PDL1 Binding
(103) DLD1 cells engineered to express PDL1 bind were used to detect binding of biotinylated CD80-Fc in the presence or absence of anti-PDL1 Abs, followed by fluorescent streptavidin. Resulting data for exemplary lead antibody candidates of the present invention are shown in FIGS.

27A and **27**B.
(104) Half-Life Measurement
(105) Serum half-life was measured using male homozygous Tg32 mice (B6.Cg-Fcgrttm1Dcr Tg(FCGRT)32Dcr/DcrJ, Jackson labs). 2 mg/kg of antibody was injected IV on Day 0 and blood was drawn on Day 1 and various later time points. Plasma was prepared and antibody titers were measured using a sandwich ELISA. Titers were normalized to Day 1 titers. Anti-antibody response was also measured and samples with high titers were removed from the analysis because they often showed sudden changes in the ELISA. Resulting data for exemplary lead antibody candidates of the present invention are shown in FIG. **28**. Half-life for different antibodies ranged from 6.9 days (3-1E4, see Example 9 below for sequence details) to 10.5 days (3-1B11, see Example 11 below for sequence details) and 12.3 days (4-1E8, see Example 5 below for sequence details).
(106) Polypeptide Sequences
(107) Examples of PD-L1 binding polypeptide sequences according to the present inventions are listed as follows:
Example 1
Antibody Code: 4-1A2
(108) TABLE-US-00001 VH DNA (SEQ ID NO: 1)
CAGGTTCAGCTGGTGCAGTCTGGGACTGAGGTGAAGAAGCCTGGGGCCT
CAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGA
TATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGA
TGGATCAACCCTAACAGTGGTGGCACAAACTATGCACAGAAGTTTCAGG
GCAGGGTCACCATGACCACAGACACTTCTACGGGCACAGCCTACATGGA
GCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGA
TTTTTATGGGGTTCGGGGAGTTATGACTACTGGGGCCAGGGAACCCTGG
TCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 2)
QVQLVQSGTEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMG
WINPNSGGTNYAQKFQGRVTMTTDTSTGTAYMELRSLRSDDTAVYYCAR
FLWGSGSYDYWGQGTLVTVSS VL DNA (SEQ ID NO: 3)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG
ACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTT
AAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT
GCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG
GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGA
TTTCGCAACTTACTACTGTCAACAGACTTACACATTCCCGCACACTTTT
GCCCAGGGGACCAACCTGGAGATCAAA AMINO ACID (SEQ ID NO: 4)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY
AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYTFPHTF AQGTNLEIK
Example 2
Antibody Code: 4-1A12
(109) TABLE-US-00002 VH DNA (SEQ ID NO: 5)
CAAGTCCAGCTGGTACAATCTGGAGCTGAGGTGAAGAAGCCTGGGGCCT
CAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGG
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
TGGATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGG
GCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGA
GCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGA
GATTGGATACAGCTATGGTTACCCCTTGACTACTGGGGCCAGGGAACCC
TGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 6)
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG
WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR

DWIQLWLPLDYWGQGTLVTVSS VL DNA (SEQ ID NO: 7)
GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG
ACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTT
AAATTGGTATCAACAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT
GGTGCATCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG
GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGA
TTTTGCAACTTACTACTGTCAACAGAGTCACAGTTCCCCCCTCACTTTC
GGCGGAGGGACCAAGGTGGACATCAAA AMINO ACID (SEQ ID NO: 8)
DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY
GASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSHSSPLTF GGGTKVDIK
Example 3
Antibody Code: 4-1B9
(110) TABLE-US-00003 VH DNA (SEQ ID NO: 9)
GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGAGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGG
CATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCA
GTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGG
GCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA
AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAA
GATTTGATCCCGTTGCGAGATAGTAGGGGGGGGTACTACTACGGTATGG
ACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGGAGT AMINO ACID
(SEQ ID NO: 10)
EVQLVQSGGGLVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA
VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
DLIPLRDSRGGYYYGMDVWGQGTTVTVSS VL DNA (SEQ ID NO: 11)
TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGA
CAGTCAGGATCACATGCCAAGGAGACAGCCTCAGAGACTATTATGCAAG
CTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTACTTGTCATCTATGGT
AAAAACAACCGGCCCTCAGGAATCCCAGACCGATTCTCTGGCTCCAGCT
CAGGAAACACAGCTTCCTTGACCATCACTGGGACTCAGGCGGAAGATGA
GGCTGACTATTACTGTAACTCCCGTGACAGCGGTGCTTACCATTATGTC
TTCGGAACTGGGACCAAGGTCACCGTCCTA AMINO ACID (SEQ ID NO: 12)
SSELTQDPAVSVALGQTVRITCQGDSLRDYYASWYQQKPGQAPVLVIYG
KNNRPSGIPDRFSGSSSGNTASLTITGTQAEDEADYYCNSRDSGAYHYV FGTGTKVTVL
Example 4
Antibody Code: 4-1B12
(111) TABLE-US-00004 VH DNA (SEQ ID NO: 13)
CAAATCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGG
CATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCA
GTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGG
GCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA
AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAA
GGAAGTATTATAGGGGATGGTGCTTTTGATATCTGGGGCCAAGGGACAA
TGGTCACCGTCTCTTCA AMINO ACID (SEQ ID NO: 14)
QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVA
VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
GSIIGDGAFDIWGQGTMVTVSS VL DNA (SEQ ID NO: 15)
GATATTGTGATGACCCAGTCTCCACTCTCCCTGCCCGTCACCCTTGGAG
AGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGACCCTCCTGCATAATGG

ATTCAACTTTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAA
CTCCTGATGTATTTGGCCTCTAGCCGGGCCTCCGGGGTCCCTGACAGGT
TCAGTGGCAGTGGATCGGGCACAGATTTCACACTGAAAATCAGCAGAGT
GGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGGTACACACTGG
CCGTACACTTTTGGCCAGGGGACCAAGCTGGATATCAAA AMINO ACID (SEQ ID
NO: 16) DIVMTQSPLSLPVTLGEPASISCRSSQTLLHNGFNFLDWYLQKPGQSPQ
LLMYLASSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHW
PYTFGQGTKLDIK
Example 5
Antibody Code: 4-1E8
(112) TABLE-US-00005 VH DNA (SEQ ID NO: 17)
CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGATGCCTGGGGCCT
CAGTGACGATTTCCTGCGAGGCGTCTGGATACAACTTCATCAGCTACTA
TATACACTGGGTGCGACAGGCCCCTGGACAAGGCCTTGAGTGGATGGGA
TTCGTCGTCCCTAGTGGTGGTGCCGCAGGCTACACACAGAAGTTCCAGG
GCAGACTCACCGTGACCAGGGACACGTCCACGAGCACAGTCTACATGGA
CCTGAACAGCCTGACATCTGACGACACGGCCGTGTATTACTGTGTGCGA
GAAATGAGTGGTGGCTGGTTTGATTTCTGGGGCCAGGGAACCCTGGTCA
CCGTCTCCTCG AMINO ACID (SEQ ID NO: 18)
QIQLVQSGAEVKMPGASVTISCEASGYNFISYYIHWVRQAPGQGLEWMG
FVVPSGGAAGYTQKFQGRLTVTRDTSTSTVYMDLNSLTSDDTAVYYCVR
EMSGGWFDFWGQGTLVTVSS VL DNA (SEQ ID NO: 19)
GACATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG
ACAGAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTT
AGGCTGGTATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT
GCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTG
GATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGA
TGTGGCAGTTTATTACTGTCAGCAATATTATAGTACTCCTCTCACTTTC
GGCCCTGGGACCAAAGTGGATATCAAA AMINO ACID (SEQ ID NO: 20)
DIVMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIY
AASTLQSGVPSRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTF GPGTKVDIK
Example 6
Antibody Code: 4-1G7
(113) TABLE-US-00006 VH DNA (SEQ ID NO: 21)
GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGG
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
TGGATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGG
GCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGA
GCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGA
GCCTCACCGGTACAGCAGCCCATATGGTGGGCGGAGTACTGGGGCCAGG
GAACCCTGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 22)
EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYGISWVRQAPGQGLEWMG
WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR
ASPVQQPIWWAEYWGQGTLVTVSS VL DNA (SEQ ID NO: 23)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGT
CGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAA
CTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATG
ATTTCTGATGTCAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTG
GCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGC

TGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCAACTACACT
TTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO:
24) QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM
ISDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSNYT LVFGGGTKLTVL
Example 7
Antibody Code: 4-1H10
(114) TABLE-US-00007 VH DNA (SEQ ID NO: 25)
CAGCTGCAGCTACAGCAGTCCGGAGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTCCTGGAGGCACCTTCAGCAGCTATGC
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
AGGATCATCCCTATCCTTGGTATAGCAAACTACGCACAGAAGTTCCAGG
GCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAAGACACGGCCGTGTATTACTGTGCGAGT
CATGGTCGGGCAGCAGCTGGTAGGTACGCTATGGACGTCTGGGGCCAAG
GGACCACGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 26)
QLQLQQSGAEVKKPGSSVKVSCKAPGGTFSSYAISWVRQAPGQGLEWMG
RIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCAS
HGRAAAGRYAMDVWGQGTTVTVSS VL DNA (SEQ ID NO: 27)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGATTCTCCGGGGAAGA
CGGTAACCATCTCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTA
TGTGCAGTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATC
TATGACGATAAGCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCGGGCT
CCATCGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAC
GACTGAGGACGAGGCTGACTACTACTGTCAGTCCTTTGATGGCAGCAGT
GTCATCTTCGGCGGAGGGACCAAGCTGACCGTCCTG AMINO ACID (SEQ ID NO:
28) NFMLTQPHSVSDSPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPTTVI
YDDKQRPSGVPDRFSGSIDSSSNSASLTISGLTTEDEADYYCQSFDGSS VIFGGGTKLTVL
Example 8
Antibody Code: 3-1H2
(115) TABLE-US-00008 VH DNA (SEQ ID NO: 29)
CAGGTTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGC
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
GGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGG
GCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGA
AAGGAGCGTTTCTATGATAGTAGTGGTTATTACGATGCTTTTGATATCT
GGGGCCAAGGGACAATGGTCACCGTCTCTTCA AMINO ACID (SEQ ID NO: 30)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG
GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR
KERFYDSSGYYDAFDIWGQGTMVTVSS VL DNA (SEQ ID NO: 31)
CAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTCTCCTGGGCAGT
CAGTCACCATCTCCTGCACTGGAACCAGCAATGATGTTGGTGGTTATAA
CTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATG
ATTTATGATGTCACTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTG
GCTCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGCCTCCAGCC
TGAGGATGAGGCTGACTATTATTGCGCCTCTTATGGAGGCAGGAACAAT
TTGCTTTTTGGCGGAGGGACTCAACTGACCGTCTTA AMINO ACID (SEQ ID NO:
32) QSALTQPRSVSGSPGQSVTISCTGTSNDVGGYNYVSWYQQHPGKAPKLM
IYDVTKRPSGVPDRFSGSKSGNTASLTVSGLQPEDEADYYCASYGGRNN

LLFGGGTQLTVL
Example 9
Antibody Code: 3-1E4
(116) TABLE-US-00009 VH DNA (SEQ ID NO: 33)
CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGC
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
GGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGG
GCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCCGGA
GGGGGAGCAGTGGCGGACAATAGTTACTGGGGCCAGGGAACCCTGGTCA
CCGTCTCCTCA AMINO ACID (SEQ ID NO: 34)
QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG
GIIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCAG
GGAVADNSYWGQGTLVTVSS VL DNA (SEQ ID NO: 35)
GACATCCGGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG
ACAGAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTT
AGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT
GCTGCATCCAGTTTACAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTG
GATCTGGCACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA
TTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCTCGAACGTTC
GGCCAAGGGACCAAGGTGGAAATCAAA AMINO ACID (SEQ ID NO: 36)
DIRMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIY
AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPRTF GQGTKVEIK
Example 10
Antibody Code: 3-1A8
(117) TABLE-US-00010 VH DNA (SEQ ID NO: 37)
CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGC
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
GGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGG
GCAGAGTCACGATTACCGCGGACGAATCCACGAGCACGGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGA
GACGGTTCGTATAGCAGCAGCTGGTACTCGTTTGACTACTGGGGCCAGG
GAACCCTGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 38)
QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG
GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR
DGSYSSSWYSFDYWGQGTLVTVSS VL DNA (SEQ ID NO: 39)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGT
CGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTCGGTGGTTATAA
CTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATG
ATTTATGATGTCAGTAATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTG
GCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGC
TGAGGACGAGGCTGATTATTACTGCTCCTCATATGCAGGTGATATTAGT
TATGTACTGTTCGGCGGCGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 40) QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM
IYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGDIS YVLFGGGTKLTVL
Example 11
Antibody Code: 3-1B11
(118) TABLE-US-00011 VH DNA (SEQ ID NO: 41)

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGAGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACTTTTAGTGACTATGA
CATGATCTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCA
GTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGG
GCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA
AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAA
GAGTTCTTTGGTGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCG TCTCTTCA
AMINO ACID (SEQ ID NO: 42)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYDMIWVRQAPGKGLEWVA
VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
EFFGAFDIWGQGTMVTVSS VL DNA (SEQ ID NO: 43)
TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCGGTGGCCTTGGGACAGA
CAGTCACGATCACATGCCAAGGAGACAGCCTCAATTACTATTATGCAAA
CTGGTTCCAGCTGAAGCCAGGGCAGGCCCCTGTACTTGTCCTCTTTGGT
AAAAACAACCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCTACT
CGGGAAGCACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGA
CGCTGACTATTACTGTAATTCGCGGGACAGCGGTGGTAATCCTTGGGTG
TTCGGCGGAGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 44)
SSELTQDPAVSVALGQTVTITCQGDSLNYYYANWFQLKPGQAPVLVLFG
KNNRPSGIPDRFSGSYSGSTASLTITGAQAEDDADYYCNSRDSGGNPWV FGGGTKLTVL
Example 12
Antibody Code: 4-1F3
(119) TABLE-US-00012 VH DNA (SEQ ID NO: 45)
CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCT
CGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGC
TATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA
AGGATCATCCCTATCCTTGGTATAGCAGACTACGCACAGAAGTTCCAGG
GCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGA
ACTGAGTAGCCTGGGATCTGAGGACACGGCCGTGTATTTTTGTGCGAGA
GAGGGGGGATCCTTTAGGCACTTTGACTTCTGGGGCCAGGGAACCCTGG
TCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 46)
QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG
RIIPILGIADYAQKFQGRVTITADKSTSTAYMELSSLGSEDTAVYFCAR
EGGSFRHFDFWGQGTLVTVSS VL DNA (SEQ ID NO: 47)
CAGCCTGTGCTGACTCAGCCACCCTCAGTCTCTGGGGCCCCAGGGCAGA
GGGTCACCATCTCCTGCGCTGGGAGCGACCCCAACATCGGGACAGGTCA
TGATGTGCACTGGTACCAGCAACTTCCAGGAACAGCCCCCAAACTCGTC
ATCTATGGTAACACCAATCGGCCCTCAGGGGTCCCTGAGCGATTCACTG
CCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCTCCAGGC
TGAGGATGAGGCTGATTATTACTGCCAGGCCTACGACAGGAGCCTGCGT
GGTTATGTCTTCGGGACTGGGACCAAGGTCACCGTCCTG AMINO ACID (SEQ ID NO: 48) QPVLTQPPSVSGAPGQRVTISCAGSDPNIGTGHDVHWYQQLPGTAPKLV
IYGNTNRPSGVPERFTASKSGTSASLAITGLQAEDEADYYCQAYDRSLR
GYVFGTGTKVTVL
Example 13
Antibody Code: 4-1G5
(120) TABLE-US-00013 DNA (SEQ ID NO: 49)
CAAATCCAGCTGGTACAGTCTGGTGCTGAAGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGACTTCTGGTTACACCTTTACCAGCTATGGTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG

ATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG
AGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGA
GGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAACTACA
GGTGACGAGTGGCTACGATTGGCTATAAATGACTACTGGGGCCAGGGAAC
CCTGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 50)
QIQLVQSGAEVKKPGASVKVSCKTSGYTFTSYGISWVRQAPGQGLEWMGW
ISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARTT
GDEWLRLAINDYWGQGTLVTVSS VL DNA (SEQ ID NO: 51)
GATATTGTGATGACACAGTCTCCCCTCTCCCTGCCCGTCACCCCTGGAGA
GCCGGCCTCCATCTCCTGCAGGTCTAGTCTGCGCCTCATGCATCCTAATG
GACTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAG
CTCCTAATCTTTTTGGGTTCTCAGCGGGCCTCCGGGGTCCCTGACAGGTT
CAGTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGG
AGGCTGAGGATGTTGGCATTTATTACTGCATGCAAGCTCTAGAACCTCCG
TACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA AMINO ACID (SEQ ID NO:
52) DIVMTQSPLSLPVTPGEPASISCRSSLRLMHPNGLNYLDWYLQKPGQSPQ
LLIFLGSQRASGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQALEPP YTFGQGTKLEIK
Example 14
Antibody Code: 4-1C9
(121) TABLE-US-00014 VH DNA (SEQ ID NO: 53)
CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCCC
GGGTATAGCAGTGGCTGGAAAGATGATGCTTTTGATATCTGGGGCCAAGG
GACAATGGTCACCGTCTCTTCA AMINO ACID (SEQ ID NO: 54)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDP
GYSSGWKDDAFDIWGQGTMVTVSS VL DNA (SEQ ID NO: 55)
GAAATTGTGATGACACAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGA
TACAGCCTCCCTCTCCTGCAGGGCCAGTCAGACTGTTAGCAGCAACTACT
TAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTAT
GATACATCCAACAGGGCCGCTGGCATCCCGGCCAGGTTCAGTGGCAGTGG
GTCTGGGACAGACTTCACTCTCACCATCAGTAGCCTAGAGCCTGAAGATT
TTGCAGTGTATTACTGTCAGCAGTACGGTAGCTCACTCTGGACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA AMINO ACID (SEQ ID NO: 56)
EIVMTQSPGTLSLSPGDTASLSCRASQTVSSNYLAWYQQKPGQAPRLLIY
DTSNRAAGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYGSSLWTFG QGTKVEIK
Example 15
Antibody Code: 11-A4
(122) TABLE-US-00015 VH DNA (SEQ ID NO: 57)
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGCGGGG
CAGCAGCTGGTAGCCCTTTGGTACTACTGGGGCCAGGGAACCCTGGTCAC

CGTCTCCTCA AMINO ACID (SEQ ID NO: 58)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARAG
QQLVALWYYWGQGTLVTVSS VL DNA (SEQ ID NO: 59)
CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCGTGGACAGTC
AGTCTCCATCTCCTGCAGTGGAAGTCGCAGTGACATTGGATATTATAACT
ATGTCTCCTGGTATCAACAACACCCAGGCAAAGCCCCCAAACTCATCATT
TTTGACGTCAATAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC
CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGCCTCCAGCCTGAGG
ATGAGGCTGACTATTATTGCGCCTCTTATGGAGGCAGGAACAATTTGCTT
TTTGGCGGAGGGACTCAACTGACCGTCTTA AMINO ACID (SEQ ID NO: 60)
QSALTQPPSASGSRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPKLII
FDVNKRPSGVPDRFSGSKSGNTASLTVSGLQPEDEADYYCASYGGRNNLL FGGGTQLTVL
Example 16
Antibody Code: 21-A1
(123) TABLE-US-00016 VH DNA (SEQ ID NO: 61)
CAGGTGCAACTGCAGGAGTCGGGCCCAGGACTGGTGGAGCCTTCGGAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTTCTACT
GGAGCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGCTAT
ATCAATTACAGTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGAGT
CACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCT
CTGTGACCGCCGCAGACACGGCTGTGTATTACTGTGCGAGACAGATATTA
TGGTTCGGGGAGTTAAGGTGGTTCGACCCCTGGGGCCAGGGAACCCTGGT
CACCGTCTCCTCA AMINO ACID (SEQ ID NO: 62)
QVQLQESGPGLVEPSETLSLTCTVSGGSISSFYWSWIRQPPGKGLEWIGY
INYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARQIL
WFGELRWFDPWGQGTLVTVSS VL DNA (SEQ ID NO: 63)
CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGACAGTC
AGTCACCATCTCCTGCACTGGAACCAGCAGTGACATTGGTGGTTATAACT
ATGTCTCCTGGTACCAACTGCGCCCAGGCAAAGCCCCCAAACTCATGATT
TATGACGTCACCAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTC
CAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGG
ATGAGGCTGATTATTACTGCAGCTCATATGCAGGCAGCAACAATGTGGTA
TTCGGCGGAGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 64)
QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQLRPGKAPKLMI
YDVTKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNVV FGGGTKLTVL
Example 17
Antibody Code: 21-H12
(124) TABLE-US-00017 VH DNA (SEQ ID NO: 65)
CAAGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAATCCC
TACGGTTTCAACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACCGT CTCCTCA
AMINO ACID (SEQ ID NO: 66)
QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARNP
YGFNWFDPWGQGTLVTVSS VL DNA (SEQ ID NO: 67)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGAC
GGTAACCATCTCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTATG
TGCAGTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATCTAT
GAGGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCAT
CGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCCGGACTGAAGACTG
AGGACGAGGCTGACTACTACTGTCAGTCTTATGATGGCTTCAATCAGGTG
TTCGGCGGAGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 68)
NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPTTVIY
EDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDGFNQV FGGGTKLTVL
Example 18
Antibody Code: 7-D12
(125) TABLE-US-00018 VH DNA (SEQ ID NO: 69)
CAAATGCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAACCGGT
AGTAGTGGTTATGTACGTTGGAGCAACTGGTTCGACCCCTGGGGCCAGGG
AACCCTGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 70)
QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARTG
SSGYVRWSNWFDPWGQGTLVTVSS VL DNA (SEQ ID NO: 71)
GACATCCAGATGACCCAGTCTCCCTCCACCCTGTCTGCATTTGTAGGAGA
CAGAGTCACCATCACTTGCCGGGCCAGTGAGAGTATTAGTAGGTGGTTGG
CCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCTAATCTCTAAG
ACGTCTAATTTAGAAAGCGGGGTCCCGTCAAGGTTCAGTGGCGCTGGATC
TGGGACAGATTTCACTCTCACCATTAGCAGTCTGCAACCTGAGGATTTTG
CAACTTACTTCTGTCAACAGGGTTCCAAAATGCCTCCGACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAG AMINO ACID (SEQ ID NO: 72)
DIQMTQSPSTLSAFVGDRVTITCRASESISRWLAWYQQKPGKAPKLLISK
TSNLESGVPSRFSGAGSGTDFTLTISSLQPEDFATYFCQQGSKMPPTFGG GTKVEIK
Example 19
Antibody Code: 9-E3
(126) TABLE-US-00019 VH DNA (SEQ ID NO: 73)
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGGCC
TACGGTGGTAACTCCGCTTTTGACTACTGGGGCCAGGGAACCCTGGTCAC
CGTCTCCTCA AMINO ACID (SEQ ID NO: 74)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGA
YGGNSAFDYWGQGTLVTVSS VL DNA (SEQ ID NO: 75)
CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAG
GGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATG
ATGTACACTGGTACCAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATG
TACAGTAATGATCAGCGGCCCTCAGGGGTCACTGAGCGATTCTCTGGCTC

CAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCAGTCTGAAG
ATGAGGGTGATTACTACTGCCAGTCCTATGACAGAAGCCTGAGAGGTTCG
GTCTTCGGCGGAGGGACCAAGCTGACCGTCCTC AMINO ACID (SEQ ID NO: 76)
QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLM
YSNDQRPSGVTERFSGSKSGTSASLAISGLQSEDEGDYYCQSYDRSLRGS VFGGGTKLTVL
Example 20
Antibody Code: 10-A6
(127) TABLE-US-00020 VH DNA (SEQ ID NO: 77)
GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTTTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG
ATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG
AGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGA
GGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATTCC
ATAGCAGCAGCTGGTACTCCGTTCGACTACTGGGGCCAGGGAACCCTGGT
CACCGTCTCCTCA AMINO ACID (SEQ ID NO: 78)
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGW
ISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDS
IAAAGTPFDYWGQGTLVTVSS VL DNA (SEQ ID NO: 79)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGAC
GGTCACCATCTCCTGCACCCGCAGCAGTGGCATCATTGCCAGCAAATATG
TGCACTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATCTAT
GAGGATAACCAAAGACCGTCTGGGGTCCCTGATCGATTCTCTGGCTCCAT
CGACAACTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGCAGACTG
AGGACGAGGCTGACTACTACTGTCAGTCTCATGACGGCATCAATCAGGTT
TTCGGCGGAGGGACCAAGGTCACCGTCCTA AMINO ACID (SEQ ID NO: 80)
NFMLTQPHSVSESPGKTVTISCTRSSGIIASKYVHWYQQRPGSAPTTVIY
EDNQRPSGVPDRFSGSIDNSSNSASLTISGLQTEDEADYYCQSHDGINQV FGGGTKVTVL
Example 21
Antibody Code: 12-A4
(128) TABLE-US-00021 VH DNA (SEQ ID NO: 81)
GAGGTGCAGCTGGTGGAGTCCCGGGGAGGCTTGGTACAGCCGGGGGGGTC
CCTGAGACTCTCCTGTGTAACTTCTGGATTCAGCTTTAACAACTATGCCA
TGAACTGGGTCCGCCAGGCTCCGGGGAAGGGGCTGGAGTGGGTCTCAGCT
GTTAGTGGTAGTGGTGGTACCACATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTTTGTGCAGATGG
ACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGACTT
TTCCCTACGATTTTTGGAGTAGGAGCAATGTTTGACTACTGGGGCCAGGG
AACCCTGGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 82)
EVQLVESRGGLVQPGGSLRLSCVTSGFSFNNYAMNWVRQAPGKGLEWVSA
VSGSGGTTYYADSVKGRFTISRDNSKNTLFVQMDSLRAEDTAVYYCAKGL
FPTIFGVGAMFDYWGQGTLVTVSS VL DNA (SEQ ID NO: 83)
TCTTCTGAGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAG
GGTCACCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATGCTG
TTAACTGGTATCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTAT
GATAATAATCACCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAA
GTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCAGTCTGAGGATG
AGGCTGATTATTATTGTGCAGCATGGGATGACACCATTCCTGGTGTGCTA
TTCGCCGGAGGGACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 84)
SSELTQPPSASGTPGQRVTISCSGSSSNIGSNAVNWYQQLPGTAPKLLIY

DNNHRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDTIPGVL FAGGTKLTVL
Example 22
Antibody Code: 14-G10
(129) TABLE-US-00022 VH DNA (SEQ ID NO: 85)
GAAGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGTGTT
TCTTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGT CTCCTCA
AMINO ACID (SEQ ID NO: 86)
EVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGV
SYYYGMDVWGQGTTVTVSS VL DNA (SEQ ID NO: 87)
CAGGCTGTGCTGACTCAGCCACCCTCGGTGTCCGTGTCCCCAGGACAGAC
AGCCATCATCTCCTGTTCTGGACATAAATTGGGTGATAAGTATGTTTCCT
GGTATCAACAGCAGCCAGGCCAGTCCCCTGTGCTGGTCCTCTTTCAGGAT
ACCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGG
GAACACAGCCACTCTGACCATCAGCGCGACCCAGGCTGCGGATGAGGCTG
ACTATTACTGTCAGGCGGGGGACACCAAGTCTGTGATCTTCGGCGGCGGG
ACCAAGCTGACCGTCCTA AMINO ACID (SEQ ID NO: 88)
QAVLTQPPSVSVSPGQTAIISCSGHKLGDKYVSWYQQQPGQSPVLVLFQD
TKRPSGIPERFSGSNSGNTATLTISATQAADEADYYCQAGDTKSVIFGGG TKLTVL
Example 23
Antibody Code: 22-A6
(130) TABLE-US-00023 VH DNA (SEQ ID NO: 89)
CAGGTTCAGGTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGGCAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGATAC
AGCTATGGTTCAGGACACCTTGACTACTGGGGCCAGGGAACCCTGGTCAC
CGTCTCCTCA AMINO ACID (SEQ ID NO: 90)
QVQVVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGY
SYGSGHLDYWGQGTLVTVSS VL DNA (SEQ ID NO: 91)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGA
CAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAACTATTTAA
ATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTACGAT
GCATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGCAGTGGATC
TGGGACAGATTTCGCTCTCACCATCAGCAGTCTCCAACCTGAAGATTTTG
CAACTTATTACTGTCTACAGCATAATAGTTACCCTCGGACTTTTGGCCAG
GGGACCAAGCTGGAGATCAAA AMINO ACID (SEQ ID NO: 92)
DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKWYDAS
NLETGVPSRFSGSGSGTDFALTISSLQPEDFATYYCLQHNSYPRTFGQGT KLEIK
Example 24
Antibody Code: 35-B1
(131) TABLE-US-00024 VH DNA (SEQ ID NO: 93)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATA
TGCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG
ATGAACCCTAACAGTGGTGACACAGCCTATACACAGAACTTCCAGGGCAG
AGTCACCATGACCAGGAACCCCTCCATAAGCACAGCCTACATGGAGCTGA
GCAACCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCCGG
GGGTTCGCGGAGAAGCCCCTTGGGTACTGGGGCCAGGGAACCCTGGTCAC
CGTCTCCTCA AMINO ACID (SEQ ID NO: 94)
EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW
MNPNSGDTAYTQNFQGRVTMTRNPSISTAYMELSNLRSEDTAVYYCARGR
GFAEKPLGYWGQGTLVTVSS VL DNA (SEQ ID NO: 95)
GATATTGTGATGACTCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGG
GAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTATTTTATCCAGCTCCA
ATAATAAGAACTATTTAGCTTGGTACCAGCAGAAACCAGGTCAGCCTCCT
AAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCG
GTTCAGCGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCC
TGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACT
CCTCCGACATTCGGCCAAGGGACCAAGGTGGAAATCAAA AMINO ACID (SEQ ID
NO: 96) DIVMTQSPDSLAVSLGGRATINCKSSQSILSSSNNKNYLAWYQQKPGQPP
KLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYST
PPTFGQGTKVEIK
Example 25
Antibody Code: 3-1F4
(132) TABLE-US-00025 DNA (SEQ ID NO: 97)
GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
GGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
ATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGGCAG
AGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGGGCCCCT
CGAGGGCAGTGGCTGGTTCACTACTTTGACTACTGGGGCCAGGGAACCCT
GGTCACCGTCTCCTCA AMINO ACID (SEQ ID NO: 98)
EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG
IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARAP
RGQWLVHYFDYWGQGTLVTVSS VL DNA (SEQ ID NO: 99)
GAAATTGTGTTGACGCAGTCTCCAGCCACCCTCTCTCTGTCTCCAGGGGA
AAGAGCCACCCTCTCCTGCTGGGCCAGTCAGGATGTTAGCAACTACTTAG
CCTGGTACCAACAGAAGCCTGGCCAGGCTCCCAGGCTCCTCATCTATGAT
GCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGCGGCAGTGGGTC
TGGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTG
CAGTGTATTACTGTCAGCAACGTAGCAACTGGCCTCTCACTTTCGGCGGC
GGGACCAAGGTGGAGCTCAAA AMINO ACID (SEQ ID NO: 100)
EIVLTQSPATLSLSPGERATLSCWASQDVSNYLAWYQQKPGQAPRLLIYD
ASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGG GTKVELK
Example 26
Antibody Code: 4-1B3
(133) TABLE-US-00026 VH DNA (SEQ ID NO: 101)
CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTA
TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGG

ATCAGCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG
AGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGA
GGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGAGTCC
TACTCGTCCGCAGGTATTGACTACTGGGGCCAGGGAACCCTGGTCACCGT CTCCTCA
AMINO ACID (SEQ ID NO: 102)
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGW
ISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARES
YSSAGIDYWGQGTLVTVSS VL DNA (SEQ ID NO: 103)
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGA
GCCGGCCTCCATCTCCTGCAGGTCTAGTCAGACCCTCCTGCATAGTAATG
GATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAA
CTCCTGATGTATTTGGGCTCTAGCCGGGCCTCCGGGGTCCCTGACAGGTT
CAGTGGCAGTGGATCGGGCACAGATTTCACACTGAAAATCAGCAGAGTGG
AGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAACTCTACAAACTCCT
CCGGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA AMINO ACID (SEQ ID
NO: 104) DIVMTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQ
LLMYLGSSRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQTP
PAFGGGTKVEIK
Example 27
Antibody Code: 21-G1
(134) TABLE-US-00027 VH DNA (SEQ ID NO: 105)
CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGACGATTTCCTGCGAGGCGTCTGGATACAACTTCATCAGCTACTATA
TACACTGGGTGCGACAGGCCCCTGGACAAGGCCTTGAGTGGATGGGATTC
GTCGTCCCTAGTGGTGGTGCCGCAGGCTACACACAGAAGTTCCAGGGCAG
ACTCACCGTGACCAGGGACACGTCCACGAGCACAGTCTACATGGACCTGA
ACAGCCTGACATCTGACGACACGGCCGTGTATTACTGTGTGCGAGAAATG
AGTGGTGGCTGGTTTGATTTCTGGGGCCAGGGAACCCTGGTCACCGTCTC CTCG
AMINO ACID (SEQ ID NO: 106)
QVQLVQSGAEVKKPGASVTISCEASGYNFISYYIHWVRQAPGQGLEWMGF
VVPSGGAAGYTQKFQGRLTVTRDTSTSTVYMDLNSLTSDDTAVYYCVREM
SGGWFDFWGQGTLVTVSS VL DNA (SEQ ID NO: 107)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGA
CAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAA
ATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCT
GCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATC
TGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTG
CAACTTACTACTGTCAACAGAGTTACAGTACCCCGATCACCTTCGGCCAA
GGGACACGACTGGAGATTAAA AMINO ACID (SEQ ID NO: 108)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA
ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQ GTRLEIK
(135) It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.
(136) Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by

reference in their entireties to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

Claims

1. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain having respective PD-L1-specific sequences, wherein the respective PD-L1-specific sequences consist of a sequence pairing selected from the group consisting of: (a) SEQ ID NO: 18 and SEQ ID NO: 20; (b) SEQ ID NO: 42 and SEQ ID NO: 44; and (c) SEQ ID NO: 34 and SEQ ID NO: 36.
2. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein: (a) the heavy chain variable domain comprises a sequence that is SEQ ID NO: 18 and the light chain variable domain comprises a sequence that is SEQ ID NO: 20; or (b) the heavy chain variable domain comprises a sequence that is SEQ ID NO: 42 and the light chain variable domain comprises a sequence that is SEQ ID NO: 44.
3. The antigen-binding polypeptide of claim 1 wherein the polypeptide is a fully human antibody.
4. The antigen-binding polypeptide of claim 3, wherein the polypeptide further comprises a human constant region, and wherein the human constant region has ADCC and/or CDC activities.
5. An antibody that binds to a human PD-L1 epitope, comprising a pair of the heavy chain variable domain and the light chain variable domain of claim 1.
6. A pharmaceutical composition comprising the antigen-binding polypeptide of claim 1, and a pharmaceutically acceptable excipient, carrier or diluent.
7. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises a sequence that is SEQ ID NO: 34 and the light chain variable domain comprises a sequence that is SEQ ID NO: 36.
8. A nucleic acid molecule that encodes the antigen-binding polypeptide of claim 1, wherein the nucleic acid molecule is a DNA molecule or RNA molecule.
9. The nucleic acid molecule of claim 8, wherein the nucleic acid molecule consists essentially of a sequence pairing selected from the group consisting of: (a) SEQ ID NO: 17 and SEQ ID NO: 19; (b) SEQ ID NO: 33 and SEQ ID NO: 35; and (c) SEQ ID NO: 41 and SEQ ID NO: 43.
10. A mammalian expression system that produces the polypeptide of claim 1.
11. A method of treating a human subject in need thereof for a cancer therapeutically, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or diluent, and an antigen-binding polypeptide that binds to a human PD-L1 epitope, wherein the polypeptide comprises a heavy chain variable domain and a light chain variable domain, and wherein the respective sequences thereof consist essentially of a sequence pairing selected from the group consisting of: (a) SEQ ID NO: 18 and SEQ ID NO: 20; (b) SEQ ID NO: 42 and SEQ ID NO: 44; and (c) SEQ ID NO: 34 and SEQ ID NO: 36.
12. The method of claim 11, further comprising administering in combination with a therapy selected from the group consisting of: (a) antibodies targeting other immunosuppressive pathways; (b) chemotherapy or radiation therapy; (c) other mechanisms of blocking immunosuppressive pathways; and (d) other immunotherapy agents.
13. The method of claim 11, wherein said cancer is selected from the group consisting of: ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck

cancer, pancreatic cancer, and combinations thereof.

14. The method of claim 13, wherein said cancer has at least a fraction of the tumor cells expressing detectable amount of PD-L1.