

21R). IL-21R is expressed not just on T cells, but also on B cells, NK cells and myeloid cells. Accordingly, care must be taken to limit broad IL-21 activation in leukocytes and avoid the potential for toxicity. Restriction of IL-21 signaling must be balanced and selective. Triggering the effects of IL-21 must be designed to occur at the right time and place.

[0007] Indeed, any success, especially clinical success with IL-21 moieties as a monotherapy or in combination with checkpoint inhibitors, has been muted. Thus, there remains a need for treatment modalities utilizing IL-21, including modalities combining IL-21 moieties with checkpoint inhibitors. There also remains a need for IL-21 therapies combined with immune checkpoint inhibition.

SUMMARY

[0008] In one aspect, the present disclosure refers to a PD-1 antigen-binding protein comprising (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 352; an HC CDR2 amino acid sequence comprising SEQ ID NO: 353; an HC CDR3 amino acid sequence comprising SEQ ID NO: 354; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 355; an LC CDR2 amino acid sequence comprising SEQ ID NO: 356; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 357; (b) an HC CDR1 amino acid sequence comprising SEQ ID NO: 322; an HC CDR2 amino acid sequence comprising SEQ ID NO: 323; an HC CDR3 amino acid sequence comprising SEQ ID NO: 324; an LC CDR1 amino acid sequence comprising SEQ ID NO: 325; an LC CDR2 amino acid sequence comprising SEQ ID NO: 326; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 327; (c) an HC CDR1 amino acid sequence comprising SEQ ID NO: 332; an HC CDR2 amino acid sequence comprising SEQ ID NO: 333; an HC CDR3 amino acid sequence comprising SEQ ID NO: 334; an LC CDR1 amino acid sequence comprising SEQ ID NO: 335; an LC CDR2 amino acid sequence comprising SEQ ID NO: 336; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 337; (d) an HC CDR1 amino acid sequence comprising SEQ ID NO: 342; an HC CDR2 amino acid sequence comprising SEQ ID NO: 343; an HC CDR3 amino acid sequence comprising SEQ ID NO: 344; an LC CDR1 amino acid sequence comprising SEQ ID NO: 345; an LC CDR2 amino acid sequence comprising SEQ ID NO: 346; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 347; (e) an HC CDR1 amino acid sequence comprising SEQ ID NO: 312; an HC CDR2 amino acid sequence comprising SEQ ID NO: 313; an HC CDR3 amino acid sequence comprising SEQ ID NO: 314; an LC CDR1 amino acid sequence comprising SEQ ID NO: 315; an LC CDR2 amino acid sequence comprising SEQ ID NO: 316; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 317; (f) an HC CDR1 amino acid sequence comprising SEQ ID NO: 362; an HC CDR2 amino acid sequence comprising SEQ ID NO: 363; an HC CDR3 amino acid sequence comprising SEQ ID NO: 364; an LC CDR1 amino acid sequence comprising SEQ ID NO: 365; an LC CDR2 amino acid sequence comprising SEQ ID NO: 366; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 367; (g) an HC CDR1 amino acid sequence comprising SEQ ID NO: 372; an HC CDR2 amino acid sequence comprising SEQ ID NO: 373; an HC CDR3 amino acid sequence comprising SEQ ID NO: 374; an LC CDR1 amino acid sequence comprising SEQ ID NO: 375; an LC CDR2 amino acid sequence comprising SEQ ID NO: 376; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 377; or (h) an HC CDR1 amino acid sequence comprising SEQ ID NO: 382; an HC CDR2 amino acid sequence comprising SEQ ID NO: 383; an HC CDR3 amino acid sequence comprising SEQ ID NO: 384; an LC CDR1 amino acid sequence comprising SEQ ID NO: 385; an LC CDR2 amino acid sequence comprising SEQ ID NO: 386; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 387. In another aspect, the present disclosure refers to an anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 352; an HC CDR2 amino acid sequence comprising SEQ ID NO: 353; an HC CDR3 amino acid sequence comprising SEQ ID NO: 354; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 355; an LC CDR2 amino acid sequence comprising SEQ ID NO: 356; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 357. In a further aspect, the present disclosure refers to an anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 362; an HC CDR2 amino acid sequence comprising SEQ ID NO: 363; an HC CDR3 amino

acid sequence comprising SEQ ID NO: 364; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 365; an LC CDR2 amino acid sequence comprising SEQ ID NO: 366; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 367. In yet another aspect, the present disclosure refers to an anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 382; an HC CDR2 amino acid sequence comprising SEQ ID NO: 383; an HC CDR3 amino acid sequence comprising SEQ ID NO: 384; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 385; an LC CDR2 amino acid sequence comprising SEQ ID NO: 386; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 387.

~~[0008]—set forth in Table D or a sequence selected from the group consisting of: SEQ ID NOs: 352, 312, 322, 332, 342, 362, 372, and 382, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; (b) an HC CDR2 amino acid sequence set forth in Table D or a sequence selected from the group consisting of: SEQ ID NOs: 353, 313, 323, 333, 343, 363, 373, and 383, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; (c) an HC CDR3 amino acid sequence set forth in Table D or a sequence selected from the group consisting of: SEQ ID NOs: 354, 314, 324, 334, 344, 364, 374, and 384, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence set forth in Table D or a sequence selected from the group consisting of: 355, 315, 325, 335, 345, 365, 375, and 385, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; (e) an LC CDR2 amino acid sequence set forth in Table D or a sequence selected from the group consisting of: 356, 316, 326, 336, 346, 366, 376, and 386, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; (f) an LC CDR3 amino acid sequence set forth in Table D or a sequence selected from the group consisting of: 357, 317, 327, 337, 347, 367, 377, and 387, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity; or (g) a combination of any two or more of (a)–(f).~~

[0008a] In another aspect, the present disclosure refers to a nucleic acid or nucleic acids comprising a nucleotide sequence encoding the PD-1 antigen-binding protein as disclosed herein.

[0008b] In another aspect, the present disclosure refers to a vector comprising the nucleic acid as disclosed herein.

[0008c] In another aspect, the present disclosure refers to a host cell comprising the nucleic acid as disclosed herein.

[0008d] In another aspect, the present disclosure refers to a kit comprising ~~any one of a~~ the PD-1 antigen-binding protein, ~~the nucleic acid, the vector~~ as disclosed herein, ~~or a combination thereof,~~ and a container.

[0008e] In another aspect, the present disclosure refers to a pharmaceutical composition comprising ~~any one of a~~ the PD-1 antigen-binding protein, ~~the nucleic acid, the vector, the host cell,~~ as disclosed herein, ~~or a combination thereof,~~ and a pharmaceutically acceptable carrier, excipient, or diluent. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the anti-PD-1 antibody as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent

[0008f] In another aspect, the present disclosure refers to a method of making PD-1 antigen-binding protein comprising culturing the host cell as disclosed herein, so as to express the PD-1 antigen-binding protein and harvesting the expressed PD-1 antigen-binding protein.

[0008g] In yet another aspect, the present disclosure refers to the use of the PD-1 antigen-binding protein as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to the use of a PD-1 antigen-binding protein pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a ~~solid~~ tumor.

[0008h] In yet another aspect, the present disclosure refers to the anti-PD-1 antibody pharmaceutical composition as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to the use of an anti-PD-1 antibody as disclosed herein in the manufacture of a medicament for treating a tumor.

[0008i] The present disclosure provides IL-21 muteins comprising the amino acid sequence of SEQ ID NO: 2, wherein SEQ ID NO: 2 is

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF
QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE
KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2), and X is any
amino acid, and wherein the IL-21 mutein amino acid sequence differs from the amino acid
sequence of human IL-21 (SEQ ID NO: 1) by at least 1 amino acid.

[0009] Thus, in one example, the present disclosure also provides IL-21 muteins comprising only one amino acid substitution, relative to the wild-type IL-21 amino acid sequence, which is provided herein as SEQ ID NO: 1. In exemplary aspects, the amino acid substitution is located at an amino acid position selected from the group consisting of: 5, 8, 9, 11, 12, 13, 14, 15, 16, 19, 23, 65, 66, 68, 69, 70, 72, 73, 75, 76, 77, 78, 79, 80, 109, 110, 112, 113, 116, 117, 119, 120, or 123, according to the amino acid position numbering of SEQ ID NO: 1.

[0010] The present disclosure further provides IL-21 muteins comprising only two amino acid substitutions, relative to SEQ ID NO: 1. In exemplary aspects, the amino acid substitutions are located at two amino acid positions selected from the group consisting of: 5, 9, 15, 70, 71, 72, 73, and 76, according to the amino acid position numbering of SEQ ID NO: 1.

[0011] In exemplary disclosures, the IL-21 muteins bind to the IL-21 receptor (IL-21R) with a reduced affinity, relative to the affinity of wild-type IL-21 for the IL-21 receptor. In exemplary aspects, the IL-21 mutein binds to the human IL-21R with a K_D that is greater than or is about 0.04 nM. For example, the IL-21 mutein bind to the cynomolgus monkey IL-21R with a K_D that is greater than or is about 0.055 nM.

[0012] The present disclosure also provides conjugates comprising an IL-21 mutein of the present disclosure linked to a heterologous moiety. For example, the heterologous moiety is a polypeptide, such that the conjugate is a fusion protein. Therefore, the present disclosure provides fusion proteins comprising an IL-21 mutein of the present disclosure. For example, the fusion protein comprises an IL-21 mutein of the present disclosure linked to an antigen-binding protein, such as an antibody, or an antigen binding antibody fragment thereof.

[0013] In particular disclosures, the fusion protein comprises an IL-21 mutein linked to a PD-1 antigen-binding protein (e.g., a PD-1 antigen-binding antibody) of the present disclosure.

[0014] The present disclosure also provides PD-1 antigen-binding proteins and conjugates and fusion proteins comprising a PD-1 antigen-binding protein.

[0015] The present disclosure further provides nucleic acids comprising a nucleotide sequence encoding an IL-21 mutein, a PD-1 antigen-binding protein (e.g., a PD-1 antigen-binding antibody), or a fusion protein comprising an IL-21 mutein and a PD-1 antigen-binding protein (e.g., a PD-1 antigen-binding antibody) of the present disclosure. In one example, the nucleic acid molecule comprises a nucleotide sequence encoding a conjugate or fusion protein of the present disclosure. Vectors comprising the nucleic acids of the present disclosure and host cells comprising the nucleic acids of the present disclosure are furthermore provided herein.

[0016] The present disclosure additionally provides kits comprising an IL-21 mutein, a PD-1 antigen-binding protein (e.g., a PD-1 antigen-binding antibody), a conjugate, fusion protein (e.g., a fusion protein comprising an IL-21 mutein and a PD-1 antigen-binding protein (e.g., a PD-1 antigen-binding antibody)), nucleic acid, vector, or host cell of the present disclosure, or a combination thereof.

WHAT IS CLAIMED IS:

1. A PD-1 antigen-binding protein, comprising

- a. ~~(a)~~-a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence ~~set forth in Table D or a sequence selected from the group consisting of: comprising~~ SEQ ID NOs: 352, ~~312, 322, 332, 342, 362, 372, and 382, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ (b) an HC CDR2 amino acid sequence ~~set forth in Table D or a sequence selected from the group consisting of: comprising~~ SEQ ID NOs: 353, ~~313, 323, 333, 343, 363, 373, and 383, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ (c) an HC CDR3 amino acid sequence ~~comprising set forth in Table D or a sequence selected from the group consisting of:~~ SEQ ID NOs: 354, ~~314, 324, 334, 344, 364, 374, and 384, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ (d) a light chain (LC) CDR1 amino acid sequence ~~comprising SEQ ID NO: set forth in Table D or a sequence selected from the group consisting of:~~ 355, ~~315, 325, 335, 345, 365, 375, and 385, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ (e) an LC CDR2 amino acid sequence ~~comprising SEQ ID NO: set forth in Table D or a sequence selected from the group consisting of:~~ 356, ~~316, 326, 336, 346, 366, 376, and 386, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ and (f) an LC CDR3 amino acid sequence ~~comprising SEQ ID NO: set forth in Table D or a sequence selected from the group consisting of:~~ 357, ~~317, 327, 337, 347, 367, 377, and 387, or a variant sequence thereof which differs by only one or two amino acids or which has at least or about 70% sequence identity;~~ or (g) a combination of any two or more of (a)-(f).
- b. an HC CDR1 amino acid sequence comprising SEQ ID NO: 322; an HC CDR2 amino acid sequence comprising SEQ ID NO: 323; an HC CDR3 amino acid sequence comprising SEQ ID NO: 324; an LC CDR1 amino acid sequence comprising SEQ ID NO: 325; an LC CDR2 amino acid sequence comprising SEQ ID NO: 326; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 327;
- c. an HC CDR1 amino acid sequence comprising SEQ ID NO: 332; an HC CDR2 amino acid sequence comprising SEQ ID NO: 333; an HC CDR3 amino acid sequence

comprising SEQ ID NO: 334; an LC CDR1 amino acid sequence comprising SEQ ID NO: 335; an LC CDR2 amino acid sequence comprising SEQ ID NO: 336; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 337;

d. an HC CDR1 amino acid sequence comprising SEQ ID NO: 342; an HC CDR2 amino acid sequence comprising SEQ ID NO: 343; an HC CDR3 amino acid sequence comprising SEQ ID NO: 344; an LC CDR1 amino acid sequence comprising SEQ ID NO: 345; an LC CDR2 amino acid sequence comprising SEQ ID NO: 346; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 347;

e. an HC CDR1 amino acid sequence comprising SEQ ID NO: 312; an HC CDR2 amino acid sequence comprising SEQ ID NO: 313; an HC CDR3 amino acid sequence comprising SEQ ID NO: 314; an LC CDR1 amino acid sequence comprising SEQ ID NO: 315; an LC CDR2 amino acid sequence comprising SEQ ID NO: 316; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 317;

f. an HC CDR1 amino acid sequence comprising SEQ ID NO: 362; an HC CDR2 amino acid sequence comprising SEQ ID NO: 363; an HC CDR3 amino acid sequence comprising SEQ ID NO: 364; an LC CDR1 amino acid sequence comprising SEQ ID NO: 365; an LC CDR2 amino acid sequence comprising SEQ ID NO: 366; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 367;

g. an HC CDR1 amino acid sequence comprising SEQ ID NO: 372; an HC CDR2 amino acid sequence comprising SEQ ID NO: 373; an HC CDR3 amino acid sequence comprising SEQ ID NO: 374; an LC CDR1 amino acid sequence comprising SEQ ID NO: 375; an LC CDR2 amino acid sequence comprising SEQ ID NO: 376; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 377; or

4.h. an HC CDR1 amino acid sequence comprising SEQ ID NO: 382; an HC CDR2 amino acid sequence comprising SEQ ID NO: 383; an HC CDR3 amino acid sequence comprising SEQ ID NO: 384; an LC CDR1 amino acid sequence comprising SEQ ID NO: 385; an LC CDR2 amino acid sequence comprising SEQ ID NO: 386; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 387.

~~2. The PD-1 antigen-binding protein of claim 1, comprising six CDR amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 352-357; (b) SEQ ID NOs: 322-327; (c) SEQ ID~~

NOs: 332-337; (d) SEQ ID NOs: 342-347; (e) SEQ ID NOs: 312-317; (f) SEQ ID NOs: 362-367; (g) SEQ ID NOs: 372-377; and (h) SEQ ID NOs: 382-387.

2. The PD-1 antigen-binding protein of claim 12, comprising ~~a pair of amino acid sequences selected from the group consisting of:~~ (a) a heavy chain variable region of SEQ ID NOs: 358 and a light chain variable region of SEQ ID NO:359; (b) a heavy chain variable region of SEQ ID NOs: 328 and a light chain variable region of SEQ ID NO:329; (c) a heavy chain variable region of SEQ ID NOs: 338 and a light chain variable region of SEQ ID NO:339; (d) a heavy chain variable region of SEQ ID NOs: 348 and a light chain variable region of SEQ ID NO:349; (e) a heavy chain variable region of SEQ ID NOs: 318 and a light chain variable region of SEQ ID NO:319; (f) a heavy chain variable region of SEQ ID NOs: 368 and a light chain variable region of SEQ ID NO:369; (g) a heavy chain variable region of SEQ ID NOs: 378 and a light chain variable region of SEQ ID NO:379; ~~and-or~~ (h) a heavy chain variable region of SEQ ID NOs: 388 and a light chain variable region of SEQ ID NO:389.
3. The PD-1 antigen-binding protein of claim 2, comprising a heavy chain constant region of SEQ ID NO: 265 or SEQ ID NO: 266.
4. The PD-1 antigen-binding protein of claim 2, comprising a kappa light chain constant region.
5. The PD-1 antigen-binding protein of claim 2, comprising a light chain constant region of SEQ ID NO: 361.
3. _____
6. The PD-1 antigen-binding protein of claim 32, comprising ~~a pair of amino acid sequences selected from the group consisting of:~~ (a) a heavy chain of SEQ ID NOs: 360 and a light chain of SEQ ID NO:361; (b) a heavy chain of SEQ ID NOs: 330 and a light chain of SEQ ID NO:331; (c) a heavy chain of SEQ ID NOs: 340 and a light chain of SEQ ID NO:341; (d) a heavy chain of SEQ ID NOs: 350 and a light chain of SEQ ID NO:351; (e) a heavy chain of SEQ ID NOs: 320 and a light chain of SEQ ID NO:321; (f) a heavy chain of SEQ ID NOs: 370 and a light chain of SEQ ID NO:371; (g) a heavy chain of SEQ ID NOs: 380 and a light chain of SEQ ID NO:381; ~~and-or~~ (h) a heavy chain of SEQ ID NOs: 390 and a light chain of SEQ ID NO:391.
7. An anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 352; an HC CDR2 amino acid sequence comprising SEQ ID NO: 353; an HC CDR3 amino acid sequence comprising SEQ ID NO: 354; a

light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 355; an LC CDR2 amino acid sequence comprising SEQ ID NO: 356; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 357.

8. The anti-PD-1 antibody of claim 7, comprising a heavy chain variable region of SEQ ID NO: 358 and a light chain variable region of SEQ ID NO: 359.

9. An anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 362; an HC CDR2 amino acid sequence comprising SEQ ID NO: 363; an HC CDR3 amino acid sequence comprising SEQ ID NO: 364; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 365; an LC CDR2 amino acid sequence comprising SEQ ID NO: 366; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 367.

10. The anti-PD-1 antibody of claim 9, comprising a heavy chain variable region of SEQ ID NO: 368 and a light chain variable region of SEQ ID NO: 369.

11. An anti-PD-1 antibody comprising a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 382; an HC CDR2 amino acid sequence comprising SEQ ID NO: 383; an HC CDR3 amino acid sequence comprising SEQ ID NO: 384; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 385; an LC CDR2 amino acid sequence comprising SEQ ID NO: 386; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 387.

12. The anti-PD-1 antibody of claim 11, comprising a heavy chain variable region of SEQ ID NO: 388 and a light chain variable region of SEQ ID NO: 389.

4.—

5.13. The PD-1 antigen-binding protein of ~~any one of claims 1-4~~, which is an antibody.

6.14. The PD-1 antigen-binding protein of ~~any one of claims 1-4~~, which is an antigen-binding fragment of an antibody.

15. The PD-1 antigen-binding protein of ~~any one of claims 1-4~~, which is an antibody protein product.

7.16. The PD-1 antigen-binding protein of claim 1, which is, ~~optionally~~, an scFv.

- ~~8~~17. A nucleic acid or nucleic acids comprising a nucleotide sequence encoding the PD-1 antigen-binding protein of ~~any one of the preceding claims~~ 1.
- ~~9~~18. The nucleic acid of claim ~~17~~8, comprising the sequence of any one of SEQ ID NOs: 392-471.
- ~~10~~19. A vector comprising the nucleic acid of claim ~~18~~or 9.
- ~~11~~20. A host cell comprising the nucleic acid of claim ~~8 or 9, or the vector of claim 10~~.
- ~~12~~21. A kit comprising ~~a~~ PD-1 antigen-binding protein of ~~any one of the preceding claims 1, the nucleic acid of claim 8 or 9, the vector of claim 10, the host cell of claim 11, or a combination thereof,~~ and a container.
22. A pharmaceutical composition comprising ~~a~~ PD-1 antigen-binding protein of ~~any one of the preceding claims 1, the nucleic acid of claim 8 or 9, the vector of claim 10, the host cell of claim 11, or a combination thereof,~~ and a pharmaceutically acceptable carrier, excipient, or diluent.
23. A pharmaceutical composition comprising the anti-PD-1 antibody of claim 7, 9 or 11 and a pharmaceutically acceptable carrier, excipient, or diluent.
- ~~13~~.
24. A method of making PD-1 antigen-binding protein comprising culturing the host cell of claim ~~13~~20 so as to express the PD-1 antigen-binding protein and harvesting the expressed PD-1 antigen-binding protein.
25. The PD-1 antigen-binding protein of claim 1 for use in therapy.
26. Use of a PD-1 antigen-binding protein of claim 1 in the manufacture of a medicament for treating a tumor.
27. The anti-PD-1 antibody of claim 7, 9 or 11 for use in therapy.
28. Use of an anti-PD-1 antibody of claim 7, 9 or 11 in the manufacture of a medicament for treating a tumor.
- ~~14~~. The use of claim 26 or 28 wherein the tumor is a solid tumor.

- ~~15. Use of a pharmaceutical composition of claim 13 in the manufacture of a medicament for treating a solid tumor.~~
- ~~16.29. The pharmaceutical composition of claim 13 for use in therapy.~~