

CLAIMS

What is claimed is:

1. ~~An antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues Ser78, Ser80, and Lys82 of human TIGIT.~~
2. ~~The antibody of claim 1, wherein the epitope comprises amino acid residues Ser80 and Lys82 of human TIGIT.~~
3. ~~The antibody of claim 1 or 2, wherein the epitope comprises amino acid residues Ser78, Ser80, and Lys82 of human TIGIT.~~
4. ~~The antibody of any one of claims 1-3, wherein the epitope further comprises amino acid residue Ala67 of human TIGIT.~~
5. ~~The antibody of any one of claims 1-4, wherein the epitope further comprises one or more additional amino acid residues selected from the group consisting of Glu60, Leu65, and Ile68 of human TIGIT.~~
6. ~~The antibody of any one of claims 1-5, wherein the epitope further comprises one or more additional amino acid residues selected from the group consisting of Gln56, Asn70, Leu73, and His111 of human TIGIT.~~
7. ~~The antibody of any one of claims 1-6, wherein the epitope further comprises one or more additional amino acid residues selected from the group consisting of Thr55, Asn58, Asp63, Gln64, His76, Ile77, and Pro79 of human TIGIT.~~
8. ~~The antibody of any one of claims 1-7, wherein the epitope consists of amino acid residues Thr55, Gln56, Asn58, Glu60, Asp63, Gln64, Leu65, Ala67, Ile68, Asn70, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.~~
9. ~~An antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues Thr55, Ser80, and Lys82 of human TIGIT.~~
10. ~~The antibody of claim 9, wherein the epitope comprises amino acid residue Lys82 of human TIGIT.~~
11. ~~The antibody of claim 9 or 10, wherein the epitope comprises amino acid residues Thr55, Ser80, and Lys82 of human TIGIT.~~

12. ~~The antibody of any one of claims 9-11, wherein the epitope further comprises amino acid residue Gln56 of human TIGIT.~~

13. ~~The antibody of any one of claims 9-12, wherein the epitope further comprises amino acid residue Ile77 or Pro79 of human TIGIT.~~

14. ~~The antibody of claim 13, wherein the epitope further comprises amino acid residues Ile77 and Pro79 of human TIGIT.~~

15. ~~The antibody of any one of claims 9-14, wherein the epitope further comprises amino acid residue Asn58 or Glu60 of human TIGIT.~~

16. ~~The antibody of claim 15, wherein the epitope further comprises amino acid residues Asn58 and Glu60 of human TIGIT.~~

17. ~~The antibody of any one of claims 9-16, wherein the epitope further comprises one or more additional amino acid residues selected from the group consisting of Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT.~~

18. ~~The antibody of claim 17, wherein the epitope further comprises amino acid residues Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT.~~

19. ~~The antibody of any one of claims 9-18, wherein the epitope consists of Thr55, Gln56, Asn58, Glu60, Leu65, Ile68, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.~~

20. ~~An antibody that specifically binds to human TIGIT, wherein the antibody comprises a paratope comprising one or more amino acid residues selected from the group consisting of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues Tyr27d, Tyr92, Ser93, Thr94, and Phe96.~~

21. ~~The antibody of claim 20, wherein the paratope consists of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues Tyr27d, Tyr92, Ser93, Thr94, and Phe96.~~

22. ~~An antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more amino acid residues selected from the group consisting of Gln53, His111, and Tyr113 of human TIGIT.~~

23. ~~The antibody of claim 22, wherein the epitope further comprises Gln56 of human TIGIT.~~

24. ~~The antibody of claim 22 or 23, wherein the epitope further comprises Glu60, Leu65, Ile68, Asn70, Leu73, and His76 of human TIGIT.~~

25. ~~An antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six hypervariable regions (HVRs):~~

- ~~an HVR-H1 comprising the amino acid sequence of SNSAAWN (SEQ ID NO: 1);~~
- ~~an HVR-H2 comprising the amino acid sequence of KTYRFRKWYSDYAVSVKG (SEQ ID NO: 2);~~
- ~~an HVR-H3 comprising the amino acid sequence of ESTTYDLLAGPFDY (SEQ ID NO: 3);~~
- ~~an HVR-L1 comprising the amino acid sequence of KSSQTVLYSSNNKKYLA (SEQ ID NO: 4);~~
- ~~an HVR-L2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 5); and~~
- ~~an HVR-L3 comprising the amino acid sequence of QQYYSTPFT (SEQ ID NO: 6).~~

26. ~~The antibody of claim 25, wherein the antibody further comprises the following light chain variable region framework regions (FRs):~~

- ~~an FR-L1 comprising the amino acid sequence of DIVMTQSPDSLAVSLGERATING (SEQ ID NO: 7);~~
- ~~an FR-L2 comprising the amino acid sequence of WYQQKPGQPPNLLIY (SEQ ID NO: 8);~~
- ~~an FR-L3 comprising the amino acid sequence of GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC (SEQ ID NO: 9); and~~
- ~~an FR-L4 comprising the amino acid sequence of FGPGTKVEIK (SEQ ID NO: 10).~~

27. ~~The antibody of claim 25 or 26, wherein the antibody further comprises the following heavy chain variable region FRs:~~

- ~~an FR-H1 comprising the amino acid sequence of X₁VQLQQSGPGLVKPSQTLSTCAISGDSVS (SEQ ID NO: 11), wherein X₁ is Q or E;~~
- ~~an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12);~~
- ~~an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and~~
- ~~an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14).~~

28. ~~The antibody of claim 27, wherein the antibody further comprises the following heavy chain variable region FRs:~~

- ~~an FR-H1 comprising the amino acid sequence of EVQLQQSGPGLVKPSQTLSTCAISGDSVS (SEQ ID NO: 15);~~
- ~~an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12);~~
- ~~an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and~~
- ~~an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14).~~

29. ~~The antibody of claim 27, wherein the antibody further comprises the following heavy chain variable region FRs:~~

~~an FR-H1 comprising the amino acid sequence of QVQLQQSGPGLVKPSQTLSTCAISGDSVS (SEQ ID NO: 16);~~

5 ~~an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12);~~

~~an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and~~

~~an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 14).~~

10 30. ~~An antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six HVRs:~~

~~an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);~~

~~an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);~~

~~an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);~~

15 ~~an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);~~

~~an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and~~

~~an HVR-L3 comprising the amino acid sequence of QHLHGYPX_iN (SEQ ID NO: 22), wherein X_i is C or S.~~

20 31. ~~The antibody of claim 30, wherein antibody comprises the following six HVRs:~~

~~an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);~~

~~an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);~~

~~an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);~~

~~an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);~~

25 ~~an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and~~

~~an HVR-L3 comprising the amino acid sequence of QHLHGYPSN (SEQ ID NO: 23).~~

32. ~~The antibody of any one of claim 30 or 31, wherein the antibody further comprises the following heavy chain variable region FRs:~~

30 ~~an FR-H1 comprising the amino acid sequence of EVQLVQSGSDLKKPGASVRVSCASGYTFT (SEQ ID NO: 24);~~

~~an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25);~~

~~an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSSLKAEDTAVYFCAR (SEQ ID NO: 26); and~~

35 ~~an FR-H4 comprising the amino acid sequence of WGQGTMTVTVSS (SEQ ID NO: 27).~~

33. ~~The antibody of claim 30, wherein antibody comprises the following six HVRs:~~

~~an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);~~

40 ~~an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);~~

~~an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);
an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);
an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and
an HVR-L3 comprising the amino acid sequence of QHLHGYPGN (SEQ ID NO: 28).~~

34. ~~The antibody of claim 33, wherein the antibody further comprises the following heavy chain variable region FRs:~~

~~an FR-H1 comprising the amino acid sequence of QVQLVQSGSDLKKPGASVRVSCKASGYTFT (SEQ ID NO: 29);~~

~~an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25);~~

~~an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and~~

~~an FR-H4 comprising the amino acid sequence of WGQGTMTVSS (SEQ ID NO: 27).~~

35. ~~The antibody of any one of claims 30-34, wherein the antibody further comprises the following light chain variable region FRs:~~

~~an FR-L1 comprising the amino acid sequence of DIQLTQSPTFLSASVGDRVTITC (SEQ ID NO: 30);~~

~~an FR-L2 comprising the amino acid sequence of WYQQNPGKAPKLLIY (SEQ ID NO: 31);~~

~~an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTEFTLTISLQPEDFVITYC (SEQ ID NO: 32); and~~

~~an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 33).~~

36. ~~An antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34 or 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).~~

37. ~~The antibody of claim 36, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).~~

38. ~~The antibody of claim 36, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).~~

39. ~~An antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID~~

NO: 37; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 38; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

40. An antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 39; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 40; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

41. The antibody of any one of claims 1-21, 25-29, and 36-38, wherein the antibody is capable of binding to rabbit TIGIT.

42. The antibody of any one of claims 1-41, wherein the antibody is capable of binding to both human TIGIT and cynomolgus monkey (cyno) TIGIT, but not murine TIGIT.

43. The antibody of claim 42, wherein the antibody binds human TIGIT with a K_d of about 10 nM or lower and cyno TIGIT with a K_d of about 10 nM or lower.

44. The antibody of claim 43, wherein the antibody binds human TIGIT with a K_d of about 0.1 nM to about 1 nM and cyno TIGIT with a K_d of about 0.5 nM to about 1 nM.

45. The antibody of claim 44, wherein the antibody binds human TIGIT with a K_d of about 0.1 nM or lower and cyno TIGIT with a K_d of about 0.5 nM or lower.

46. The antibody of any one of claims 1-45, wherein the antibody is an antagonist antibody.

47. The antibody of claim 46, wherein the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR).

48. The antibody of claim 47, wherein the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR.

49. The antibody of any one of claims 46-48, wherein the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC₅₀ value of 10 nM or lower.

50. The antibody of any one of claims 46-49, wherein the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC₅₀ value of 1 nM to about 10 nM.

51. ~~The antibody of any one of claims 46-50, wherein the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 50 nM or lower.~~
52. ~~The antibody of claim 51, wherein the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 50 nM.~~
53. ~~The antibody of claim 52, wherein the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 5 nM.~~
54. ~~The antibody of any one of claims 1-45, wherein the antibody is an agonist antibody.~~
55. ~~The antibody of claim 54, wherein the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 or CD96.~~
56. ~~The antibody of claim 55, wherein the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 and CD96.~~
57. ~~The antibody of claim 56, wherein the agonist antibody specifically binds TIGIT and stimulates the interaction of human PVR with human CD226 and human CD96.~~
58. ~~The antibody of claim 56, wherein the agonist antibody specifically binds TIGIT and stimulates the interaction of cyno PVR with cyno CD226 and cyno CD96.~~
59. ~~An isolated antibody that competes for binding to TIGIT with the antibody of any one of claims 1-58.~~
60. ~~An isolated antibody that binds to the same epitope as the antibody of any one of claims 1-58.~~
61. ~~The antibody of any one of claims 1-60, wherein the antibody is monoclonal.~~
62. ~~The antibody of any one of claims 1-60, wherein the antibody is human, humanized, or chimeric.~~
63. ~~The antibody of claim 62, wherein at least a portion of the framework sequence is a human consensus framework sequence.~~
64. ~~The antibody of any one of claims 1-63, wherein the antibody is a full-length antibody.~~
65. ~~The antibody of any one of claims 1-64, wherein the antibody has a clearance following intravenous injection of about 3 ml/kg/day to about 10 ml/kg/day.~~

66. ~~The antibody of any one of claims 65, wherein the antibody has a clearance following intravenous injection of about 3 ml/kg/day to about 8 ml/kg/day.~~

5 67. ~~The antibody of any one of claims 1-63, wherein the antibody is an antibody fragment that binds TIGIT.~~

68. ~~The antibody of claim 67, wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, single chain variable fragment (scFv), and (Fab')₂ fragments.~~

10 69. ~~The antibody of any one of claims 1-68, wherein the antibody is an IgG class antibody.~~

70. ~~The antibody of claim 69, wherein the IgG class antibody is an IgG1 subclass antibody.~~

15 71. ~~A polynucleotide encoding the antibody of any one of claims 1-70.~~

72. ~~A vector comprising the polynucleotide of claim 71.~~

73. ~~A host cell comprising the vector of claim 72.~~

20 74. ~~The host cell of claim 73, wherein the host cell is prokaryotic.~~

75. ~~The host cell of claim 74, wherein the host cell is *Escherichia coli*.~~

25 76. ~~The host cell of claim 73, wherein the host cell is eukaryotic.~~

77. ~~The host cell of claim 76, wherein the host cell is a 293 cell, a CHO cell, a yeast cell, or a plant cell.~~

30 78. ~~A method of producing the antibody of any one of claims 1-70, the method comprising culturing the host cell of claim 73 in a culture medium.~~

79. ~~The method of claim 78, wherein the method further comprises recovering the antibody from the host cell or culture medium.~~

35 80. ~~An immunoconjugate comprising the antibody of any one of claims 1-70 and a cytotoxic agent.~~

81. ~~A composition comprising the antibody of any one of claims 1-70.~~

40 82. ~~The composition of claim 81, further comprising a pharmaceutically acceptable carrier, excipient, or diluent.~~

5

10

15

20

25

30

35

40

- ~~83. The composition of claim 82, wherein the composition is a pharmaceutical composition.~~
- ~~84. The composition of any one of claims 81-83, wherein the composition further comprises a PD-1 axis-binding antagonist or an additional therapeutic agent.~~
- ~~85. The antibody of any one of claims 1-70 for use as a medicament.~~
- ~~86. The antibody of any one of claims 1-70 for use in treating or delaying progression of a cancer in a subject in need thereof.~~
- ~~87. The antibody of claim 86, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy.~~
- ~~88. The antibody of claim 87, wherein the myeloma is multiple myeloma (MM).~~
- ~~89. The antibody of any one of claims 1-70 for use in treating or delaying progression of an immune-related disease in a subject in need thereof.~~
- ~~90. The antibody of claim 89, wherein the immune-related disease is associated with a T cell dysfunctional disorder.~~
- ~~91. The antibody of claim 90, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.~~
- ~~92. The antibody of any one of claims 89-91, wherein the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.~~
- ~~93. The antibody of any one of claims 1-70 for use in increasing, enhancing, or stimulating an immune response or function in a subject in need thereof.~~
- ~~94. Use of the antibody of any one of claims 1-70 in the manufacture of a medicament for treating or delaying progression of a cancer in a subject in need thereof.~~
- ~~95. The use of claim 94, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast~~

~~cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy.~~

5

~~96. The use of claim 95, wherein the myeloma is MM.~~

~~97. Use of the antibody of any one of claims 1-70 in the manufacture of a medicament for treating or delaying progression of an immune-related disease in a subject in need thereof.~~

10

~~98. The use of claim 97, wherein the immune-related disease is associated with a T cell dysfunctional disorder.~~

15

~~99. The use of claim 98, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.~~

~~100. The use of any one of claims 97-99, wherein the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.~~

20

~~101. Use of the antibody of any one of claims 1-70 in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in a subject in need thereof.~~

25

~~102. A method for treating or delaying progression of a cancer in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-70, thereby treating or delaying the progression of the cancer in the subject.~~

30

~~103. The method of claim 102, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy.~~

35

~~104. The method of claim 103, wherein the myeloma is MM.~~

40

~~105. A method for treating or delaying progression of an immune-related disease in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-70, thereby treating or delaying the progression of the immune-related disease in the subject.~~

~~106. The method of claim 105, wherein the immune-related disease is associated with a T cell dysfunctional disorder.~~

~~107. The method of claim 106, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.~~

~~108. The method of any one of claims 105-107, wherein the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.~~

~~109. A method of increasing, enhancing, or stimulating an immune response or function in a subject, the comprising administering to the subject an effective amount of the antibody of any one of claims 1-70, thereby increasing, enhancing, or stimulating an immune response or function in the subject.~~

~~110. The method of any one of 102-109, further comprising administering to the subject a PD-1 axis binding antagonist.~~

~~111. The method of claim 110, wherein the PD-1 axis binding antagonist is administered prior to or subsequent to the administration of the antibody.~~

~~112. The method of claim 110, wherein the PD-1 axis binding antagonist is administered concurrently with the antibody.~~

~~113. The method of any one of claims 110-112, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist.~~

~~114. The method of claim 113, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.~~

~~115. The method of claim 114, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.~~

~~116. The method of claim 115, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.~~

~~117. The method of claim 115, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.~~

~~118. The method of claim 115, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.~~

~~119. The method of any one of claims 115-118, wherein the PD-1 binding antagonist is an anti-PD-1 antibody.~~

~~120. The method of claim 115, wherein the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (pembrolizumab), CT-011 (pidilizumab), MEDI-0680 (AMP-514), PDR001, REGN2810, and BGB-108.~~

~~121. The method of claim 113, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.~~

~~122. The method of claim 121, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.~~

~~123. The method of claim 121, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.~~

~~124. The method of claim 121, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.~~

~~125. The method of claim 121-124, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.~~

~~126. The method of claim 125, wherein the anti-PD-L1 antibody is selected from the group consisting of: MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, MEDI4736 (durvalumab), and MSB0010718C (avolumab).~~

~~127. The method of claim 126, wherein the antibody is MPDL3280A.~~

~~128. The method of claim 113, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.~~

~~129. The method of claim 128, wherein the PD-L2 binding antagonist is an anti-PD-L2 antibody.~~

~~130. The method of claim 128, wherein the PD-L2 binding antagonist is an immunoadhesin.~~

~~131. The method of any one of claims 102-130, further comprising administering to the subject an OX40 binding agonist.~~

~~132. The method of claim 131, wherein the OX40 binding agonist is administered prior to or subsequent to the administration of the antibody and/or the PD-1 axis binding antagonist.~~

~~133. The method of claim 131, wherein the OX40 binding agonist is administered concurrently with the antibody and/or the PD-1 axis binding antagonist.~~

~~134. The method of any one of claims 131-133, wherein the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin.~~

~~135. The method of claim 134, wherein the OX40 agonist antibody depletes cells that express human OX40.~~

~~136. The method of claim 135, wherein the cells that express human OX40 are CD4⁺ effector T cells.~~

~~137. The method of claim 135, wherein the cells that express human OX40 are regulatory T (Treg) cells.~~

~~138. The method of any one of claims 135-137, wherein the depleting is by ADCC and/or phagocytosis.~~

~~139. The method of any one of claims 134-138, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 1 nM.~~

~~140. The method of claim 139, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM.~~

~~141. The method of claim 140, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM.~~

~~142. The method of any one of claims 134-141, wherein the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.3 µg/ml.~~

~~143. The method of claim 142, wherein the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.2 µg/ml.~~

~~144. The method of any one of claims 134-143, wherein the OX40 agonist antibody increases CD4⁺ effector T cell proliferation and/or increases cytokine production by the CD4⁺ effector T cell as compared to proliferation and/or cytokine production prior to treatment with the OX40 agonist antibody.~~

~~145. The method of any one of claims 134-144, wherein the OX40 agonist antibody increases memory T cell proliferation and/or cytokine production by a memory T cell.~~

~~146. The method of claim 144 or 145, wherein the cytokine production is IFN- γ production.~~

~~147. The method of any one of claims 134-146, wherein the OX40 agonist antibody inhibits Treg function.~~

~~148. The method of claim 147, wherein the OX40 agonist antibody inhibits Treg suppression of effector T cell function.~~

~~149. The method of claim 148, wherein effector T cell function is effector T cell proliferation and/or cytokine production.~~

~~150. The method of claim 148 or 149, wherein the effector T cell is a CD4⁺ effector T cell.~~

~~151. The method of any one of claims 134-150, wherein the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40.~~

~~152. The method of claim 151, wherein OX40 signal transduction is detected by monitoring NF κ B downstream signaling.~~

~~153. The method of any one of claims 134-152, wherein the OX40 agonist antibody comprises a variant IgG1-Fc polypeptide comprising a mutation that eliminates binding to human effector cells and has diminished activity relative to the OX40 agonist antibody comprising a native sequence IgG1-Fc portion.~~

~~154. The method of claim 153, wherein the OX40 agonist antibody comprises a variant IgG1-Fc polypeptide comprising a DANA mutation.~~

~~155. The method of any one of claims 134-154, wherein the OX40 agonist antibody comprises (a) a VH domain comprising (i) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278, 279, or 280, (ii) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281, 282, 283, 284, 285, or 286, and (iii) a HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 287, 288, or 289; and (b) a VL domain comprising (i) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290, (ii) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291, and (iii) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 292, 293, 294, 295, 296, 297, 298, or 299.~~

~~156. The method of claim 155, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 292.~~

157. The method of claim 155, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 297.

158. The method of claim 155, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 298.

159. The method of any one of claims 134-158, wherein the OX40 agonist antibody comprises a VH sequence having at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 300-325.

160. The method of claim 159, wherein the OX40 agonist antibody comprises a VH sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 300.

161. The method of claim 160, wherein a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 300.

162. The method of any one of claims 159-161, wherein the OX40 agonist antibody comprises a VH comprising one, two, or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287.

163. The method of any one of claims 134-162, wherein the OX40 agonist antibody comprises a VL sequence having at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 326-351.

164. The method of claim 163, wherein the OX40 agonist antibody comprises a VL having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 326.

165. The method of claim 164, wherein a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 326.

166. The method of any one of claims 162-165, wherein the OX40 agonist antibody comprises a VL comprising one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of

SEQ ID NO: 290; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 292.

167. The method of any one of claims 134-166, wherein the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 300; (b) a VL sequence of SEQ ID NO: 326; or (c) a VH sequence as in (a) and a VL sequence as in (b).

168. The method of any one of claims 134-166, wherein the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 319; (b) a VL sequence of SEQ ID NO: 345; or (c) a VH sequence as in (a) and a VL sequence as in (b).

169. The method of any one of claims 134-166, wherein the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 320; (b) a VL sequence of SEQ ID NO: 346; or (c) a VH sequence as in (a) and a VL sequence as in (b).

170. The method of any one of claims 134-154, wherein the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562.

171. The method of any one of claims 134-170, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

172. The method of claim 134, wherein the OX40 immunoadhesin is a trimeric OX40-Fc protein.

173. The method of any one of claims 102-172, further comprising administering to the subject an agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

174. The method of claim 173, wherein the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.

175. The method of any one of claims 102-174, further comprising administering to the subject an additional therapeutic agent.

176. The method of claim 175, wherein the additional therapeutic agent is a chemotherapeutic agent.

177. The method of any one of claims 102-176, wherein the antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

178. The method of any one of claims 102-177, wherein the subject is a human.

~~179. A kit comprising the antibody of any one of claims 1-70 and a package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject.~~

~~180. A kit comprising the antibody of any one of claims 1-70 and a package insert comprising instructions for using the antibody for treating or delaying progression of an immune-related disease in a subject.~~

~~181. A kit comprising the antibody of any one of claims 1-70 and a package insert comprising instructions for increasing, enhancing, or stimulating an immune response or function in a subject.~~

~~182. The kit of any one of claims 179-181, wherein the subject is a human.~~

1. An antibody that specifically binds to human T-cell immunoreceptor with Ig and ITIM domains (TIGIT), wherein the antibody comprises the following six hypervariable regions (HVRs):

an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);

an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);

an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);

an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);

an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and

an HVR-L3 comprising the amino acid sequence of QHLHGYPX₁N (SEQ ID NO: 22), wherein X₁ is C or S.

2. The antibody of claim 1, wherein antibody comprises the following six HVRs:

an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);

an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);

an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);

an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);

an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and

an HVR-L3 comprising the amino acid sequence of QHLHGYPSN (SEQ ID NO: 23).

3. The antibody of any one of claim 1 or 2, wherein the antibody further comprises the following heavy chain variable region framework regions (FRs):

an FR-H1 comprising the amino acid sequence of EVQLVQSGSDLKKPGASVRVSKASGYTFT (SEQ ID NO: 24);

an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25);

an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and

an FR-H4 comprising the amino acid sequence of WGQGTMTVTVSS (SEQ ID NO: 27).

4. The antibody of claim 1, wherein antibody comprises the following six HVRs:

an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17);

an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18);

an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19);
an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20);
an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and
an HVR-L3 comprising the amino acid sequence of QHLHGYPNC (SEQ ID NO: 28).

5
5. The antibody of claim 4, wherein the antibody further comprises the following heavy chain variable region FRs:

10 an FR-H1 comprising the amino acid sequence of QVQLVQSGSDLKKPGASVRVSCASGYTFT (SEQ ID NO: 29);

an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25);

an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and

15 an FR-H4 comprising the amino acid sequence of WGQGTMTVSS (SEQ ID NO: 27).

6. The antibody of any one of claims 1-5, wherein the antibody further comprises the following light chain variable region FRs:

an FR-L1 comprising the amino acid sequence of DIQLTQSPTFLSASVGDRVITTC (SEQ ID NO: 30);

an FR-L2 comprising the amino acid sequence of WYQQNPGKAPKLLIY (SEQ ID NO: 31);

20 an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTEFTLTISLQPEDFVITYC (SEQ ID NO: 32); and

an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 33).

25 7. The antibody of any one of claims 1-6, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 37 and (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 38.

30 8. An antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a VH having the amino acid sequence of SEQ ID NO: 37 and (b) a VL having the amino acid sequence of SEQ ID NO: 38.

35 9. The antibody of any one of claims 1-8, wherein the antibody is capable of binding to both human TIGIT and cynomolgus monkey (cyno) TIGIT, wherein optionally the antibody binds human TIGIT with a Kd of about 10 nM or lower and cyno TIGIT with a Kd of about 10 nM or lower.

40 10. The antibody of any one of claims 1-9, wherein the antibody is an antagonist antibody; wherein optionally the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR); and wherein optionally the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR.

11. The antibody of claim 10, wherein (i) the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 10 nM or lower; wherein optionally (ii) the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 1 nM to about 10 nM; and wherein optionally (iii) the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 50 nM or lower.

12. The antibody of claim 11, wherein the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 50 nM; wherein optionally the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 5 nM.

13. The antibody of any one of claims 1-12, wherein the antibody is monoclonal.

14. The antibody of any one of claims 1-12, wherein the antibody is human, humanized, or chimeric; wherein optionally at least a portion of the framework sequence is a human consensus framework sequence.

15. The antibody of any one of claims 1-14, wherein the antibody is a full-length antibody.

16. The antibody of any one of claims 1-15, wherein the antibody has a clearance following intravenous injection of about 3 ml/kg/day to about 10 ml/kg/day.

17. The antibody of any one of claims 1-14, wherein the antibody is an antibody fragment that binds TIGIT; wherein optionally the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, single chain variable fragment (scFv), and (Fab')₂ fragments.

18. The antibody of any one of claims 1-16, wherein the antibody is an IgG class antibody; wherein optionally the IgG class antibody is an IgG1 subclass antibody.

19. A polynucleotide encoding the antibody of any one of claims 1-18.

20. A vector comprising the polynucleotide of claim 19.

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

22. The host cell of claim 21, wherein the host cell is: (a) prokaryotic, wherein optionally the host cell is *Escherichia coli*; or (b) eukaryotic, wherein optionally the host cell is a 293 cell, a CHO cell, a yeast cell, or a plant cell.

23. A method of producing the antibody of any one of claims 1-18, the method comprising culturing the host cell of claim 21 or 22 in a culture medium.

24. The method of claim 23, wherein the method further comprises recovering the antibody from the host cell or culture medium.

25. A composition comprising the antibody of any one of claims 1-18.

26. The composition of claim 25, further comprising a pharmaceutically acceptable carrier, excipient, or diluent; wherein optionally the composition is a pharmaceutical composition.

27. The composition of claim 25 or 26, wherein the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

28. The antibody of any one of claims 1-18 for use as a medicament.

29. The antibody of any one of claims 1-18 for use in treating or delaying progression of a cancer in a subject in need thereof.

30. The antibody for use of claim 29, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycosis fungoides, a Merkel cell cancer, and a hematologic malignancy; wherein optionally the myeloma is multiple myeloma (MM).

31. Use of the antibody of any one of claims 1-18 in the manufacture of a medicament for treating or delaying progression of a cancer.

32. The use of claim 31, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycosis fungoides, a Merkel cell cancer, and a hematologic malignancy; wherein optionally the myeloma is MM.

33. The use of claim 31 or 32, wherein the medicament is to be administered with a PD-1 axis binding antagonist; wherein optionally the PD-1 axis binding antagonist is to be administered prior to or subsequent to the administration of the antibody, or concurrently with the antibody.

34. The use of claim 33, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist; wherein optionally the PD-L1 binding antagonist is an anti-PD-L1 antibody.

35. The use of claim 34, wherein the anti-PD-L1 antibody is atezolizumab.

36. The use of any one of claims 31-35, wherein the medicament is to be administered with an additional therapeutic agent; wherein optionally the additional therapeutic agent is a chemotherapeutic agent.

5

37. The use of any one of claims 31-36, wherein the antibody is to be administered subcutaneously or intravenously.

38. A kit comprising the antibody of any one of claims 1-18 and a package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject.

10