[005] PD-1 has been shown to play a role in cancer. In humans, expression of PD-1 and/or PD-L1 has been found in a number of primary tumor biopsies assessed by immunohistochemistry. Such tissues include cancers of the lung, liver, ovary, cervix, skin, colon, glioma, bladder, breast, kidney, esophagus, stomach, oral squamous cell, urothelial cell, and pancreas as well as tumors of the head and neck. Furthermore, PD-ligand expression on tumor cells has been correlated to poor prognosis of cancer patients across multiple tumor types.

[006] There is an ongoing need for new therapeutics, including antibodies and other antigen-binding proteins that target PD-1 and function either as agonists of PD-1 or antagonists thereof.

Summary

[007] The present disclosure describes antigen-binding proteins such as antibodies and chimeric antigen receptors that are able to specifically bind a protein receptor associated with programmed cell death, PD-1, on T cells, thereby modulating immune response by the T cells. By inhibiting the binding of PD-1 to its ligand, PD-L1, blockade of the PD-1 signaling pathway inhibits apoptosis of the T cells.

The present disclosure relates to the following:

In one aspect, the present disclosure refers to a recombinant antigen-binding protein or antigen-binding fragment thereof comprising one of:

(A) an antigen binding region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 32, SEQ ID NO: 53,

and a homologous sequence of any one of the foregoing amino acid sequences;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), respectively, with amino acid sequences selected from SEQ ID NOS: 28 and 30; SEQ ID NOS: 49 and 51; and homologous sequences of any one of the foregoing amino acid sequences;

(C) an antigen binding region comprising:

(i) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGNNA (SEQ ID NO: 23), YND and AAWDDSVNGYV (SEQ ID NO: 24) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRFG (SEQ ID NO: 25), ISVNNGNT (SEQ ID NO. 26) and ARYMYGRRDS (SEQ ID NO: 27); and homologous sequences of any one of the foregoing amino acid sequences;

(ii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48); and homologous sequences of any one of the foregoing amino acid sequences;

wherein homologous sequences comprise sequences with at least 80% identity and said antigen-binding protein comprises a secretable scFv and the secretable scFv specifically binds to programmed cell death (PD-1).

In another aspect, the present disclosure refers to a nucleic acid encoding an antigen-binding protein of the present disclosure.
In yet another aspect, the present disclosure refers to a vector comprising a nucleic acid of the present disclosure.
In yet another aspect, the present disclosure refers to a cell comprising an antigen-binding protein of the present disclosure, a nucleic acid of the present disclosure or a vector comprising a nucleic acid of the present disclosure.
In another aspect, the present disclosure refers to a pharmaceutical composition comprising an antigen-binding protein of the present disclosure, a nucleic acid of the present disclosure, a vector of the present disclosure, a cell of the present disclosure.
In yet another aspect, the present disclosure refers to the use of an antigen-binding protein or an antigen binding fragment thereof of the present disclosure, a nucleic acid of the present disclosure, a vector of the present disclosure, a cell of the present disclosure, or a pharmaceutical composition the present disclosure in the manufacture of a medicament for treating cancer.
In another aspect, the present disclosure refers to a bicistronic vector comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in the present disclosure and a nucleic acid encoding a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.
In yet another aspect, the present disclosure refers to a cell comprising the vector of the present disclosure.
In yet another aspect, the present disclosure refers to a cell comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in the present disclosure and a nucleic acid encoding a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.

In yet another aspect, the present disclosure refers to a cell comprising a recombinant anti-PD-1 antigen-binding protein as defined in the present disclosure and a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.
In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a vector or a cell of the present disclosure.
In yet another aspect, the present disclosure refers to the use of a vector or cell of the present disclosure, or a pharmaceutical composition of the present disclosure, in the manufacture of a medicament for treating cancer, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist. In one other aspect, the present disclosure refers to the use of a combination of a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in the present disclosure and a nucleic acid encoding a CD19-specific chimeric antigen receptor in the manufacture of a pharmaceutical for treating cancer, wherein the use comprises that at least one T cell of the subject is to be transduced with the medicament, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor. In yet another aspect, the present disclosure refers to the antigen-binding protein or an antigen binding fragment thereof of the present disclosure, a nucleic acid of the present disclosure, a vector of the present disclosure, a cell of the present disclosure, a pharmaceutical composition of the present disclosure or a vector or cell of the present disclosure for use in therapy.
Also disclosed herein is:
[008] In one example, the disclosure relates to recombinant antigen-binding proteins, antibodies and chimeric antigen receptors or antigen-binding portions thereof that bind specifically to PD-1 and prevent binding of its ligand.

[009] In one example, the disclosure relates to a recombinant antigen-binding protein or antigen-binding fragment thereof comprising one of:

CLAIMS

We claim:

1. A recombinant antigen-binding protein or antigen-binding fragment thereof comprising one of:

(A) an antigen binding region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 32, SEQ ID NO: 53, and a homologous sequence to any one of the foregoing amino acid sequences;

(B) an antigen binding region comprising a variable light chain (VL) and variable heavy chain (VH), respectively, with amino acid sequences selected from SEQ ID NOS: 28 and 30; SEQ ID NOS: 49 and 51; and homologous sequences to the foregoing amino acid sequences;

(C) an antigen binding region comprising:
(i) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence SSNIGNNA (SEQ ID NO: 23), YND and AAWDDSVNGYV (SEQ ID NO: 24) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GYTFTRFG (SEQ ID NO: 25), ISVNNGNT (SEQ ID NO. 26) and ARYMYGRRDS (SEQ ID NO: 27), and homologous sequences to the foregoing amino acid sequences;

(ii) a light chain (LC) comprising LCCDR1, LCCDR2 and LCCDR3 respectively, having the amino acid sequence NIGSKS (SEQ ID NO: 34), YDS and QVWDSSSDYV (SEQ ID NO: 45) and a heavy chain (HC) comprising HCCDR1, HCCDR2 and HCCDR3 respectively, having amino acid sequences GFTFSSYA (SEQ ID NO: 46), ISGSGGST (SEQ ID NO. 47) and ARNYISMFDS (SEQ ID NO: 48);, and homologous sequences to the foregoing amino acid sequences;

wherein homologous sequences comprise sequences with at least 80% identity and said antigen-binding protein comprises a secretable scFv and the secretable scFv specifically binds to programmed cell death (PD-1).

2. The recombinant antigen-binding protein of claim 1, wherein homologous sequences comprise sequences with at least 95% sequence identity.

3. The antigen-binding protein of claim 1 or 2, wherein said antigen-binding protein is a PD-1 antagonist.

4. The antigen-binding protein of claim 1 or 2, wherein said antigen-binding protein is a chimeric antigen receptor (CAR).

5. A nucleic acid encoding an antigen-binding protein of any one of claims 1-4.

6. A vector comprising a nucleic acid of claim 5.

7. A cell comprising an antigen-binding protein of any one of claims 1-4, a nucleic acid of claim 5 or a vector of claim 6.

8. A pharmaceutical composition comprising an antigen-binding protein of any one of claims 1-4, a nucleic acid of claim 5, a vector of claim 6, or a cell of claim 7.

9. Use of an antigen-binding protein or an antigen binding fragment thereof of any one of claims 1-4, a nucleic acid of claim 5, a vector of claim 6, a cell of claim 7, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating cancer.

10. The use of claim 9, wherein the antigen-binding protein thereof inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

11. A bicistronic vector comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in any one of claims 1 to 4 and a nucleic acid encoding a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.

12. A cell comprising the vector of claim 11.

13. A cell comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in any one of claims 1 to 4 and a nucleic acid encoding a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.

14. A cell comprising a recombinant anti-PD-1 antigen-binding protein as defined in any one of claims 1 to 4 and a CD19-specific chimeric antigen receptor, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.

15. The vector or the cell of any one of claims 11-14, wherein the chimeric antigen receptor does not specifically bind to PD-1.

16. The vector or the cell of any one of claims 11-15, wherein the recombinant anti-PD-1 antigen-binding protein is an antibody.

17. The vector or the cell of any one of claims 11-16, wherein the recombinant anti-PD-1 antigen-binding protein is a human antibody.

18. The vector or the cell of any one of claims 11-17, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist.

19. The vector or the cell of any one of claims 11-18, wherein the chimeric antigen receptor specifically binds to CD-19.

20. The vector or the cell of any one of claims 11-19, wherein the chimeric antigen receptor can be inserted in a human T cell membrane.

21. The cell of any one of claims 11-20, wherein the cell is a T cell.

22. A pharmaceutical composition comprising a vector or a cell of any one of claims 11-21.

23. Use of a vector or cell of any one of claims 14-21, or a pharmaceutical composition of claim 22, in the manufacture of a medicament for treating cancer, wherein the recombinant anti-PD-1 antigen-binding protein is a PD-1 antagonist.

24. The use of claim 23, wherein the recombinant anti-PD-1 antigen-binding protein inhibits, reduces, modulates or abolishes signal transduction mediated by PD-1.

25. Use of a bicistronic vector composition comprising a nucleic acid encoding a recombinant anti-PD-1 antigen-binding protein as defined in any one of claims 1 to 4 and a nucleic acid encoding a CD19-specific chimeric antigen receptor in the manufacture of a pharmaceutical for treating cancer, wherein the use comprises that at least one T cell of the subject is to be transduced with the medicament, wherein said recombinant anti-PD-1 antigen-binding protein is not identical to said CD19-specific chimeric antigen receptor.

26. The use of claim 25, wherein the chimeric antigen receptor does not specifically bind to PD-1.

27. The antigen-binding protein or an antigen binding fragment thereof of any one of claims 1-4, a nucleic acid of claim 5, a vector of claim 6, a cell of claim 7, a pharmaceutical composition of claim 8 or 25 or a vector or cell of any one of claims 11 and 15-20 for use in therapy.