SUMMARY

[0006] The present disclosure provides proteins, such as antibodies, that include an antigen binding portion that specifically binds to Programmed Death 1 Ligand 1 (PD-L1). Also provided are nucleic acids encoding the proteins, and cells (*e.g.*, genetically modified cytotoxic lymphocytes) that include such nucleic acids. In some examples, a subject method includes reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell. For example, the methods and compositions provided can be used in the treatment of viral infection and cancer, such as the treatment of solid tumors via ACT or via administration of a subject protein that specifically binds to PD-L1.

[0007] The compositions and methods of the present disclosure can allow genetically modified cytotoxic lymphocytes, *e.g.*, activated T-cells, TILs, and NK cells, to be propagated and infused as a cell therapy which allows for the secretion of a PD-L1 binding protein (*e.g.*, an scFV, a maxibody) in the genetically modified cytotoxic lymphocytes to be administered to the subject. In this way, the cytotoxic lymphocytes of the present disclosure are able to "relieve" themselves of the inhibitory effect of the PD-1 checkpoint, providing for an improved anti-cancer effect in the subject to which the genetically modified cytotoxic lymphocytes are administered. Specific binding proteins of the disclosure (*e.g.*, anti-PD-L1 antibodies) can also be administered to an individual directly, *e.g.*, intravenous (i.v.) or intratumoral injection.

[0008] In one example, there is provided a protein that specifically binds to PD-L1 and comprises an antigen binding portion that comprises: (a) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or (b) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs: 10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16, with the exception that each of the three CDR amino acid sequences of the first and/or second polypeptide comprises two or less conservative amino acid substitutions relative to the specified SEQ ID number.

[0008a] In one aspect, the present disclosure refers to a protein that specifically binds to PD-L1 and comprises an antigen binding portion that comprises:

(a) a first polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(a) (ii) a first polypeptide comprising three CDR amino acid sequences, each CDR comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(b) (i) a first polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs: 10-12, and a second polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16; or

(b) (ii) a first polypeptide comprising three CDR amino acid sequences, each comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

[0009] In some examples, the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8.

[0010] In some examples, the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5.

[0011] In some examples, the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

[0012] In some examples, the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13.

[0013] In some examples, the first polypeptide is a light chain, and the second polypeptide is a heavy chain.

[0014] In some examples, the protein that specifically binds to PD-L1 is a single-chain antibody (scFv) and the first and second polypeptides are fused directly or via a linker to one another. In some examples, the scFv comprises the amino acid sequence set forth in SEQ ID NO:17 or SEQ ID NO:19.

[0015] In some examples, the protein that specifically binds to PD-L1 is a maxibody comprising an immunoglobulin Fc domain fused directly or via a linker to the antigen binding portion. In some examples, the immunoglobulin Fc domain is an IgG1 Fc domain. In some examples, the protein comprises the amino acid sequence set forth in SEQ ID NO:18 or SEQ ID NO:20. In some examples, the immunoglobulin Fc domain is an IgG4 Fc domain.

[0016] In some examples, the protein that specifically binds to PD-L1 is a humanized antibody.

[0017] In another example, there is also provided a nucleic acid comprising a nucleotide sequence encoding the protein that specifically binds to PD-L1, as discussed herein. In some examples, the nucleic acid comprises a promoter that is operably linked to the nucleotide sequence encoding the protein. In some examples, the promoter is a constitutive promoter. In some examples, the promoter is an inducible promoter.

[0017a] In another aspect, the present disclosure refers to a nucleic acid comprising a nucleotide sequence encoding the protein as disclosed herein.

[0018] In another example, there is also provided a cell comprising the nucleic acid that encodes the protein that specifically binds to PD-L1. In some examples, the nucleic acid is integrated into the cell's genome. In some examples, the cell is a cytotoxic lymphocyte genetically modified to express and secrete the protein. In some examples, the cytotoxic lymphocyte is a T-cell. In some examples, the T-cell is a CD8+ T-cell. In some examples, the T-cell is a CD4+ T-helper cell. In some examples, the T-cell is derived from peripheral blood. In some examples, the cytotoxic lymphocyte is a natural killer (NK) cell. In some examples, the NK is derived from peripheral blood.

[0018a] In another aspect, the present disclosure refers to a cell comprising the nucleic acid as disclosed herein.

[0019] In some examples, the cytotoxic lymphocyte is a tumor infiltrating lymphocyte (TIL) derived from a tumor from a subject.

[0020] In some examples, the TIL comprises a receptor specific for an antigen from the tumor.

[0021] In some examples, the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell. In some examples, the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

[0022] In some examples, the cytotoxic lymphocyte comprises a T-cell receptor specific for a tumor associated antigen.

[0023] The present disclosure also provides a method comprising: genetically modifying a cytotoxic lymphocyte isolated from a tumor of a subject by introducing into the cytotoxic lymphocyte the nucleic acid encoding a protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1; expanding the genetically modified cytotoxic lymphocyte to generate a population of genetically modified cytotoxic lymphocytes; and administering the population of genetically modified cytotoxic lymphocytes to the subject to treat the tumor.

[0023a] In another aspect, the present disclosure refers to use of a population of genetically modified cytotoxic lymphocytes in the manufacture of a medicament for treating a tumor in a subject, wherein the population of genetically modified cytotoxic lymphocytes is generated by genetically modifying a cytotoxic lymphocyte that has been isolated from the tumor of the subject by introducing into the cytotoxic lymphocyte a nucleic acid encoding a protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1; and expanding the genetically modified cytotoxic lymphocyte to generate the population of genetically modified cytotoxic lymphocytes.

[0024] In some examples, the genetically modified cytotoxic lymphocyte constitutively expresses the protein that specifically binds to PD-L1. In some examples, the genetically modified cytotoxic lymphocyte inducibly expresses the protein that specifically binds to PD-L1. In some examples, the nucleic acid integrates into the cytotoxic lymphocyte's genome.

[0025] In some examples, the cytotoxic lymphocyte is a T-cell. In some examples, the T-cell is a CD8+ T-cell. In some examples, the T-cell is a CD4+ T-helper cell. In some examples, the cytotoxic lymphocyte is a natural killer (NK) cell.

[0026] In some examples, the genetically modified cytotoxic lymphocyte comprises a receptor specific for an antigen from the tumor.

[0027] In some examples, the method comprises isolating the cytotoxic lymphocyte from the subject prior to genetically modifying.

[0028] In some examples of the method, the protein that specifically binds to PD-L1 and comprises an antigen binding portion that comprises: (a) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or (b) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs: 10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16, with the exception that each of the three CDR amino acid sequences of the first and/or second

polypeptide comprises two or less conservative amino acid substitutions relative to the specified SEQ ID number.

[0029] In some examples of the method, the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8.

[0030] In some examples of the method, the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5.

[0031] In some examples of the method, the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

[0032] In some examples of the method, the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13.

[0033] In some examples of the method, the first polypeptide is a light chain, and the second polypeptide is a heavy chain.

[0034] In some examples of the method, the protein is a single-chain antibody (scFv) and the first and second polypeptides are fused directly or via a linker to one another.

[0035] In some examples of the method, the scFv comprises the amino acid sequence set forth in SEQ ID NO:17 or SEQ ID NO:19.

[0036] In some examples of the method, the protein is a maxibody comprising an immunoglobulin Fc domain fused directly or via a linker to the antigen binding portion.

[0037] In some examples of the method, the immunoglobulin Fc domain is an IgG1 Fc domain.

[0038] In some examples of the method, the protein comprises the amino acid sequence set forth in SEQ ID NO:18 or SEQ ID NO:20.

[0039] The present disclosure also provides a method of making a genetically modified cytotoxic lymphocyte, the method comprising: genetically modifying a cytotoxic lymphocyte isolated from a subject having or suspected of having cancer by introducing into the cytotoxic lymphocyte the nucleic acid encoding for the protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1. In some examples, the genetically modified cytotoxic lymphocyte constitutively expresses the protein that specifically binds to PD-L1. In some

examples, the genetically modified cytotoxic lymphocyte inducibly expresses the protein that specifically binds to PD-L1.

[0039a] In another aspect, the present disclosure refers to a method of making a genetically modified cytotoxic lymphocyte, the method comprising: genetically modifying a cytotoxic lymphocyte that has been isolated from a subject having or suspected of having cancer by introducing into the cytotoxic lymphocyte a nucleic acid encoding a protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1.

[0040] In some examples, the method comprises expanding the cytotoxic lymphocyte in vitro to provide an expanded population of genetically modified cytotoxic lymphocytes.

[0041] In some examples, the method comprises isolating the cytotoxic lymphocyte from the subject prior to the genetically modifying.

[0042] In some examples, the isolating comprises isolating the cytotoxic lymphocyte from a tumor of the subject. In some examples, the isolating comprises isolating the cytotoxic lymphocyte from peripheral blood of the subject.

[0043] In some examples of the method, the cytotoxic lymphocyte is a T-cell. In some examples of the method, the T-cell is a CD8+ T-cell. In some examples of the method, the T-cell is a CD4+ T-helper cell. In some examples of the method, the cytotoxic lymphocyte is a natural killer (NK) cell.

[0044] In some examples of the method, the nucleic acid integrates into the cytotoxic lymphocyte's genome.

[0045] In some examples of the method, the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell. In some examples of the method, the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

[0046] In some examples of the method, the genetically modified cytotoxic lymphocyte comprises a T-cell receptor specific for an antigen from a tumor of the subject.

[0047] The present disclosure also provides a method of treating an individual who has or is suspected of having cancer, the method comprising: administering the protein that specifically binds to PD-L1 to the individual (*e.g.*, subject or patient, including for example a mammal such as a human).

[0047a] In another aspect, the present disclosure refers to use of the protein that specifically binds to PD-L1 as disclosed herein in the manufacture of a medicament for treating cancer in an individual who has or is suspected of having cancer.

[0048] In some examples of the method, the administering comprises introducing into the subject a nucleic acid encoding the protein that specifically binds to PD-L1.

[0049] In some examples of the method, administering comprises introducing into the subject a genetically modified cytotoxic lymphocyte that expresses and secretes the protein that specifically binds to PD-L1.

[0050] In some examples of the method, the genetically modified cytotoxic lymphocyte constitutively expresses the protein that specifically binds to PD-L1. In some

examples of the method, the genetically modified cytotoxic lymphocyte inducibly expresses the protein that specifically binds to PD-L1. In some examples, the method, comprises inducing expression of the protein that specifically binds to PD-L1.

[0051] In some examples of the method, the cytotoxic lymphocyte is a T-cell. In some examples of the method, the T-cell is a CD8+ T-cell. In some examples of the method, the T-cell is a CD4+ T-helper cell. In some examples of the method, the cytotoxic lymphocyte is a natural killer (NK) cell.

[0052] In some examples of the method, the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell. In some examples of the method, the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

[0053] In some examples of the method, the genetically modified cytotoxic lymphocyte comprises a T-cell receptor specific for an antigen from a tumor of the subject.

[0054] The present disclosure also provides a method of reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell, the method comprising: contacting PD-L1 on the first-cell with the protein that specifically binds to PD-L1.

[0054a] In another aspect, the present disclosure refers to an *in vitro* method of reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell, the method comprising: contacting PD-L1 on the first-cell with the protein as disclosed herein.

[0054b] In another aspect, the present disclosure refers to use of the protein as disclosed herein in the manufacture of a medicament for reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell, wherein the protein as disclosed herein is to be administered to an individual having the first and second cells.

[0055] In some examples of the method, the first and second cells are introduced to an individual, and the contacting comprises administering the protein that specifically binds to PD-L1. In some examples of the method, introducing comprises systemic administration. In some examples of the method, the introducing comprises local administration. In some examples of the method, the local administration comprises intratumoral administration. In some examples of the method, the individual has cancer. In some examples of the method, the individual has a solid tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0056] The invention may be best understood from the following detailed description when read in conjunction with the accompanying drawings. Included in the drawings are the following figures:

[0057] **Figure 1** provides a schematic representation of the lentiviral plasmid used to produce 38A1-Fc, 19H9-Fc and FMC63-Fc. Anti PD-L1 maxibodies are encoded downstream of the U3 promoter from MSCV promoter and upstream of an IRES-eGFP cassette.

CLAIMS

What Is Claimed Is:

1. Use of a population of genetically modified cytotoxic lymphocytes in the manufacture of a medicament for treating a tumor in a subject, wherein the population of genetically modified cytotoxic lymphocytes is generated by genetically modifying a cytotoxic lymphocyte that has been isolated from the tumor of the subject by introducing into the cytotoxic lymphocyte a nucleic acid encoding a protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1; and

expanding the genetically modified cytotoxic lymphocyte to generate the population of genetically modified cytotoxic lymphocytes.

2. The use of claim 1, wherein the genetically modified cytotoxic lymphocyte constitutively expresses the protein that specifically binds to PD-L1.

3. The use of claim 1, wherein the genetically modified cytotoxic lymphocyte inducibly expresses the protein that specifically binds to PD-L1.

4. The use of any one of claims 1-3, wherein the nucleic acid integrates into the cytotoxic lymphocyte's genome.

5. The use of any one of claims 1-4, wherein the cytotoxic lymphocyte is a T-cell.

6. The use of claim 5, wherein the T-cell is a CD8+ T-cell.

7. The use of claim 5, wherein the T-cell is a CD4+ T-helper cell.

8. The use of any one of claims 1-4, wherein the cytotoxic lymphocyte is a natural killer (NK) cell.

9. The use of any one of claims 1-8, wherein the genetically modified cytotoxic lymphocyte comprises a receptor specific for an antigen from the tumor.

10. The use of any one of claims 1-9, wherein the cytotoxic lymphocyte is to be isolated from the subject prior to the genetically modifying.

11. The use of any one of claims 1-10, wherein said protein that specifically binds to PD-L1 and comprises an antigen binding portion that comprises:

(a) (i) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(a) ii) a first polypeptide comprising three CDR amino acid sequences, each CDR comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(b) (i) a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs: 10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16; or

(b) (ii) a first polypeptide comprising three CDR amino acid sequences, each comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

12. The use of claim 11, wherein said wherein the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8.

13. The use of claim 12, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5.

14. The use of claim 11, wherein the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12, and a

second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

15. The use of claim 14, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13.

16. The use of any of claims 11-15, wherein the first polypeptide is a light chain, and the second polypeptide is a heavy chain.

17. The use of any of claims 11-16, wherein the protein is a single-chain antibody (scFv) and the first and second polypeptides are fused directly or via a linker to one another.

18. The use of claim 17, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO:17 or SEQ ID NO:19.

19. The use of any of claims 11-18, wherein the protein is a maxibody comprising an immunoglobulin Fc domain fused directly or via a linker to the antigen binding portion.

20. The use of claim 19, wherein the immunoglobulin Fc domain is an IgG1 Fc domain.

21. The use of claim 20, wherein the protein comprises the amino acid sequence set forth in SEQ ID NO:18 or SEQ ID NO:20.

22. A method of making a genetically modified cytotoxic lymphocyte, the method comprising:

genetically modifying a cytotoxic lymphocyte that has been isolated from a subject having or suspected of having cancer by introducing into the cytotoxic lymphocyte a nucleic acid encoding a protein that specifically binds to PD-L1, wherein the genetically modified cytotoxic lymphocyte expresses and secretes the protein that specifically binds to PD-L1.

23. The method of claim 22, wherein the genetically modified cytotoxic lymphocyte constitutively expresses the protein that specifically binds to PD-L1.

24. The method of claim 22, wherein the genetically modified cytotoxic lymphocyte inducibly expresses the protein that specifically binds to PD-L1.

25. The method of any one of claims 22-24, comprising expanding the cytotoxic lymphocyte *in vitro* to provide an expanded population of genetically modified cytotoxic lymphocytes.

26. The method of any one of claims 22-25, wherein the cytotoxic lymphocyte is to be isolated from the subject prior to the genetically modifying.

27. The method of claim 26, wherein the cytotoxic lymphocyte is to be isolated from a tumor of the subject.

28. The method of any one of claims 26, wherein the cytotoxic lymphocyte is to be isolated from peripheral blood of the subject.

29. The method of any one of claims 22-28, wherein the cytotoxic lymphocyte is a T-cell.

30. The method of claim 29, wherein the T-cell is a CD8+ T-cell.

31. The method of claim 29, wherein the T-cell is a CD4+ T-helper cell.

32. The method of any one of claims 22-28, wherein the cytotoxic lymphocyte is a natural killer (NK) cell.

33. The method of any one of claims 22-32, wherein the nucleic acid integrates into the cytotoxic lymphocyte's genome.

34. The method of any one of claims 29-31, wherein the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell.

35. The method of claim 34, wherein the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

36. The method of claim 34 or claim 35, wherein the genetically modified cytotoxic lymphocyte comprises a T-cell receptor specific for an antigen from a tumor of the subject.

37. A protein that specifically binds to PD-L1 and comprises an antigen binding portion that comprises:

(a) a first polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(a) (ii) a first polypeptide comprising three CDR amino acid sequences, each CDR comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8; or

(b) (i) a first polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs: 10-12, and a second polypeptide comprising 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16; or

(b) (ii) a first polypeptide comprising three CDR amino acid sequences, each comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12 and a second polypeptide comprising three CDR amino acid sequences comprising two or less conservative amino acid substitutions relative to the respective 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

38. The protein of claim 37, wherein the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:2-4, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:6-8.

39. The protein of claim 38, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5.

40. The protein of claim 37, wherein the antigen binding portion comprises a first polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:10-12, and a second polypeptide comprising the 3 CDR amino acid sequences set forth in SEQ ID NOs:14-16.

41. The protein of claim 40, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13.

42. The protein of any of claims 37-41, wherein the first polypeptide is a light chain, and the second polypeptide is a heavy chain.

43. The protein of any of claims 37-42, wherein the protein is a single-chain antibody (scFv) and the first and second polypeptides are fused directly or via a linker to one another.

44. The protein of claim 43, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO:17 or SEQ ID NO:19.

45. The protein of any of claims 37-44, wherein the protein is a maxibody comprising an immunoglobulin Fc domain fused directly or via a linker to the antigen binding portion.

46. The protein of claim 45, wherein the immunoglobulin Fc domain is an IgG1 Fc domain.

47. The protein of claim 46, wherein the protein comprises the amino acid sequence set forth in SEQ ID NO:18 or SEQ ID NO:20.

48. The protein of claim 45, wherein the immunoglobulin Fc domain is an IgG4 Fc domain.

49. The protein of any of claims 37-42, wherein the protein is a humanized antibody.

50. A nucleic acid comprising a nucleotide sequence encoding the protein of any one of claims 37-49.

51. The nucleic acid of claim 50, wherein the nucleic acid comprises a promoter that is operably linked to the nucleotide sequence encoding the protein.

52. The nucleic acid of claim 51, wherein the promoter is a constitutive promoter.

53. The nucleic acid of claim 51, wherein the promoter is an inducible promoter.

54. A cell comprising the nucleic acid of any one of claims 50-53.

55. The cell of claim 54, wherein the nucleic acid is integrated into the cell's genome.

56. The cell of claim 54 or claim 55, wherein the cell is a cytotoxic lymphocyte genetically modified to express and secrete the protein.

57. The cell of claim 56, wherein the cytotoxic lymphocyte is a T-cell.

58. The cell of claim 57, wherein the T-cell is a CD8+ T-cell.

59. The cell of claim 57, wherein the T-cell is a CD4+ T-helper cell.

60. The cell of claim 57, wherein the T-cell is derived from peripheral blood.

61. The cell of claim 56, wherein the cytotoxic lymphocyte is a natural killer (NK) cell.

62. The cell of claim 61, wherein the NK is derived from peripheral blood.

63. The cell of claim 56, wherein the cytotoxic lymphocyte is a tumor infiltrating lymphocyte (TIL) derived from a tumor that has been obtained from a subject.

64. The cell of claim 63, wherein the TIL comprises a receptor specific for an antigen from the tumor.

65. The cell of claim of any of claims 57-60, wherein the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell.

66. The cell of claim 65, wherein the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

67. The cell of claim 65 or claim 66, wherein the cytotoxic lymphocyte comprises a T-cell receptor specific for a tumor associated antigen.

68. Use of the protein that specifically binds to PD-L1 according to any of claims 37-49 in the manufacture of a medicament for treating cancer in an individual who has or is suspected of having cancer.

69. The use of claim 68, wherein a nucleic acid encoding the protein is to be introduced into the individual.

70. The use of claim 68, wherein a genetically modified cytotoxic lymphocyte that expresses and secretes the protein is to be introduced into the individual.

71. The use of claim 70, wherein the genetically modified cytotoxic lymphocyte constitutively expresses the protein.

72. The use of claim 71, wherein the genetically modified cytotoxic lymphocyte inducibly expresses the protein.

73. The use of claim 72, comprising inducing expression of the protein.

74. The use of any one of claims 70-73, wherein the cytotoxic lymphocyte is a T-cell.

75. The use of claim 74, wherein the T-cell is a CD8+ T-cell.

76. The use of claim 74, wherein the T-cell is a CD4+ T-helper cell.

77. The use of any one of claims 70-73, wherein the cytotoxic lymphocyte is a natural killer (NK) cell.

78. The use of any one of claims 74-76, wherein the cytotoxic lymphocyte exhibits an increased level of expression of one or more activation antigens relative to a naïve T-cell.

79. The use of claim 78, wherein the one or more activation antigens are selected from CD25, CD26, CD27, CD28, CD38, CD40L, CD69, CD134, CD137, BTLA, PD-1, HVEM, LIGHT, and HLA-DR.

80. The use of claim 78 or claim 79, wherein the genetically modified cytotoxic lymphocyte comprises a T-cell receptor specific for an antigen from a tumor of the subject.

81. An *in vitro* method of reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell, the method comprising:

contacting PD-L1 on the first-cell with the protein of any one of claims 37-49.

82. Use of the protein of any one of claims 37-49 in the manufacture of a medicament for reducing the interaction between PD-L1 on a first-cell and PD-1 on a second cell, wherein the protein of any of claims 37-49 is to be administered to an individual having the first and second cells.

83. The use of claim 82, wherein the protein is to be administered systemically.

84. The use of claim 82, wherein the protein is to be administered locally.

85. The use of claim 84, wherein the protein is to be administered intratumorally.

86. The use of any of claims 82-85, wherein the individual has cancer.

87. The use of claim 82, wherein the individual has a solid tumor.