[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 having a tumor or a chronic viral infection.

[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 having a tumor or a chronic viral infection.

[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 having a tumor or a chronic viral infection.

~~**[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

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

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 having a tumor or a chronic viral infection.

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 having a tumor or a chronic viral infection.

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 having a tumor or a chronic viral infection.

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

5. The use according to claim 4, wherein the chronic 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~~and 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.