

PD-1 Antibodies

Summary

5 In one aspect of the present disclosure, there is provided an antibody that binds human PD-1 (SEQ ID NO: 1), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11),
10 respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3,
 wherein
 (1) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT
15 (SEQ ID NO: 11), respectively, and
 wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences KASGGTFSSY AIS (SEQ ID NO: 2), LIIPMFGTAGYAQKFQG (SEQ ID NO: 4), and ARAEYSSTGTFDY (SEQ ID NO: 7), respectively; or
 (2) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences
20 RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences KASGGTFSSY AIS (SEQ ID NO: 2), LIIPMFDTAGYAQKFQG (SEQ ID NO: 5), and ARAEHSSTGTFDY (SEQ ID NO: 8), respectively; or
25 (3) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences KASGGTLSSY AIS (SEQ ID NO: 3), LIIPMFGAAGYAQRFG (SEQ ID NO: 6), and ARAEHSSTGTFDY (SEQ ID NO: 8),
30 respectively.

In another aspect of the present disclosure, there is provided an antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR has the amino acid sequence given in SEQ ID NO: 15, and the HCVR has the amino acid sequence given in SEQ ID NO: 12, SEQ ID NO: 13, or SEQ ID NO: 14.

In a further aspect of the present disclosure, there is provided a mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 22 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 22 and a heavy chain having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20.

In yet another aspect of the present disclosure, there is provided a process for producing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 22 and a heavy chain having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20, comprising cultivating the mammalian cell as defined herein under conditions such that the antibody is expressed, and recovering the expressed antibody.

In another aspect of the present disclosure, there is provided an antibody produced by the process as defined herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody as defined herein, and an acceptable carrier, diluent, or excipient.

In yet another aspect of the present disclosure, there is provided a use of the antibody as defined herein, in the manufacture of a pharmaceutical composition for treating cancer in a patient in need thereof.

In another aspect of the present disclosure, there is provided a use of an antibody as defined herein, and one or more anti-tumor agents in the manufacture of a medicament for treating cancer, wherein the antibody is to be administered simultaneously, separately, or sequentially with said one or more anti-tumor agents.

In another aspect of the present disclosure, there is provided the antibody as defined herein, for use in therapy.

In a further aspect of the present disclosure, there is provided the antibody as defined herein, for use in the treatment of cancer.

5 In yet another aspect of the present disclosure, there is provided a combination of an antibody as defined herein and one or more anti-tumor agents, for simultaneous, separate, or sequential use in treating cancer.

Description

10 The present invention relates to the field of medicine. More particularly, the present invention relates to antibodies that bind human programmed cell death 1 (PD-1), and may be useful for treating cancer alone and in combination with chemotherapy and other cancer therapeutics.

Tumor cells escape detection and elimination by the immune system through
15 multiple mechanisms. Immune checkpoint pathways are used in self-tolerance maintenance and activated T cell control, but cancer cells can use the pathways to prevent destruction. The PD-1 / human programmed cell death 1 ligand 1 (PD-L1) pathway is one such immune checkpoint. Human PD-1 is found on T cells, and the binding of PD-L1 and human programmed cell death 1 ligand 2 (PD-L2) to PD-1 inhibits T cell
20 proliferation and cytokine production. Tumor cell production of PD-L1 and PD-L2 can therefore allow escape from T cell surveillance.

A fully human IgG4 (S228P) antibody against human PD-1, nivolumab, has been shown to inhibit the binding of PD-1 to PD-L1 and PD-L2, and has been tested in various clinical trials. (Wang et al., Cancer Immunol Res (2014) 2(9):846). A humanized IgG4
25 (S228P) antibody against PD-1, pembrolizumab (formerly lambrolizumab), has been shown to inhibit the binding of PD-1 to PD-L1 and PD-L2, and has been tested in various clinical trials. (WO2008156712 and Hamid et al., N Engl J Med (2013) 369:2).

There remains a need to provide alternative antibodies that bind and neutralize human PD-1 interaction with PD-L1 and PD-L2. In particular, there remains a need to
30 provide antibodies that bind human PD-1 with higher affinity than certain prior art antibodies. Also, there remains a need to provide antibodies that more effectively block the human PD-1 interaction with PD-L1 and PD-L2 than certain prior art antibodies.

Higher affinity and better blocking, alone or together, can translate into greater *in vivo* activity or lower required dosing amounts.

Certain antibodies of the present invention bind human PD-1 with higher affinity than nivolumab and pembrolizumab. Furthermore, certain antibodies of the present
5 invention mediate preferential enhanced alloreactivity compared to nivolumab and pembrolizumab in an *in vivo* model.

WE CLAIM:

1. An antibody that binds human PD-1 (SEQ ID NO: 1), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, wherein(1) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences KASGGTFSSY AIS (SEQ ID NO: 2), LIIPMFGTAGYAQKFQG (SEQ ID NO: 4), and ARAEYSSTGTFDY (SEQ ID NO: 7), respectively; or (2) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences KASGGTFSSY AIS (SEQ ID NO: 2), LIIPMFDTAGYAQKFQG (SEQ ID NO: 5), and ARAEHSSTGTFDY (SEQ ID NO: 8), respectively; or

(3) wherein LCDR1, LCDR2, and LCDR3 consist of the amino acid sequences RASQGISSWLA (SEQ ID NO: 9), SAASSLQS (SEQ ID NO: 10), and QQANHLPFT (SEQ ID NO: 11), respectively, and wherein HCDR1, HCDR2, and HCDR3 consist of the amino acid sequences
5 KASGGTLSSY AIS (SEQ ID NO: 3), LIIPMFGAAGYAQRFGG (SEQ ID NO: 6), and ARAEHSSTGTFDY (SEQ ID NO: 8), respectively.

2. An antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the
10 LCVR has the amino acid sequence given in SEQ ID NO: 15, and the HCVR has the amino acid sequence given in SEQ ID NO: 12, SEQ ID NO: 13, or SEQ ID NO: 14.

3. The antibody of Claim 2,
(1) wherein the LCVR has the amino acid sequence given in SEQ ID NO: 15, and the HCVR has the amino acid sequence given in SEQ ID NO: 12; or
15 (2) wherein the LCVR has the amino acid sequence given in SEQ ID NO: 15, and the HCVR has the amino acid sequence given in SEQ ID NO: 13; or
(3) wherein the LCVR has the amino acid sequence given in SEQ ID NO: 15, and the HCVR has the amino acid sequence given in SEQ ID NO: 14.

20 4. The antibody of Claim 2, wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21.

5. The antibody of Claim 4,
25 (1) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 16; or

(2) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 17; or

(3) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 18; or

5 (4) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 19; or

(5) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 20; or

10 (6) wherein the LC has the amino acid sequence given in SEQ ID NO: 22, and the HC has the amino acid sequence given in SEQ ID NO: 21.

6. The antibody of Claim 4, comprising two light chains and two heavy chains, wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21.

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7. The antibody of Claim 6,

(1) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 16; or

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(2) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 17; or

(3) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 18; or

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(4) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 19; or

5 (5) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 20; or

(6) wherein each light chain has the amino acid sequence given in SEQ ID NO: 22, and each heavy chain has the amino acid sequence given in SEQ ID NO: 21.

10 8. The antibody of Claim 6 or 7, wherein one of the heavy chains forms an inter-chain disulfide bond with one of the light chains, and the other heavy chain forms an inter-chain disulfide bond with the other light chain, and one of the heavy chains forms two inter-chain disulfide bonds with the other heavy chain.

15 9. The antibody of any one of Claims 1-8, wherein the antibody is glycosylated.

20 10. A mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 22 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 22 and a heavy chain having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20.

25 11. A process for producing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 22 and a heavy chain having an amino acid sequence of SEQ ID NO: 17 or SEQ ID NO: 20, comprising cultivating the mammalian cell of Claim 10 under conditions such that the antibody is expressed, and recovering the expressed antibody.

12. An antibody produced by the process of Claim 11.

13. A pharmaceutical composition, comprising the antibody of any one of Claims 1-9, and an acceptable carrier, diluent, or excipient.

14. A use of the antibody of any one of Claims 1-9 in the manufacture of a pharmaceutical composition for treating cancer in a patient in need thereof.

5 15. The use of Claim 14, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, or hepatocellular carcinoma.

10 16. Use of an antibody according to any one of claims 1-9, and one or more anti-tumor agents in the manufacture of a medicament for treating cancer, wherein the antibody is to be administered simultaneously, separately, or sequentially with said one or more anti-tumor agents.

15 17. The use of claim 16, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, or hepatocellular carcinoma.

18. The antibody of any one of Claims 1-9, for use in therapy.

19. The antibody of any one of Claims 1-9, for use in the treatment of cancer.

20 20. The antibody for use of Claim 19, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, or hepatocellular carcinoma.

25 21. A combination of an antibody of any one of Claims 1-9 and one or more anti-tumor agents for simultaneous, separate, or sequential use in treating cancer.

30 22. The combination for use of Claim 21, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, or hepatocellular carcinoma.