

Claims

1. An isolated antagonist antibody that specifically binds to PD-1 and comprises:

a heavy chain variable region (VH) comprising a VH complementarity determining region one (CDR1), VH CDR2, and VH CDR3 of the VH having an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6; and

a light chain variable region (VL) comprising a VL CDR1, VL CDR2, and VL CDR3 of the VL having an amino acid sequence selected from the group consisting of SEQ ID NO: 2; SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9.

2. The isolated antagonist antibody of claim 1, wherein the antibody comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, 14, or 15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16, 17, 24, 25, 27, 28, 35, or 36, a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 18, 23, 26, or 37, a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 10, 22, 30, or 32, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 11, 20, or 33 and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 12, 21, 31, or 34.

3. The isolated antagonist antibody of claim 1 or 2, wherein the antibody comprises a VH comprising the amino acid sequence shown in SEQ ID NO: 3, 4, 5, or 6, or a variant thereof with one or several conservative amino acid substitutions in residues that are not within a CDR.

4. The isolated antagonist antibody of claim 3, wherein the antibody comprises a VL comprising the amino acid sequence shown in SEQ ID NO: 2, 7, 8, or 9, or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

5. The isolated antagonist antibody of any one of claims 1 to 4, wherein the antibody comprises a VH comprising the amino acid sequence shown in SEQ ID NO: 3,

4, 5, or 6, and a VL comprising the amino acid sequence shown in SEQ ID NO: 2, 7, 8, or 9.

6. The isolated antagonist antibody of any one of claims 1 to 5, wherein the antibody comprises a heavy chain comprising the amino acid sequence shown in SEQ ID NO: 29 or 38 and a light chain comprising the amino acid sequence shown in SEQ ID NO: 39.

7. The isolated antagonist antibody any one of claims 1 to 5, wherein the antibody comprises a constant region.

8. The isolated antagonist antibody of claim 7, wherein the antibody has an isotype that is selected from the group consisting of IgG₂, IgG_{2Δa}, IgG₄, IgG_{4Δb}, IgG_{4Δc}, IgG₄ S228P, IgG_{4Δb} S228P and IgG_{4Δc} S228P.

9. The isolated antagonist antibody of claim 7, wherein the constant region is IgG₄ S228P.

10. The isolated antagonist antibody of claim 1, wherein each CDR of the antibody is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the AbM definition, or the contact definition of CDR.

11. An isolated antagonist antibody that specifically binds to PD-1 and competes for binding to PD-1 with, and/or binds to an epitope that is the same as or overlaps with the epitope on PD-1 recognized by, the antibody of claim 1.

12. An isolated anti-PD-1 antibody, wherein the antibody comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 17, a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 23, a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 10, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 20, and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 21.

13. The isolated antibody of any one of the preceding claims, wherein the antibody promotes IFN γ and/or TNF secretion from T cells.

14. The isolated antibody of any one of the preceding claims, wherein the antibody promotes proliferation of T cells.

15. The isolated antibody of any one of the preceding claims, wherein the antibody inhibits tumor growth.

16. The isolated antibody of any one of the preceding claims, wherein the antibody binds human PD-1 and mouse PD-1.

17. The isolated antibody of claim 16, wherein the antibody binds human PD-1 with an affinity of about 0.73 nM at 25°C as measured by surface plasmon resonance.

18. An isolated cell line that produces the antibody of any one of the preceding claims.

19. An isolated nucleic acid encoding the antibody of any one of the preceding claims.

20. A recombinant expression vector comprising the nucleic acid of claim 19.

21. A host cell comprising the expression vector of claim 20.

22. A hybridoma capable of producing the antibody of any one of the preceding claims.

23. A method of producing an anti-PD-1 antagonist antibody, the method comprising: culturing a cell line that recombinantly produces the antibody of any one of the preceding claims under conditions wherein the antibody is produced; and recovering the antibody.

24. A method of producing an anti-PD-1 antagonist antibody, the method comprising: culturing a cell line comprising nucleic acid encoding an antibody comprising a heavy chain comprising the amino acid sequence shown in SEQ ID NO: 29 or 38 and a light chain comprising the amino acid sequence shown in SEQ ID NO: 39 under conditions wherein the antibody is produced; and recovering the antibody.

25. The method of claim 21, wherein the heavy and light chains of the antibody are encoded on separate vectors.

26. The method of claim 21, wherein the heavy and light chains of the antibody are encoded on the same vector.

27. A pharmaceutical composition comprising the antibody of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

28. A kit for the treatment of cancer comprising the pharmaceutical composition of claim 27.

29. The use of the anti-PD-1 antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for the treatment of cancer in an individual.

30. The use of claim 29, wherein the cancer is selected from the group consisting of gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma.

31. The use of claim 29 or 30 wherein the individual is a previously treated adult patient with locally advanced or metastatic melanoma, squamous cell head and neck cancer (SCHNC), ovarian carcinoma, sarcoma, or relapsed or refractory classic Hodgkin's Lymphoma (cHL).

32. The use of any one of claims 29 to 31, wherein the anti-PD-1 antibody is to be administered at a dosage of about 0.5 mg/kg, about 1.0 mg/kg, about 3.0 mg/kg, or about 10 mg/kg.

33. The use of any one of claims 29 to 32, wherein the anti-PD-1 antibody is to be administered once every 7, 14, 21, or 28 days.

34. The use of any one of claims 29 to 33, wherein the anti-PD-1 antibody is to be administered intravenously or subcutaneously.

35. The use of any one of claims 29 to 34, wherein the treatment further comprises the administration of an effective amount of a second therapeutic agent.
36. The use of claim 35, wherein the second therapeutic agent is selected from the group consisting of an anti-CTLA4 antibody, an anti-4-1BB antibody, a second PD-1 antagonist, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-TIGIT antibody, an anti-OX40 antibody, an anti-GITR antibody, a tyrosine kinase inhibitor, and an ALK inhibitor.
37. The use of claim 36, wherein the tyrosine kinase inhibitor is axitinib or palbociclib.
38. The use of claim 36, wherein the ALK inhibitor is sunitinib or crizotinib.
39. The use of the anti-PD-1 antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for the treatment of cancer in an individual in need, wherein the treatment when carried out comprises the administration of the medicament and a vaccine capable of eliciting an immune response against cells of the cancer.
40. The use of the anti-PD-1 antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for the enhancement of the immunogenicity or therapeutic effect of a vaccine, wherein the enhancement comprises administering to an individual in need an effective amount of the anti-PD-L1 antibody or the pharmaceutical composition.
41. The use of claim 39 or 40, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, and colorectal cancer.
42. The use of claim 39 or 40, wherein the treatment or enhancement further comprises the administration to the individual an effective amount of one or more other immune modulators.
43. The use of claim 42, wherein the other immune modulators are selected from the group consisting of protein kinase receptor inhibitor, a CTLA-4 antagonist, a CD40 agonist, and a TLR9 agonist.