Patent Claims

1. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain and a light chain variable region sequence, wherein:
(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein further: (i) the HVR-H1 sequence is SYIMM (SEQ ID NO: 15); (ii) the HVR-H2 sequence is SIYPSGGITFYADTVKG (SEQ ID NO: 16); (iii) the HVR-H3 sequence is IKLGTVTTVDY (SEQ ID NO: 17);
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further: (iv) the HVR-L1 sequence is TGTSSDVGGYNYVS (SEQ ID NO: 18); (v) the HVR-L2 sequence is DVSNRPS (SEQ ID NO: 19); (vi) the HVR-L3 sequence is SSYTSSSTRV (SEQ ID NO: 20).

2. The antibody or antibody fragment of Claim 1 further comprising:
(a) variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)- (HVR-H3)-(HC-FR4), and
(b) variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)- (HVR-L3)-(LC-FR4).

3. The antibody or antibody fragment of Claim 2 wherein the framework sequences are derived from human consensus framework sequences.

4. The antibody or antibody fragment of Claim 2 wherein the framework sequences are derived from human germline framework sequences.

5. The antibody or antibody fragment of Claim 2 wherein one or more of the framework sequences is the following:
HC-FR1 is EVQLLESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO:4);
HC-FR2 is WVRQAPGKGLEWVS (SEQ ID NO:5);

HC-FR3 is RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:6);
HC-FR4 is WGQGTLVTVSS (SEQ ID NO:7).

6. The antibody or antibody fragment of Claim 2 wherein one or more of the framework sequences is the following:
LC-FR1 is QSALTQPASVSGSPGQSITISC (SEQ ID NO: 11);
LC-FR2 is WYQQHPGKAPKLMIY (SEQ ID NO: 12);
LC-FR3 is GVSNRFSGSKSGNTASLTISGLQAEDEADYYC; (SEQ ID NO: 13);
LC-FR4 is FGTGTKVTVL (SEQ ID NO: 14).

7. The antibody or antibody fragment of Claim 2 wherein:
(a) the variable heavy chain framework sequences are the following:
(i) HC-FR1 is EVQLLESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO:4);
(ii) HC-FR2 is WVRQAPGKGLEWVS (SEQ ID NO: 5);
(iii) HC-FR3 is RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:6);
(iv) HC-FR4 is WGQGTLVTVSS (SEQ ID NO: 7); and
(b) the variable light chain framework sequences are the following:
(i) LC-FR1 is QSALTQPASVSGSPGQSITISC (SEQ ID NO:11);
(ii) LC-FR2 is WYQQHPGKAPKLMIY (SEQ ID NO: 12);
(iii) LC-FR3 is GVSNRFSGSKSGNTASLTISGLQAEDEADYYC (SEQ ID NO: 13);
(iv) LC-FR4 is FGTGTKVTVL (SEQ ID NO: 14).

8. The antibody or antibody fragment of Claim 7 further comprising at least a C_H1 domain.

9. The antibody or antibody fragment of Claim 7 or 8 further comprising a C_L domain.

10. The antibody or antibody fragment of any of Claims 7-9 further comprising a C_H1, a C_H2 and a C_H3 domain.

11. The antibody or antibody fragment of Claim 7 further comprising a human or murine constant region.

12. The antibody or antibody fragment of Claim 11, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.

13. The antibody or antibody fragment of Claim 12 wherein the constant region is IgG1.

14. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain variable region sequence and light chain variable region sequence, wherein:
(a) the heavy chain comprises the sequence:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSI
YPSGGITFYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTV
TTVDYWGQGTLVTVSS (SEQ ID NO: 24), and
(b) the light chain comprises the sequence:
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIY
DVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFG
TGTKVTVL (SEQ ID NO: 25).

15. The antibody of Claim 14 wherein the antibody further comprises a C_H1, a C_H2, a C_H3 and a C_L domain.

16. The antibody of any of Claims 1-15 wherein the antibody binds to human, mouse or cynomolgus monkey PD-L1.

17. The antibody of any of Claims 1-16 wherein the antibody is capable of blocking the interaction between human, mouse or cynomolgus monkey PD-L1 and the respective human, mouse or cynomolgus monkey PD-1 receptors.

18. The antibody of any of Claims 1-17 wherein the antibody binds to human PD-L1 with a K_D of $5x10^{-9}$ M or less.

19. An isolated anti-PD-L1 antibody or antigen binding fragment thereof which binds to a functional epitope comprising residues Y56 and D61 of human PD-L1 (SEQ ID NO:28).

20. The isolated anti-PD-L1 antibody or antigen binding fragment of claim 19 wherein the functional epitope further comprises residues E58, E60, Q66, R113 and M115 of human PD-L1 (SEQ ID NO:28).

21. An isolated anti-PD-L1 antibody or antigen binding fragment thereof which binds to a conformational epitope comprising residues 54-66 and 112-122 of human PD-L1 (SEQ ID NO:28).

22. An isolated anti-PD-L1 antibody or antigen binding fragment thereof wherein the antibody cross-competes for binding to PD-L1 with an antibody or antigen binding fragment of any of Claims 1-21.

23. A composition comprising the anti-PD-L1 antibody or antigen binding fragment of any of Claims 1-22 and at least one pharmaceutically acceptable carrier.

24. An isolated nucleic acid encoding the light chain or a heavy chain sequence of an anti-PD-L1 antibody or antigen binding fragment of any of Claims 1-22.

25. The nucleic acid of Claim 24, wherein the anti-PD-L1 antibody comprises a constant region derived from a human or murine antibody.

26. The nucleic acid of Claim 25, wherein the constant region is IgG1.

27. The nucleic acid of Claim 26, which is SEQ ID NO: 30 for the heavy chain, and SEQ ID NO: 31 for the light chain.

28. A vector comprising the nucleic acid of any of claims 24-27.

29. A host cell comprising the vector of Claim 28.

30. The host cell of Claim 29 which is eukaryotic.

31. The host cell of Claim 29 which is mammalian.

32. The host cell of Claim 31 which is a Chinese Hamster Ovary (CHO) cell.

33. The host cell of Claim 29 which is prokaryotic.

34. The host cell of Claim 33 which is *E. coli*.

35. A process for making an anti-PD-L1 antibody or antigen binding fragment thereof comprising culturing the host cell of any of Claims 29-34 under conditions suitable for the expression of the vector encoding the anti-PD-L1 antibody or antigen binding fragment, and recovering the antibody or fragment.

36. A kit comprising the composition of Claim 23 and at least one further therapeutic agent or vaccine for use in the treatment of cancer.

37. The kit according to Claim 36, wherein the further therapeutic agent is a chemotherapeutic agent.

38. The kit according to Claim 37, wherein the chemotherapeutic agent is gemcitabine.

39. The kit according to Claim 37, wherein the chemotherapeutic agent is cyclophosphamide.

40. The kit according to Claim 37, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.

41. The use of an effective amount of an anti-PD-L1 antibody of any of Claims 1-22 which induces antibody dependent cell-mediated cytotoxicity (ADCC) in the manufacture of a medicament for the treatment of cancer.

42. The use of Claim 41 wherein the constant region of the anti-PD-L1 antibody is IgG1.

43. The use of an effective amount of the composition of Claim 23 in the manufacture of a medicament for the treatment of cancer.

44. The use of any of Claims 41-43 wherein the cancer is selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

45. The use of an effective amount of the composition of Claim 23 in the manufacture of a medicament for enhancing T-cell function, wherein the said composition is administered to a dysfunctional T-cell.

46. The use of the composition of Claim 23 in the manufacture of a medicament for treating a T-cell dysfunctional disorder.

47. The use of Claim 46, wherein the T-cell dysfunctional disorder is tumor immunity.

48. The use of Claim 47, wherein the tumor immunity results from a cancer selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

49. The use of any of Claims 41-48, wherein at least one further therapeutic agent or vaccine is to be administered.

50. The use of Claim 49, wherein the further therapeutic agent is a chemotherapeutic agent.

51. The use of Claim 50, wherein the chemotherapeutic agent is gemcitabine.

52. The use of Claim 50, wherein the chemotherapeutic agent is cyclophosphamide.

53. The use of Claim 50, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.

Patent Claims

1. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain and a light chain variable region sequence, wherein:
(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein further: (i) the HVR-H1 sequence is SYIMM (SEQ ID NO: 15); (ii) the HVR-H2 sequence is SIYPSGGITFYADTVKG (SEQ ID NO: 16); (iii) the HVR-H3 sequence is IKLGTVTTVDY (SEQ ID NO: 17);
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further: (iv) the HVR-L1 sequence is TGTSSDVGGYNYVS (SEQ ID NO: 18); (v) the HVR-L2 sequence is DVSNRPS (SEQ ID NO: 19); (vi) the HVR-L3 sequence is SSYTSSSTRV (SEQ ID NO: 20).

2. The antibody or antibody fragment of Claim 1 further comprising:
(a) variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)- (HVR-H3)-(HC-FR4), and
(b) variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)- (HVR-L3)-(LC-FR4).

3. The antibody or antibody fragment of Claim 2 wherein the framework sequences are derived from human consensus framework sequences.

4. The antibody or antibody fragment of Claim 2 wherein the framework sequences are derived from human germline framework sequences.

5. The antibody or antibody fragment of Claim 2 wherein one or more of the framework sequences is the following:
HC-FR1 is EVQLLESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO:4);
HC-FR2 is WVRQAPGKGLEWVS (SEQ ID NO:5);
HC-FR3 is RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:6);

HC-FR4 is WGQGTLVTVSS (SEQ ID NO:7).

6. The antibody or antibody fragment of Claim 2 wherein one or more of the framework sequences is the following:
LC-FR1 is QSALTQPASVSGSPGQSITISC (SEQ ID NO: 11);
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LC-FR3 is GVSNRFSGSKSGNTASLTISGLQAEDEADYYC; (SEQ ID NO: 13);
LC-FR4 is FGTGTKVTVL (SEQ ID NO: 14).

7. The antibody or antibody fragment of Claim 2 wherein:
(a) the variable heavy chain framework sequences are the following:
(i) HC-FR1 is EVQLLESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO:4);
(ii) HC-FR2 is WVRQAPGKGLEWVS (SEQ ID NO: 5);
(iii) HC-FR3 is RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:6);
(iv) HC-FR4 is WGQGTLVTVSS (SEQ ID NO: 7); and
(b) the variable light chain framework sequences are the following:
(i) LC-FR1 is QSALTQPASVSGSPGQSITISC (SEQ ID NO:11);
(ii) LC-FR2 is WYQQHPGKAPKLMIY (SEQ ID NO: 12);
(iii) LC-FR3 is GVSNRFSGSKSGNTASLTISGLQAEDEADYYC (SEQ ID NO: 13);
(iv) LC-FR4 is FGTGTKVTVL (SEQ ID NO: 14).

8. The antibody or antibody fragment of Claim 7 further comprising at least a C_H1 domain.

9. The antibody or antibody fragment of Claim 7 or 8 further comprising a C_L domain.

10. The antibody or antibody fragment of any of Claims 7-9 further comprising a C_H1, a C_H2 and a C_H3 domain.

11. The antibody or antibody fragment of Claim 7 further comprising a human or murine constant region.

12. The antibody or antibody fragment of Claim 11, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.

13. The antibody or antibody fragment of Claim 12 wherein the constant region is IgG1.

14. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain variable region sequence and light chain variable region sequence, wherein:
(a) the heavy chain comprises the sequence:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSG GITFYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQ GTLVTVSS (SEQ ID NO: 24), and
(b) the light chain comprises the sequence:
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL (SEQ ID NO: 25).

15. The antibody of Claim 14 wherein the antibody further comprises a C_H1, a C_H2, a C_H3 and a C_L domain.

16. The antibody of any of Claims 1-15 wherein the antibody binds to human, mouse or cynomolgus monkey PD-L1.

17. The antibody of any of Claims 1-16 wherein the antibody is capable of blocking the interaction between human, mouse or cynomolgus monkey PD-L1 and the respective human, mouse or cynomolgus monkey PD-1 receptors.

18. The antibody of any of Claims 1-17 wherein the antibody binds to human PD-L1 with a K_D of $5x10^{-9}$ M or less.

19. A composition comprising the anti-PD-L1 antibody or antigen binding fragment of any of Claims 1-18 and at least one pharmaceutically acceptable carrier.

20. An isolated nucleic acid encoding the light chain or a heavy chain sequence of an anti-PD-L1 antibody or antigen binding fragment of any of Claims 1-18.

21. The nucleic acid of Claim 20, wherein the anti-PD-L1 antibody comprises a constant region derived from a human or murine antibody.

22. The nucleic acid of Claim 21, wherein the constant region is IgG1.

23. The nucleic acid of Claim 22, which is SEQ ID NO: 30 for the heavy chain, and SEQ ID NO: 31 for the light chain.

24. A vector comprising the nucleic acid of any of claims 20-23.

25. A host cell comprising the vector of Claim 24.

26. The host cell of Claim 25 which is eukaryotic.

27. The host cell of Claim 25 which is mammalian.

28. The host cell of Claim 27 which is a Chinese Hamster Ovary (CHO) cell.

29. The host cell of Claim 25 which is prokaryotic.

30. The host cell of Claim 29 which is *E. coli*.

31. A process for making an anti-PD-L1 antibody or antigen binding fragment thereof comprising culturing the host cell of any of Claims 25-30 under conditions suitable for the expression of the vector encoding the anti-PD-L1 antibody or antigen binding fragment, and recovering the antibody or fragment.

32. A kit comprising the composition of Claim 19 and at least one further therapeutic agent or vaccine for use in the treatment of cancer.

33. The kit according to Claim 32, wherein the further therapeutic agent is a chemotherapeutic agent.

34. The kit according to Claim 33, wherein the chemotherapeutic agent is gemcitabine.

35. The kit according to Claim 33, wherein the chemotherapeutic agent is cyclophosphamide.

36. The kit according to Claim 33, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.

37. The use of an effective amount of an anti-PD-L1 antibody of any of Claims 1-18 which induces antibody dependent cell-mediated cytotoxicity (ADCC) in the manufacture of a medicament for the treatment of cancer.

38. The use of Claim 37 wherein the constant region of the anti-PD-L1 antibody is IgG1.

39. The use of an effective amount of the composition of Claim 19 in the manufacture of a medicament for the treatment of cancer.

40. The use of any of Claims 37-39 wherein the cancer is selected from the group consisting of: breast, lung, colon, ovarian, melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

41. The use of any of Claims 37-40, wherein at least one further therapeutic agent or vaccine is to be administered.

42. The use of Claim 41, wherein the further therapeutic agent is a chemotherapeutic agent.

43. The use of Claim 42, wherein the chemotherapeutic agent is gemcitabine.

44. The use of Claim 42, wherein the chemotherapeutic agent is cyclophosphamide.

45. The use of Claim 42, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.