

CLAIMS

We claim:

1. A fusion protein comprising: (i) an antigen-binding moiety that binds specifically to human programmed cell death protein 1 (PD-1) and (ii) an interleukin 2 (IL2) moiety;
wherein the antigen-binding moiety comprises an antibody or antigen-binding fragment thereof that binds specifically to PD-1 and comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) and a light chain variable region (LCVR) comprising three light chain CDRs (LCDR1, LCDR2, and LCDR3), wherein the antigen-binding moiety comprises a heavy chain constant region linked to the HCVR, and wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of:
(i) SEQ ID NOs: 43, 45, 47, 12, 14, and 16;
(ii) SEQ ID NOs: 4, 6, 8, 12, 14, and 16; or
(iii) SEQ ID NOs: 24, 26, 28, 32, 14, and 35;
wherein the IL2 moiety comprises: (i) IL2 or a fragment thereof and (ii) IL2 receptor alpha (IL2R α) or a fragment thereof; and
wherein the IL2 or fragment thereof is connected to the C-terminal of the IL2R α or fragment thereof via a first linker, and the IL2 moiety is connected to the C-terminal of the heavy chain constant region via a second linker.
2. The fusion protein of claim 1, wherein the antibody or antigen-binding fragment thereof is a human monoclonal antibody.
3. The fusion protein of claim 1 or 2, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 43, 45, 47, 12, 14, and 16.
4. The fusion protein of claim 1 or 2, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 2 and the LCVR comprises the amino acid sequence of SEQ ID NO: 10.

5. The fusion protein of claim 1 or 2, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 22 and the LCVR comprises the amino acid sequence of SEQ ID NO: 30.
6. The fusion protein of claim 1 or 2, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 41 and the LCVR comprises the amino acid sequence of SEQ ID NO: 10.
7. The fusion protein of any one of claims 1-6, wherein the antigen-binding moiety comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 55 and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 56.
8. The fusion protein of any one of claims 1-7, wherein the antigen-binding moiety comprises a heavy chain/light chain amino acid sequence pair of SEQ ID NOs: 61/62, 57/58, or 59/60.
9. The fusion protein of any one of claims 1-8, wherein the antigen-binding moiety comprises a heavy chain/light chain amino acid sequence pair of SEQ ID NOs: 61/62.
10. The fusion protein of claim 9, wherein the IL2 or fragment thereof is human IL2 (hIL2) or a fragment thereof.
11. The fusion protein of claim 10, wherein the IL2R α or fragment thereof is human IL2R α (hIL2R α) or a fragment thereof.
12. The fusion protein of any one of claims 9-11, wherein the IL2 or fragment thereof comprises the amino acid sequence of SEQ ID NO: 53.
13. The fusion protein of any one of claims 9-11, wherein the IL2R α or fragment thereof comprises the amino acid sequence of SEQ ID NO: 51.
14. The fusion protein of any one of claims 1-13, wherein the first and/or second linker comprises the amino acid sequence of one or more repeats of GGGGS (SEQ ID NO: 67).

15. The fusion protein of any one of claims 1-14, wherein the first linker comprises the amino acid sequence of SEQ ID NO: 52, and the second linker comprises the amino acid sequence of SEQ ID NO: 50.

16. The fusion protein of any one of claims 1-15, wherein the IL2 moiety comprises the amino acid sequence of SEQ ID NO: 54.

17. A fusion protein comprising: (i) a first polypeptide comprising a light chain variable region (LCVR) of an antibody; and (ii) a second polypeptide comprising (a) a heavy chain variable region (HCVR) of the antibody and a heavy chain constant region linked to the HCVR of the antibody; and (b) an IL2 moiety;

wherein the antibody binds specifically to human programmed cell death protein 1 (PD-1) and the HCVR comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) and the LCVR comprises three light chain CDRs (LCDR1, LCDR2, and LCDR3), wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of:

(i) SEQ ID NOs: 43, 45, 47, 12, 14, and 16;

(ii) SEQ ID NOs: 4, 6, 8, 12, 14, and 16; or

(iii) SEQ ID NOs: 24, 26, 28, 32, 14, and 35; and

wherein the IL2 moiety comprises: (i) IL2 or a fragment thereof and (ii) IL2 receptor alpha (IL2R α) or a fragment thereof;

wherein the IL2 or fragment thereof is connected to the C-terminal of the IL2R α or fragment thereof via a first linker, and the IL2 moiety is connected to the C-terminal of the heavy chain constant region via a second linker.

18. The fusion protein of claim 17, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 43, 45, 47, 12, 14, and 16.

19. The fusion protein of claim 17 or 18, wherein the HCVR and the LCVR comprise respective amino acid sequences of (i) SEQ NOs: 41 and 10; (ii) SEQ ID NOs: 2 and 10; or (iii) SEQ ID NOs: 22 and 30.

20. The fusion protein of any one of claims 17-19, wherein the first polypeptide comprises a light chain constant region linked to the LCVR.

21. The fusion protein of claim 20, wherein the light chain constant region comprises the amino acid sequence of SEQ ID NO: 56.
22. The fusion protein of any one of claims 17-21, wherein the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 55.
23. The fusion protein of any one of claims 17-22, wherein:
- (i) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 43, 45, 47, 12, 14, and 16; and the first polypeptide comprises a light chain comprising the amino acid sequence of SEQ ID NO: 62;
 - (ii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 4, 6, 8, 12, 14, and 16; and the first polypeptide comprises a light chain comprising the amino acid sequence of SEQ ID NO: 58; or
 - (iii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 24, 26, 28, 32, 14, and 35; and the first polypeptide comprises a light chain comprising the amino acid sequence of SEQ ID NO: 60.
24. The fusion protein of any one of claims 17-23, wherein:
- (i) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 43, 45, 47, 12, 14, and 16; and the second polypeptide comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 61;
 - (ii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 4, 6, 8, 12, 14, and 16; and the second polypeptide comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 57; or
 - (iii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the respective amino acid sequences of SEQ ID NOs: 24, 26, 28, 32, 14, and 35; and the second polypeptide comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 59.
25. The fusion protein of any one of claims 17-24, wherein the fusion protein comprises:
- (i) a heavy chain comprising the amino acid sequence of SEQ NO: 61 and a light chain comprising the amino acid sequence of SEQ ID NO: 62;
 - (ii) a heavy chain comprising the amino acid sequence of SEQ NO: 57 and a light chain comprising the amino acid sequence of SEQ ID NO: 58; or

(iii) a heavy chain comprising the amino acid sequence of SEQ NO: 59 and a light chain comprising the amino acid sequence of SEQ ID NO: 60.

26. The fusion protein of any one of claims 17-25, comprising a heavy chain/light chain amino acid sequence pair of SEQ ID NOs: 61/62.

27. The fusion protein of any one of claims 17-26, wherein the IL2 or fragment thereof is human IL2 (hIL2) or a fragment thereof.

28. The fusion protein of any one of claims 17-27, wherein the IL2R α or fragment thereof is human IL2R α (hIL2R α) or a fragment thereof.

29. The fusion protein of any one of claims 17-28, wherein the IL2 or fragment thereof comprises the amino acid sequence of SEQ ID NO: 53.

30. The fusion protein of any one of claims 17-29, wherein the IL2R α or fragment thereof comprises the amino acid sequence of SEQ ID NO: 51.

31. The fusion protein of any one of claims 17-30, wherein the first and/or second linker comprises the amino acid sequence of one or more repeats of GGGGS (SEQ ID NO: 67).

32. The fusion protein of any one of claims 17-30, wherein the first linker comprises the amino acid sequence of SEQ ID NO: 52, and the second linker comprises the amino acid sequence of SEQ ID NO: 50.

33. The fusion protein of any one of claims 17-32, wherein the IL2 moiety comprises the amino acid sequence of SEQ ID NO: 54.

34. The fusion protein of any one of claims 17-33, wherein:

(i) the first polypeptide comprises the amino acid sequence of SEQ ID NO: 58, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 64,

(ii) the first polypeptide comprises the amino acid sequence of SEQ ID NO: 60, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 63, or

(iii) the first polypeptide comprises the amino acid sequence of SEQ ID NO: 62, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 65.

35. The fusion protein of any one of claims 17-34, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 58 and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 64.
36. The fusion protein of any one of claims 17-34, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 60 and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 63.
37. The fusion protein of any one of claims 17-34, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 62 and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 65.
38. The fusion protein of any one of claims 1-37, wherein the fusion protein forms a dimeric fusion protein comprising two monomers.
39. The fusion protein of any one of claims 1-38, wherein each monomer comprises a heavy chain constant region, and the fusion protein dimerizes through the heavy chain constant regions of the monomers.
40. The fusion protein of any one of claims 1-39, wherein the fusion protein does not cross-compete with cemiplimab, pembrolizumab or nivolumab for binding to PD-1.
41. The fusion protein of any one of claims 1-40, wherein the fusion protein exhibits reduced activity in activating human IL2R α / β / γ and IL2R β / γ complexes as compared to IL2.
42. The fusion protein of any one of claims 1-41, wherein the fusion protein exhibits increased activity in activating human IL2R α as compared to a non-targeted IL2R α -IL2.
43. The fusion protein of any one of claims 1-42, wherein the fusion protein exhibits increased activity in stimulating T cells as measured by a level of IFN- γ release as compared to a wild-type human IL2.
44. The fusion protein of any one of claims 1-43, wherein the fusion protein exhibits attenuated binding to IL2R α , IL2R β and IL2R γ as compared to binding to wild-type human IL2.

45. A nucleic acid or plurality of nucleic acids comprising a polynucleotide sequence encoding the fusion protein of any one of claims 1-44.
46. A vector comprising the nucleic acid or plurality of nucleic acids of claim 45.
47. A host cell comprising the nucleic acid or plurality of nucleic acids of claim 45 or the vector of claim 46.
48. The host cell of claim 47 expressing a polynucleotide sequence that is comprised in a first vector and encodes the first polypeptide of the fusion protein set forth in any one of claims 17-44 and a polynucleotide sequence that is comprised in a second vector and encodes the second polypeptide of the fusion protein set forth in any one of claims 17-44.
49. A method of producing the fusion protein of any one of claims 1-44, comprising culturing the host cell of claim 47 or 48 under conditions permitting production of the fusion protein, and recovering the fusion protein so produced.
50. A pharmaceutical composition comprising the fusion protein of any one of claims 1-44.
51. The pharmaceutical composition of claim 50, further comprising an anti-PD-1 antibody or antigen-binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment thereof does not cross-compete with the fusion protein for binding to PD-1.
52. Use of the fusion protein of any one of claims 1-44 or the pharmaceutical composition of claim 50 or 51 for the manufacture of a medicament for treating cancer in a subject.
53. The use of claim 52, wherein the fusion protein is to be administered to the subject in an amount of 0.005 mg/kg to 10 mg/kg of the subject's body weight.
54. The use of claim 52 or 53, wherein the fusion protein is to be administered to the subject in combination with a second therapeutic agent or therapy.