Patent Claims

1. An isolated heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein:
(a) the HVR-H1 sequence is $X_1YX_2MX_3$ (SEQ ID NO:1);
(b) the HVR-H2 sequence is SIYPSGGX_4TFYADX_5VKG (SEQ ID NO:2);
(c) the HVR-H3 sequence is IKLGTVTTVX_6Y (SEQ ID NO:3);
further wherein: X_1 is K, R, T, Q, G, A, W, M, I or S; X_2 is V, R, K, L, M or I; X_3 is H, T, N, Q, A, V, Y, W, F or M; X_4 is F or I; X_5 is S or T; X_6 is E or D.

2. The polypeptide of Claim 1 wherein X_1 is M, I or S; X_2 is R, K, L, M or I; X_3 is F or M; X_4 is F or I; X_5 is S or T; X_6 is E or D.

3. The polypeptide of Claim 1 wherein X_1 is M, I or S; X_2 is L, M or I; X_3 is F or M; X_4 is I; X_5 is S or T; X_6 is D.

4. The polypeptide of Claim 1 wherein X_1 is S; X_2 is I; X_3 is M; X_4 is I; X_5 is T; X_6 is D.

5. The polypeptide of any of Claims 1-4 further comprising 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).

6. The polypeptide of Claim 5 wherein the framework sequences are derived from human consensus framework sequences.

7. The polypeptide of Claim 5 wherein the framework sequences are derived from human germline framework sequences.

8. The polypeptide of Claim 5 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).

9. The polypeptide of Claim 8 further comprising at least a C_H1 domain.

10. The polypeptide of Claim 9 further comprising a C_H1, a C_H2 and a C_H3 domain.

11. The isolated heavy chain polypeptide of any of Claims 1-10 in combination with a variable region light chain comprising an HVR-L1, HVR-L2 and HVR-L3, wherein:
(a) the HVR-L1 sequence is $TGTX_7X_8DVGX_9YNYVS$ (SEQ ID NO: 8);
(b) the HVR-L2 sequence is $X_{10}VX_{11}X_{12}RPS$ (SEQ ID NO: 9);
(c) the HVR-L3 sequence is $SSX_{13}TX_{14}X_{15}X_{16}X_{17}RV$ (SEQ ID NO: 10);
further wherein: X_7 is N or S; X_8 is T, R or S; X_9 is A or G; X_{10} is E or D; X_{11} is I, N or S; X_{12} is D, H or N; X_{13} is F or Y; X_{14} is N or S; X_{15} is R, T or S; X_{16} is G or S; X_{17} is I or T.

12. The polypeptide of Claim 11 wherein X_7 is N or S; X_8 is T, R or S; X_9 is A or G; X_{10} is E or D; X_{11} is N or S; X_{12} is N; X_{13} is F or Y; X_{14} is S; X_{15} is S; X_{16} is G or S; X_{17} is T.

13. The polypeptide of Claim 11 wherein X_7 is S; X_8 is S; X_9 is G; X_{10} is D; X_{11} is S; X_{12} is N; X_{13} is Y; X_{14} is S; X_{15} is S; X_{16} is S; X_{17} is T.

14. The polypeptide of any of Claims 11-13 further comprising 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).

15. The polypeptide of Claim 14 wherein the framework sequences are derived from human consensus framework sequences.

16. The polypeptide of Claim 14 wherein the framework sequences are derived from human germline framework sequences.

17. The polypeptide of Claim 14 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).

18. The polypeptide of claim 17 further comprising a C_L domain.

19. 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 $X_1YX_2MX_3$ (SEQ ID NO: 1); (ii) the HVR-H2 sequence is SIYPSGGX_4TFYADX_5VKG (SEQ ID NO: 2); (iii) the HVR-H3 sequence is IKLGTVTTVX_6Y, and (SEQ ID NO: 3);
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further: (iv) the HVR-L1 sequence is TGTX_7X_8DVGX_9YNYVS (SEQ ID NO: 8); (v) the HVR-L2 sequence is $X_{10}VX_{11}X_{12}$RPS (SEQ ID NO: 9); (vi) the HVR-L3 sequence is SSX_{13}T$X_{14}X_{15}X_{16}X_{17}$RV (SEQ ID NO: 10);
wherein further: X_1 is K, R, T, Q, G, A, W, M, I or S; X_2 is V, R, K, L, M or I; X_3 is H, T, N, Q, A, V, Y, W, F or M; X_4 is F or I; X_5 is S or T; X_6 is E or D; X_7 is N or S; X_8 is T, R or S; X_9 is A or G; X_{10} is E or D; X_{11} is I, N or S; X_{12} is D, H or N; X_{13} is F or Y; X_{14} is N or S; X_{15} is R, T or S; X_{16} is G or S; X_{17} is I or T.

20. The antibody or antibody fragment of Claim 19 wherein X_1 is M, I or S; X_2 is R, K, L, M or I; X_3 is F or M; X_4 is F or I; X_5 is S or T; X_6 is E or D; X_7 is N or S; X_8 is T, R or S; X_9 is A or G; X_{10} is E or D; X_{11} is N or S; X_{12} is N; X_{13} is F or Y; X_{14} is S; X_{15} is S; X_{16} is G or S; X_{17} is T.

21. The antibody or antibody fragment of Claim 19, wherein X_1 is M, I or S; X_2 is L, M or I; X_3 is F or M; X_4 is I; X_5 is S or T; X_6 is D; X_7 is N or S; X_8 is T, R or S; X_9 is A or G; X_{10} is E or D; X_{11} is N or S; X_{12} is N; X_{13} is F or Y; X_{14} is S; X_{15} is S; X_{16} is G or S; X_{17} is T.

22. The antibody or antibody fragment of Claim 19, wherein X_1 is S; X_2 is I; X_3 is M; X_4 is I; X_5 is T; X_6 is D; X_7 is S; X_8 is S; X_9 is G; X_{10} is D; X_{11} is S; X_{12} is N; X_{13} is Y; X_{14} is S; X_{15} is S; X_{16} is S; X_{17} is T.

23. The antibody or antibody fragment of any of Claims 19-22 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).

24. The antibody or antibody fragment of Claim 23 wherein the framework sequences are derived from human consensus framework sequences.

25. The antibody or antibody fragment of Claim 23 wherein the framework sequences are derived from human germline framework sequences.

26. The antibody or antibody fragment of Claim 23 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).

27. The antibody or antibody fragment of Claim 23 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).

28. The antibody or antibody fragment of Claim 23 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).

29. The antibody or antibody fragment of Claim 28 further comprising at least a C_H1 domain.

30. The antibody or antibody fragment of Claim 28 or 29 further comprising a C_L domain.

31. The antibody or antibody fragment of any of Claims 28-30 further comprising a C_H1, a C_H2 and a C_H3 domain.

32. The antibody or antibody fragment of Claim 28 further comprising a human or murine constant region.

33. The antibody or antibody fragment of Claim 32, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.

34. The antibody or antibody fragment of Claim 33 wherein the constant region is IgG1.

35. An 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 an HVR-H3, having at least 80% overall sequence identity to SYIMM (SEQ ID NO: 15), SIYPSGGITFYADTVKG

(SEQ ID NO: 16) and IKLGTVTTVDY (SEQ ID NO: 17), respectively, and
(b) the light chain comprises an HVR-L1, HVR-L2 and an HVR-L3, having at least 80% overall sequence identity to TGTSSDVGGYNYVS (SEQ ID NO: 18), DVSNRPS (SEQ ID NO: 19) and SSYTSSSTRV (SEQ ID NO: 20), respectively.

36. The antibody or antibody fragment of Claim 35, wherein the sequence identity is at least 90%.

37. The antibody or antibody fragment of Claim 35, wherein, as compared to the sequences of HVR-H1 (SEQ ID NO: 15), HVR-H2 (SEQ ID NO: 16) and HVR-H3 (SEQ ID NO: 17), at least those amino acids remain unchanged that are highlighted by underlining as follows:
(a) in HVR-H1 SYIMM (SEQ ID NO: 15),
(b) in HVR-H2 SIYPSGGITFYADTVKG (SEQ ID NO: 16),
(c) in HVR-H3 IKLGTVTTVDY (SEQ ID NO: 17);
and further wherein, as compared to the sequences of HVR-L1 (SEQ ID NO: 18), HVR-L2 (SEQ ID NO: 19) and HVR-L3 (SEQ ID NO: 20 at least those amino acids remain unchanged that are highlighted by underlining as follows:
(a) HVR-L1 TGTSSDVGGYNYVS (SEQ ID NO: 18)
(b) HVR-L2 DVSNRPS (SEQ ID NO: 19)
(c) HVR-L3 SSYTSSSTRV (SEQ ID NO: 20).

38. The antibody or antibody fragment of any of Claims 35-37 further comprising:
(a) variable region heavy chain (VH) 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 (VL) framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formulat: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)- (HVR-L3)-(LC-FR4).

39. The antibody or antibody fragment of Claim 38, wherein the VH and VL framework sequences are derived from human germline sequences.

40. The antibody or antibody fragment of Claim 38 wherein the VH framework sequences are 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).

41. The antibody or antibody fragment of Claim 38 wherein the VL framework sequences are 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).

42. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain variable region sequence and a light chain variable region sequence, wherein:
(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSG GITFYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQ GTLVTVSS (SEQ ID NO: 24), and
(b) the light chain sequence has at least 85% sequence identity to the light chain sequence:
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSN RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL (SEQ ID NO: 25).

43. The antibody or antigen binding fragment of Claim 42, wherein the sequence identity is at least 90%.

44. 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:
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSN
RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL
(SEQ ID NO: 25).

45. The antibody of Claim 44 wherein the antibody further comprises a C_H1, a C_H2, a C_H3 and a C_L domain.

46. The antibody of any of Claims 19-45 wherein the antibody binds to human, mouse or cynomolgus monkey PD-L1.

47. The antibody of any of Claims 19-46 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.

48. The antibody of any of Claims 19-47 wherein the antibody binds to human PD-L1 with a K_D of $5x10^{-9}$ M or less.

49. 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).

50. The isolated anti-PD-L1 antibody or antigen binding fragment of claim 49 wherein the functional epitope further comprises residues E58, E60, Q66, R113 and M115 of human PD-L1 (SEQ ID NO:28).

51. 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).

52. 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 19-51.

53. A composition comprising the anti-PD-L1 antibody or antigen binding fragment of any of Claims 19-52 and at least one pharmaceutically acceptable carrier.

54. An isolated nucleic acid encoding the polypeptide of any of Claims 1-18.

55. 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 19-52.

56. An isolated nucleic acid encoding a light chain or a heavy chain variable sequence of an anti-PD-L1 antibody or antigen binding fragment, wherein:
(a) the heavy chain comprises an HVR-H1, HVR-H2 and an HVR-H3 sequence having at least 80% sequence identity to SYIMM (SEQ ID NO: 15), SIYPSGGITFYADTVKG (SEQ ID NO: 16) and IKLGTVTTVDY (SEQ ID NO: 17), respectively, or
(b) the light chain comprises an HVR-L1, HVR-L2 and an HVR-L3 sequence having at least 80% sequence identity to TGTSSDVGGYNYVS (SEQ ID NO: 18), DVSNRPS (SEQ ID NO: 19) and SSYTSSSTRV (SEQ ID NO: 20), respectively.

57. The nucleic acid of Claim 56, wherein sequence identity is at least 90%.

58. The nucleic acid of Claim 56 or 57, wherein the anti-PD-L1 antibody further comprises a VL and a VH framework region derived from a human germline sequence.

59. The nucleic acid of any of Claims 55-57, wherein the anti-PD-L1 antibody comprises a constant region derived from a human or murine antibody.

60. The nucleic acid of Claim 59, wherein the constant region is IgG1.

61. The nucleic acid of Claim 60, which is SEQ ID NO: 30 for the heavy chain, and SEQ ID NO: 31 for the light chain.

62. A vector comprising the nucleic acid of any of claims 54-61.

63. A host cell comprising the vector of Claim 62.

64. The host cell of Claim 63 which is eukaryotic.

65. The host cell of Claim 63 which is mammalian.

66. The host cell of Claim 65 which is a Chinese Hamster Ovary (CHO) cell.

67. The host cell of Claim 63 which is prokaryotic.

68. The host cell of Claim 67 which is *E. coli*.

69. A process for making an anti-PD-L1 antibody or antigen binding fragment thereof comprising culturing the host cell of any of Claims 63-68 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.

70. A kit of parts comprising the composition of Claim 53 and at least one further therapeutic agent or vaccine.

71. A kit of parts according to Claim 70, wherein the further therapeutic agent is a chemotherapeutic agent.

72. The kit of parts according to Claim 71, wherein the chemotherapeutic agent is gemcitabine.

73. A kit of parts according to Claim 71, wherein the chemotherapeutic agent is cyclophosphamide.

74. A kit of parts according to Claim 71, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.

75. The kit of parts according to Claim 70, wherein the further therapeutic agent is cyclophosphamide and the vaccine is Stimuvax.

76. Use of an effective amount of an anti-PD-L1 antibody which induces antibody dependent cell-mediated cytotoxicity (ADCC) for the manufacture of a medicament for the treatment of cancer.

77. The use of Claim 76 wherein the constant region of the anti-PD-L1 antibody is IgG1.

78. The use of Claim 77 wherein the anti-PD-L1 antibody is an antibody of any of Claims 19-52.

79. Use of an effective amount of the composition of Claim 53 for the manufacture of a medicament for the treatment of cancer.

80. The use of any of Claims 76 - 79 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.

81. Use of an effective amount of the composition of Claim 53 for the manufacture of a medicament for enhancing T-cell function, wherein the said composition is administered to a dysfunctional T-cell.

82. Use of the composition of Claim 53 for the manufacture of a medicament for treating a T-cell dysfunctional disorder.

83. The use of Claim 82, wherein the T-cell dysfunctional disorder is tumor immunity.

84. The use of Claim 83, 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.

85. The use of any of Claims 76 - 84, wherein at least one further therapeutic agent or vaccine is administered.

86. The use of Claim 85, wherein the further therapeutic agent is a chemotherapeutic agent.

87. The use of Claim 86, wherein the chemotherapeutic agent is gemcitabine.

88. The use of Claim 86, wherein the chemotherapeutic agent is cyclophosphamide.

89. The use of Claim 86, wherein the chemotherapeutic agents are 5-fluorouracil and oxaliplatin.

90. The use of Claim 85, wherein the further therapeutic agent is cyclophosphamide and the vaccine is Stimuvax.

91. The use of any of Claims 76 - 90, wherein the method further comprises the application of a treatment regimen selected from the group consisting of: surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, angiogenesis inhibiton and palliative care.

92. The use of Claim 91, wherein the treatment regime is radiation therapy.

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.