HUMAN ANTIBODIES TO PD-L1

FIELD OF THE INVENTION

[001] The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to the immunomodulatory receptor ligand programmed death-ligand 1 (PD-L1), and therapeutic and diagnostic methods of using those antibodies.

STATEMENT OF RELATED ART

[002] Programmed death-ligand 1 (PD-L1) (also called B7-H1 or CD274) is a 290 amino acid protein receptor ligand expressed widely on both lymphoid and non-lymphoid tissues such as CD4 and CD8 T-cells, macrophage lineage cells, peripheral tissues as well as on tumor cells, and virally-infected cells (Dong et al 1999, Nature Med.). PD-L1 binds to receptors PD-1 and B7-1 which belong to the CD28/CTLA-4 (cytotoxic T lymphocyte antigen)/ ICOS (inducible co-stimulator) family of T-cell co-inhibitory receptors (Chen et al 2013, Nature Rev. Immunol. 13: 227-242) and attenuates the immune response by inhibiting T-cell activation. PD-L1 binding to PD-1 or B7-1 results in decreased T-cell proliferation and cytokine secretion, compromising humoral and cellular immune responses in diseases such as cancer, and viral infection.

[003] The expression of PD-L1 on tumor cells and virally-infected cells is exploited by tumors and chronic viral infections to evade immune response. PD-L1 is expressed on a wide variety of tumors and studies on animal models have shown that PD-L1 on tumors inhibits T-cell activation and lysis of tumor cells and may lead to increased death of tumor-specific T-cells. In chronic viral infections, PD-L1 expressed on virally-infected cells binds to PD-1 on virus-specific T-cells and these T-cells become "exhausted" with loss of effector functions and proliferative capacity (Freeman 2008, PNAS 105: 10275-10276). The PD-1: PD-L1 system also plays an important role in induced T-regulatory (Treg) cell development and in sustaining Treg function (Francisco et al 2010, Immunol. Rev. 236: 219-242).

[004] Since PD-L1 plays an important role in tumor immunity and infectious immunity, it is an ideal target for immunotherapy. Blocking PD-L1 with antagonists, including monoclonal antibodies, has been studied in treatments of cancer and chronic viral infections (Ribas 2012, NEJM 366: 2517-2519; Freeman 2008, PNAS 105: 10275-10276; Sheridan 2012, Nature Biotechnology 30: 729-730).

[005] Monoclonal antibodies to PD-L1 are known in the art and have been described, for example, in US Patent/Publication Nos. 7943742, 8383796, 8217149, 20090055944, 20120003056, 20130034559, 20130045200, 20130045201, 20130045202, and in WO2007005874, WO2011066389, WO2010077634, EP1907424, and EP1899379.

BRIEF SUMMARY

[006] The present disclosure provides antibodies and antigen-binding fragments thereof that bind PD-L1. The antibodies of the present disclosure are useful, *inter alia*, for targeting cells expressing PD-L1 such as cancer cells or virally-infected cells, and for modulating PD-L1 activity. In certain embodiments, the antibodies of the disclosure are useful for inhibiting or neutralizing PD-L1 activity and for stimulating T cell activation, *e.g.*, under circumstances where T cell-mediated killing is beneficial or desirable. The anti-PD-L1 antibodies of the disclosure, or antigen-binding portions thereof, may be included as part of a multi-specific antigen-binding molecule, for example, to modulate the immune responseand/or to target the antibodies to a specific cell type, such as a tumor cell, or a virally infected cell. The antibodies are useful in treating a disease or disorder such as cancer and viral infection.

[006a] In a first aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for enhancing an immune response in a subject.

[006b] In a second aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for enhancing T cell activation in a subject.

[006c] In a third aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for inhibiting a T-regulatory (Treg) cell in a subject.

[006d] In a fourth aspect, there is provided use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID

NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for inhibiting the growth of a tumor or tumor cell in a subject.

[007] The antibodies of the disclosure can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.*, to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933). In certain embodiments, the antibodies may be bispecific.

[008] In an embodiment, the present disclosure provides isolated monoclonal antibodies or antigen-binding fragments thereof that bind specifically to PD-L1. Exemplary anti-PD-L1 antibodies of the present disclosure are listed in Tables 1 and 2 herein. Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-PD-L1 antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-PD-L1 antibodies.

[009] The present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[010] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[011] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain embodiments, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid

sequence pair contained within any of the exemplary anti-PD-L1 antibodies listed in Table 1. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/170, 186/194, 202/210, 218/226, 234/242, 250/258, 266/274, 282/274, 290/274, 298/274, 306/274, 314/274, 322/274, 330/274, and 338/274. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from one of SEQ ID NOs: 82/90 (*e.g.*, H2M8314N), 162/170 (*e.g.*, H2M8718N), 306/274 (*e.g.*, H1H9364P2), and 314/274 (*e.g.*, H1H9373P2). In certain other embodiments, the HCVR/LCVR amino acid sequence pair is selected from one of SEQ ID NOs: 98/106 (*e.g.*, H2M8316N), 146/154 (*e.g.*, H2M8323N), 290/274 (*e.g.*, H1H9351P2), and 330/274 (*e.g.*, H1H9387P2).

[012] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[013] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[014] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[015] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[016] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[017] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[018] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino

acid sequences listed in Table 1. According to certain embodiments, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-PD-L1 antibodies listed in Table 1. In certain embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 88/96 (*e.g.*, H2M8314N), 168/176 (*e.g.*, H2M8718N), 312/280 (*e.g.*, H1H9364P2), and 320/280 (*e.g.*, H1H9373P2). In certain other embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 104/112 (*e.g.*, H2M8316N), 152/160 (*e.g.*, H2M8323N), 296/280 (*e.g.*, H1H9351P2), and 336/280 (*e.g.*, H1H9387P2).

[019] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-PD-L1 antibodies listed in Table 1. In certain embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 84-86-88-92-94-96 (*e.g.*, H2M8314N); 164-166-168-172-174-176 (*e.g.*, H2M8718N); 308-310-312-276-278-280 (*e.g.*, H1H9364P2); and 316-318-320-276-278-280 (*e.g.*, H1H9373P2). In certain other embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 100-102-104-108-110-112 (*e.g.*, H2M8316N); 148-150-152-156-158-160 (*e.g.*, H2M8323N); 292-294-296-276-278-280 (*e.g.*, H1H9351P2); and 332-334-336-276-278-280 (*e.g.*, H1H9387P2).

[020] In a related embodiment, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-PD-L1 antibodies listed in Table 1. For example, the present disclosure includes antibodies, or antigen-binding fragments thereof, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 82/90 (*e.g.*, H2M8314N), 98/106 (*e.g.*, H2M8316N), 146/154 (*e.g.*, H2M8323N), 162/170 (*e.g.*, H2M8718N), 290/274 (*e.g.*, H1H9351P2), 306/274 (*e.g.*, H1H9364P2), 314/274 (*e.g.*, H1H9373P2) and 330/274 (*e.g.*, H1H9387P2). Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md.

(1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[021] The present disclosure includes anti-PD-L1 antibodies having a modified glycosylation pattern. In some embodiments, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[022] The present disclosure also provides for antibodies and antigen-binding fragments thereof that compete for specific binding to PD-L1 with an antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[023] The present disclosure also provides isolated antibodies and antigen-binding fragments thereof that block PD-L1 binding to PD-1 or to B7-1. In some embodiments, the antibody or antigen-binding fragment thereof that blocks PD-L1 binding to PD-1 or to B7-1 may bind to the same epitope on PD-L1 as PD-1/B7-1 or may bind to a different epitope on PD-L1 as PD-1/B7-1. In certain embodiments, the antibodies of the disclosure that block PD-L1 binding to PD-1 or to B7-1 comprise the CDRs of an HCVR having an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1; and the CDRs of a LCVR having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.

[024] In alternate embodiments, the present disclosure provides antibodies and antigen-binding fragments thereof that do not block PD-L1 binding to PD-1 or to B7-1. In certain embodiments, the present disclosure provides isolated antibodies or antigen-binding fragments thereof that bind PD-L1, wherein the antibodies or antigen-binding fragments thereof enhance PD-L1 binding to PD-1 or to B7-1. In some embodiments, the isolated antibodies or antigen-binding fragments thereof that enhance PD-L1 binding to PD-1/B7-1 comprise the CDRs of a HCVR, wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 66, 114, 130, 202, 218, 266, 282, 298, 322 and 338; and the CDRs of a LCVR, wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 74, 122, 138, 210, 226, and 274. In some embodiments, the isolated antibodies or antigen-binding fragments thereof comprise an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26 (*e.g.*, H2M8307N), 66/74 (*e.g.*, H2M8312N), 114/122 (*e.g.*, H2M8317N), 130/138 (*e.g.*, H2M8321N), 202/210 (*e.g.*, H1H9323P), 218/226 (*e.g.*, H1H9327P), 266/274 (*e.g.*, H1H9344P2), 282/274 (*e.g.*, H1H9345P2), 298/274 (*e.g.*, H1H9354P2), 322/274 (*e.g.*, H1H9382P2), and 338/274 (*e.g.*, H1H9396P2).

[025] The present disclosure also provides antibodies and antigen-binding fragments thereof that

bind specifically to PD-L1 from human or other species. In certain embodiments, the antibodies may bind to human PD-L1 and/or to cynomolgus PD-L1.

[026] The present disclosure also provides antibodies and antigen-binding fragments thereof that cross-compete for binding to PD-L1 with a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[027] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment that has one or more of the following characteristics: (a) blocks the binding of PD-L1 to PD-1 or to B7-1; (b) binds specifically to human PD-L1 and/or cynomolgus PD-L1; (c) inhibits T-cell proliferation in a mixed lymphocyte reaction (MLR) assay; and (d) increases IL-2 and/or interferon-gamma secretion in a MLR assay.

[028] In some embodiments, the antibody or antigen binding fragment thereof may bind specifically to PD-L1 in an agonist manner, i.e., it may enhance or stimulate PD-L1 binding and/or activity; in other embodiments, the antibody may bind specifically to PD-L1 in an antagonist manner, i.e., it may block PD-L1 from binding to its receptor.

[029] In certain embodiments, the antibodies or antigen-binding fragments of the present disclosure are bispecific comprising a first binding specificity to PD-L1 and a second binding specificity for a second target epitope. The second target epitope may be another epitope on PD-L1 or on a different protein such as a T-cell co-inhibitor. In certain embodiments, the target epitope may be on a different cell including *e.g.*, a different T-cell, a B-cell, a tumor cell, an autoimmune tissue cell or a virally infected cell.

[030] In another embodiment, the present disclosure provides nucleic acid molecules encoding anti-PD-L1 antibodies or portions thereof. For example, the present disclosure provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[031] The present disclosure also provides nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[032] The present disclosure also provides nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences

listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[032a] In a fifth aspect, there is provided an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR and/or a LCVR of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90.

[033] The present disclosure also provides nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[034] The present disclosure also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[035] The present disclosure also provides nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[036] The present disclosure also provides nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[037] The present disclosure also provides nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[038] The present disclosure also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-PD-L1 antibodies listed in Table 1.

[039] The present disclosure also provides nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-PD-L1 antibodies listed in Table 1.

[040] The present disclosure also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino

acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain embodiments according to the disclosure, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-PD-L1 antibody listed in Table 1.

[041] In a related embodiment, the present disclosure provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-PD-L1 antibody. For example, the present disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also included within the scope of the present disclosure are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[041a] In a sixth aspect, there is provided a vector comprising the polynucleotide sequence of the fifth aspect.

[041b] In a seventh aspect, there is provided a host cell expressing the vector of the sixth aspect.

[041c] In an eighth aspect, there is provided a method of producing an anti-PD-L1 antibody or antigen-binding fragment thereof, comprising growing the host cell of the seventh aspect under conditions permitting production of the antibody or antigen-binding fragment thereof, and recovering the antibody or antigen-binding fragment thereof so produced.

[042] In a further embodiment, the present disclosure provides multi-specific antigen-binding molecules and antigen-binding fragments thereof comprising a first antigen-binding specificity that binds specifically to PD-L1 and a second antigen-binding specificity that binds specifically to an antigen selected from the group consisting of PD-L1, a tumor cell-specific antigen, an infected-cell-specific antigen, and a T-cell co-inhibitor. In certain embodiments, the first antigen-binding specificity may comprise three CDRs derived from a HCVR with an amino acid sequence selected from the HCVR sequences in Table 1 and three CDRs derived from a LCVR with an amino acid sequence selected from the LCVR sequences in Table 1. In one embodiment, the first antigen-binding specificity may comprise an extracellular

domain of PD-1 or of B7-1, or a fragment thereof. The second antigen-binding specificity may target an antigen on the same cell as PD-L1 or on a different cell of the same tissue type or of a different tissue type. For example, the multi-specific antigen-binding molecule may bind to a T-cell wherein the first antigen-binding specificity may bind specifically to PD-L1 and the second antigen-binding specificity may bind to a T-cell co-inhibitor on the T-cell. Alternatively, in another embodiment, the first antigen-binding specificity binds specifically to PD-L1 on a T-cell and the second antigen-binding specificity is targeted to an antigen/receptor on a B-cell or a macrophage or antigen-presenting cell. In certain embodiments, the second antigen-binding specificity is directed to an antigen on a tumor cell, or on a cell infected with a virus. In one embodiment, the first antigen-binding specificity

comprises an extracellular domain of PD-1 and the second antigen-binding specificity binds to a different epitope on PD-L1. In certain embodiments, the first antigen-binding specificity binds to PD-L1 with a lower affinity, for example, with a K_D more than 10^{-8} M, more than 10^{-7} M, more than 10^{-6} M, or more than 10^{-5} M.

[043] In yet another embodiment, the disclosure provides a pharmaceutical composition comprising a recombinant human antibody or antigen-binding fragment thereof which specifically binds PD-L1 and a pharmaceutically acceptable carrier. In a related embodiment, the disclosure features a composition which is a combination of an anti-PD-L1 antibody and a second therapeutic agent. In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-PD-L1 antibody. Exemplary agents that may be advantageously combined with an anti-PD-L1 antibody include, without limitation, other agents that bind and/or modulate PD-L1 signaling (including other antibodies or antigen-binding fragments thereof, etc.) and/or agents which do not directly bind PD-L1 but nonetheless modulate immune cell activation. Additional combination therapies and co-formulations involving the anti-PD-L1 antibodies and multi-specific antigen-binding molecules of the present disclosure are disclosed elsewhere herein.

[044] In a further embodiment, the disclosure provides methods to modulate the immune response in a subject, the method comprising administering a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof of the disclosure to the subject in need thereof. In certain embodiments, the disclosure provides methods to enhance the immune response in a subject, the methods comprising administering to the subject an effective amount of an antibody or fragment thereof of the disclosure that binds PD-L1 and blocks PD-L1 binding to PD-1 or to B7-1. In one embodiment, the disclosure provides a method to stimulate or enhance T-cell activation in a subject, the method comprising administering a blocking antibody or antigen-binding fragment thereof of the disclosure to the subject in need thereof. In one embodiment, the disclosure provides methods to inhibit a T-regulatory (Treg) cell in a subject, the methods comprising administering a blocking antibody or antigen-binding fragment thereof of the disclosure to the subject in need thereof. In certain embodiments, the subject in need thereof may suffer from a disease or disorder such as cancer or viral infection. In alternate embodiments, the present disclosure provides methods to inhibit T-cell activation, the methods comprising administering an activating antibody or antigen-binding fragment thereof of the disclosure to a subject in need thereof. In certain further embodiments, the subject in need thereof may suffer from an autoimmune disease.

[045] In a further embodiment, the disclosure provides therapeutic methods for treating a disease or disorder, for example, cancer or viral infection, in a subject using an anti-PD-L1 antibody or antigen-binding portion of an antibody of the disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or fragment of an antibody of the disclosure to the subject in need

thereof. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by stimulation or inhibition of PD-L1 binding or activity. In certain embodiments, the antibody or antigen-binding fragment thereof the disclosure is administered in combination with a second therapeutic agent to the subject in need thereof. The second therapeutic agent may be selected from the group consisting of an antibody to a T-cell co-inhibitor, an antibody to a tumor cell antigen, an antibody to a T-cell receptor, an antibody to a Fc receptor, an antibody to an epitope on a virally infected cell, an antibody to PD-1, a cytotoxic agent, an anti-cancer drug, an anti-viral drug, an anti-inflammatory drug (*e.g.*, corticosteroids), a VEGF antagonist, and any other drug or therapy known in the art. In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with an antibody or antigen-binding fragment thereof of the disclosure, if such side effect(s) should occur.

[046] In certain embodiments, the present disclosure provides methods for suppressing tumor growth. In certain embodiments, the present disclosure provides methods to enhance survival of cancer patients. Examples of cancer include, but are not limited to, primary and/or recurrent cancer, including brain cancer (*e.g.*, glioblastoma multiforme), lung cancer (e.g., non-small cell lung cancer), squamous cell carcinoma of head and neck, renal cell carcinoma, melanoma, multiple myeloma, prostate cancer, and colon cancer. The methods comprise administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-PD-L1 antibody of the present disclosure in combination with a second therapeutic agent selected from the group consisting of a vascular endothelial growth factor (VEGF) antagonist (e.g., aflibercept, bevacizumab), an angiopoietin-2 (Ang2) inhibitor (*e.g.*, an anti-Ang2 antibody such as nesvacumab), a lymphocyte activation gene 3 (LAG-3) inhibitor, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor (*e.g.*, ipilimumab), a CCR4 inhibitor (*e.g.*, mogamulizumab), a chemotherapeutic agent, and radiation therapy. Additional examples of additional therapies/therapeutic agents that can be used in combination with an anti-PD-L1 antibody of the disclosure for use in treating cancer are described elsewhere herein.

[047] The antibody or fragment thereof may be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly, or intracranially. The antibody or fragment thereof may be administered at a dose of about 0.1 mg/kg of body weight to about 100 mg/kg of body weight of the subject.

[048] The present disclosure also includes use of an anti-PD-L1 antibody or antigen-binding fragment thereof of the disclosure in the manufacture of a medicament for the treatment of a disease or disorder (*e.g.*, cancer, and chronic viral infection) that would benefit from the blockade or enhancement of PD-L1 binding and/or signaling.

[049] Other embodiments will become apparent from a review of the ensuing detailed description.

What is claimed is:

1. Use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for enhancing an immune response in a subject.

2. Use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for enhancing T cell activation in a subject.

3. Use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for inhibiting a T-regulatory (Treg) cell in a subject.

4. The use according to any one of claims 1-3, wherein the subject has a viral infection.

5. The use according to claim 4, wherein the viral infection comprises HIV, HBV, HCV, HPV, LCMV, SIV, or a combination thereof.

6. The use according to any one of claims 1-4, wherein the subject has a tumor.

7. Use of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein or a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof and a carrier, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR)

having an amino acid sequence of SEQ ID NO: 90, in the manufacture of a medicament for inhibiting the growth of a tumor or tumor cell in a subject.

8. The use according to claim 6 or 7, wherein the tumor comprises renal cell carcinoma, brain cancer, squamous cell carcinoma of head and neck, gastric cancer, kidney cancer, breast cancer, ovarian cancer, prostate cancer, non-small-cell lung cancer, colorectal cancer, multiple myeloma or melanoma.

9. The use according to any one of claims 1-8, wherein the antibody or antigen-binding fragment thereof or the pharmaceutical composition is to be administered to the subject in combination with a second therapeutic agent or therapy.

10. The use of claim 9, wherein the second therapeutic agent or therapy comprises a NSAID, a corticosteroid, an antibody to a T-cell co-inhibitor, an antibody to a tumor specific antigen, an antibody to PD-1, an IDO inhibitor, an Ang2 inhibitor, a cancer vaccine, an EGFR inhibitor, a TGFβ inhibitor, a dietary supplement such as an antioxidant, a VEGF antagonist such as an anti-VEGF antibody, a small molecule kinase inhibitor of VEGF receptor or a VEGF-inhibiting fusion protein, surgery, radiation, a chemotherapeutic agent, a cytotoxic agent, or a combination thereof.

11. The use according to any one of claims 1-10, wherein the antibody or antigen-binding fragment thereof or the pharmaceutical composition is to be administered to the subject subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially.

12. The use according to any one of claims 1-11, wherein the antibody or antigen-binding fragment or the pharmaceutical composition is to be administered to the subject at a dose of about 0.1 mg/kg of body weight to about 60 mg/kg of body weight of the subject.

13. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR and/or a LCVR of an isolated antibody or antigen-binding fragment thereof that binds to human programmed death-ligand 1 (PD-L1) protein, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 82, and a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 90.

14. A vector comprising the polynucleotide sequence of claim 13.

15. A host cell expressing the vector of claim 14.

16. A method of producing an anti-PD-L1 antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 15 under conditions permitting production of the antibody or antigen-binding fragment thereof, and recovering the antibody or antigen-binding fragment thereof so produced.

17. The method of claim 16, wherein the host cell is a CHO cell.

18. The method of claim 16 or 17, further comprising formulating the antibody or antigen-binding fragment thereof as a pharmaceutical composition comprising an acceptable carrier.