

WHAT IS CLAIMED:

1. An isolated multispecific antibody that specifically binds to human OX40, wherein the antibody comprises:
 - (a) a first antigen-binding domain that specifically binds to human OX40; comprising:
 - (i) a heavy chain variable domain (VH)-complementarity determining region (CDR) 1 comprising the amino acid sequence of GSAMH (SEQ ID NO:47);
 - (ii) a VH-CDR2 comprising the amino acid sequence of RIRSKANSYATAYAASVKG (SEQ ID NO:48);
 - (iii) a VH-CDR3 comprising the amino acid sequence of GIYDSSGYDY (SEQ ID NO:49);
 - (iv) a light chain variable domain (VL)-CDR1 comprising the amino acid sequence of RSSQSLHSHNGYNYLD (SEQ ID NO:50);
 - (v) a VL-CDR2 comprising the amino acid sequence of LGSNRAS (SEQ ID NO:51); and
 - (vi) a VL-CDR3 comprising the amino acid sequence of MQGSKWPLT (SEQ ID NO:52) or MQALQTPLT (SEQ ID NO:53); and
 - (b) a second antigen-binding domain.
2. An isolated multispecific antibody that specifically binds to human OX40, wherein the antibody comprises:
 - (a) a first antigen-binding domain that specifically binds to the same epitope of human OX40 as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:54 and a VL comprising the amino acid sequence of SEQ ID NO:55 or 56; and
 - (b) a second antigen-binding domain.
3. An isolated multispecific antibody that specifically binds to human OX40, wherein the antibody comprises:
 - (a) a first antigen-binding domain that specifically binds to human OX40 and exhibits, as

compared to binding to a human OX40 sequence of SEQ ID NO:72, reduced or absent binding to a protein identical to SEQ ID NO:72 except for the presence of an amino acid mutation selected from the group consisting of: N60A, R62A, R80A, L88A, P93A, P99A, P115A, and a combination thereof, numbered according to SEQ ID NO: 72; and

(b) a second antigen-binding domain.

4. An isolated multispecific antibody that specifically binds to human OX40, wherein the antibody comprises:

(a) a first antigen-binding domain that specifically binds to human OX40 comprising a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO:54; and

(b) a second antigen-binding domain.

5. An isolated multispecific antibody that specifically binds to human OX40, wherein the antibody comprises:

(a) a first antigen-binding domain that specifically binds to human OX40 comprising a VH and a VL, wherein the VL comprises the amino acid sequence of SEQ ID NO:55 or SEQ ID NO:56;

(b) a second antigen-binding domain.

6. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:

(a) a first antigen-binding domain; and

(b) a second antigen-binding domain that specifically binds to human GITR comprising

(i) a VH-CDR1 comprising the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO:87), wherein X_1 is D, E or G; X_2 is A or V; and X_3 is Y or H;

(ii) a VH-CDR2 comprising the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO:88), wherein X_1 is V or L; X_2 is R, K or Q; X_3 is Y or F; X_4 is D, E or G; X_5 is V or L; X_6 is T or S; X_7 is K, R or Q; and X_8 is D, E or G;

- (iii) a VH-CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO:3);
 - (iv) a VL-CDR1 comprising the amino acid sequence of KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO:90), wherein X₁ is G or S; and X₂ is T or S;
 - (v) a VL-CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO:5); and
 - (vi) a VL-CDR3 comprising the amino acid sequence of QNX₁YSX₂PYT (SEQ ID NO:92), wherein X₁ is D or E; and X₂ is Y, F or S.
7. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
- (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to the same epitope of human GITR as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:18 and a VL comprising the amino acid sequence of SEQ ID NO:19.
8. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
- (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to an epitope of human GITR comprising at least one amino acid in residues 60-63 of SEQ ID NO:41.
9. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
- (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to each of i) human GITR comprising residues 26 to 241 of SEQ ID NO:41 and ii) a variant of cynomolgus GITR, the variant comprising residues 26-234 of SEQ ID NO:46, wherein the antibody does not

specifically bind to cynomolgus GITR comprising residues 26-234 of SEQ ID NO:44.

10. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
 - (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to human GITR and exhibits, as compared to binding to a human GITR sequence of residues 26 to 241 of SEQ ID NO:41, reduced or absent binding to a protein identical to residues 26 to 241 of SEQ ID NO:41 except for the presence of a D60A or G63A amino acid substitution, numbered according to SEQ ID NO:41.
11. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
 - (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to human GITR and comprises a VH and a VL, wherein the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:18, 20, 22, 24, and 25.
12. An isolated multispecific antibody that specifically binds to human GITR, wherein the antibody comprises:
 - (a) a first antigen-binding domain; and
 - (b) a second antigen-binding domain that specifically binds to human GITR and comprises a VH and a VL, wherein the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, 23, and 26.

13. The antibody of any one of claims 1-5, wherein the second antigen-binding domain specifically binds to a tumor necrosis factor receptor (TNFR) superfamily protein.
14. The antibody of claim 13, wherein the TNFR superfamily protein is selected from the group consisting of: GITR, CD137, DR3, CD40, BAFRR, CD27, and HVEM.
15. The antibody of any one of claims 6-12, wherein the first antigen-binding domain specifically binds to a TNFR superfamily protein.
16. The isolated antibody of claim 15, wherein the TNFR superfamily protein is selected from the group consisting of: OX40, CD137, DR3, CD40, BAFRR, CD27, and HVEM.
17. The antibody of any one of claims 1-5, 13, or 14, wherein the second antigen-binding domain specifically binds to human GITR.
18. The antibody of claim 17, wherein the second antigen-binding domain that specifically binds to human GITR comprises:
 - (i) a VH-CDR1 comprising the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO:87), wherein X_1 is D, E or G; X_2 is A or V; and X_3 is Y or H;
 - (ii) a VH-CDR2 comprising the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO:88), wherein X_1 is V or L; X_2 is R, K or Q; X_3 is Y or F; X_4 is D, E or G; X_5 is V or L; X_6 is T or S; X_7 is K, R or Q; and X_8 is D, E or G;
 - (iii) a VH-CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO:3);
 - (iv) a VL-CDR1 comprising the amino acid sequence of $KSSQSLNSX_1NQKNYLX_2$ (SEQ ID NO:90), wherein X_1 is G or S; and X_2 is T or S;
 - (v) a VL-CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO:5); and
 - (vi) a VL-CDR3 comprising the amino acid sequence of QNX_1YSX_2PYT (SEQ ID

NO:92), wherein X_1 is D or E; and X_2 is Y, F or S.

19. The antibody of claim 17 or 18, wherein the second antigen-binding domain that specifically binds to human GITR binds to the same epitope of human GITR as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:18 and a VL comprising the amino acid sequence of SEQ ID NO:19.
20. The antibody of any one of claims 17-19, wherein the second antigen-binding domain that specifically binds to human GITR binds to an epitope of human GITR comprising at least one amino acid in residues 60-63 of SEQ ID NO:41.
21. The antibody of any one of claims 17-20, wherein the second antigen-binding domain that specifically binds to human GITR binds to each of i) human GITR comprising residues 26 to 241 of SEQ ID NO:41 and ii) a variant of cynomolgus GITR, the variant comprising residues 26-234 of SEQ ID NO:46, wherein the second antigen-binding domain does not specifically bind to cynomolgus GITR comprising residues 26-234 of SEQ ID NO:44.
22. The antibody of any one of claims 17-21, wherein the second antigen-binding domain that specifically binds to human GITR exhibits, as compared to binding to a human GITR sequence of residues 26 to 241 of SEQ ID NO:41, reduced or absent binding to a protein identical to residues 26 to 241 of SEQ ID NO:41 except for the presence of a D60A or G63A amino acid substitution, numbered according to SEQ ID NO:41.
23. The antibody of any one of claims 17-22, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH and a VL, wherein the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:18, 20, 22, 24, and 25.
24. The antibody of any one of claims 17-23, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH and a VL, wherein the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, 23, and 26.

25. The antibody of any one of claims 6-12, 15, or 16, wherein the first antigen-binding domain specifically binds to human OX40.
26. The antibody of claim 25, wherein the first antigen-binding domain that specifically binds to human OX40 comprises:
- (i) a VH-CDR1 comprising the amino acid sequence of GSAMH (SEQ ID NO:47);
 - (ii) a VH-CDR2 comprising the amino acid sequence of RIRSKANSYATAYAASVKG (SEQ ID NO:48);
 - (iii) a VH-CDR3 comprising the amino acid sequence of GIYDSSGYDY (SEQ ID NO:49);
 - (iv) a VL-CDR1 comprising the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO:50);
 - (v) a VL-CDR2 comprising the amino acid sequence of LGSNRAS (SEQ ID NO:51); and
 - (vi) a VL-CDR3 comprising the amino acid sequence of MQGSKWPLT (SEQ ID NO:52) or MQALQTPLT (SEQ ID NO:53).
27. The antibody of claim 25 or 26, wherein the first antigen-binding domain that specifically binds to human OX40 binds to the same epitope of human OX40 as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:54 and a VL comprising the amino acid sequence of SEQ ID NO:55 or 56.
28. The antibody of any one of claims 25-27, wherein the first antigen-binding domain that specifically binds to human OX40 exhibits, as compared to binding to a human OX40 sequence of SEQ ID NO:72, reduced or absent binding to a protein identical to SEQ ID NO:72 except for the presence of an amino acid mutation selected from the group consisting of: N60A, R62A, R80A, L88A, P93A, P99A, P115A, and a combination thereof, numbered according to SEQ ID NO: 72.

29. The antibody of any one of claims 25-28, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO:54.
30. The antibody of any one of claims 25-29, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH and a VL, wherein the VL comprises the amino acid sequence of SEQ ID NO:55 or SEQ ID NO:56.
31. The antibody of any one of claims 6-12 or 25-30, wherein the second antigen-binding domain that specifically binds to human GITR comprises:
- (i) a VH-CDR1 comprising the amino acid sequence of X_1YAMX_2 (SEQ ID NO:1), wherein X_1 is D, G, or E; and X_2 is Y or H;
 - (ii) a VH-CDR2 comprising the amino acid sequence of $X_1IRTYSGX_2VX_3YNQKFX_4X_5$ (SEQ ID NO:2), wherein X_1 is V or L; X_2 is D or G; X_3 is T or S; X_4 is K, R, or Q; and X_5 is D, E, or G;
 - (iii) a VH-CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO:3);
 - (iv) a VL-CDR1 comprising the amino acid sequence of $KSSQSLN\text{SX}_1\text{NQKNYLT}$ (SEQ ID NO:4), wherein X_1 is G or S;
 - (v) a VL-CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO:5); and
 - (vi) a VL-CDR3 comprising the amino acid sequence of QNX_1YSX_2PYT (SEQ ID NO:6), wherein X_1 is D or E; and X_2 is Y or F.
32. The antibody of any one of claims 6-12 or 25-31, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH-CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:7-9.
33. The antibody of any one of claims 6-12 or 17-32, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH-CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:10-13.

34. The antibody of any one of claims 6-12 or 17-33, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL-CDR1 comprising the amino acid sequence of SEQ ID NO:14 or 15.
35. The antibody of any one of claims 6-12 or 17-34, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:16 or 17.
36. The antibody of any one of claims 6-12 or 17-35, wherein the second antigen-binding domain that specifically binds to human GITR comprises
VH-CDR1, VH-CDR2, and VH-CDR3 sequences set forth in SEQ ID NOs:7, 10, and 3; SEQ ID NOs:8, 11, and 3; SEQ ID NOs:9, 12, and 3; or SEQ ID NOs:9, 13, and 3, respectively; and/or
VL-CDR1, VL-CDR2, and VL-CDR3 sequences set forth in SEQ ID NOs:14, 5, and 16; or SEQ ID NOs:15, 5, and 17, respectively.
37. The antibody of any one of claims 6-12 or 17-36, wherein the second antigen-binding domain that specifically binds to human GITR comprises VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences set forth in SEQ ID NOs:7, 10, 3, 14, 5, and 16, respectively.
38. The antibody of any one of claims 6-12 or 17-37, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH comprising the amino acid sequence set forth in SEQ ID NO:25.
39. The antibody of any one of claims 6-12 or 17-38, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH comprising an amino acid sequence at least 75%, 80%, 85%, 90%, 95%, or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs:18, 20, 22, and 24.
40. The antibody of claim 39, wherein the second antigen-binding domain that specifically binds

to human GITR comprises a VH comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:18, 20, 22, and 24.

41. The antibody of claim 40, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH comprising the amino acid sequence of SEQ ID NO:18.
42. This antibody of claim 41, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:29, 30 and 36.
43. This antibody of claim 41, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:74, 75, and 81.
44. The antibody of any one of claims 6-10, 12, 15-22, or 24-35, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH comprising an amino acid sequence derived from a human IGHV1-2 germline sequence.
45. The antibody of any one of claims 6-12, 15-43 or 44, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL comprising the amino acid sequence of SEQ ID NO:26.
46. The antibody of any one of claims 6-12, 15-45, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL comprising an amino acid sequence at least 75%, 80%, 85%, 90%, 95%, or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, and 23.
47. The antibody of claim 46, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, and 23.
48. The antibody of claim 46, wherein the second antigen-binding domain that specifically binds

to human GITR comprises a VL comprising the amino acid sequence of SEQ ID NO:19.

49. The antibody of claim 48, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain comprising the amino acid sequence of SEQ ID NO:37.
50. The antibody of claim 48, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain comprising the amino acid sequence of SEQ ID NO:38.
51. The antibody of any one of claims 6-11, 13-23, 25-434 wherein the second antigen-binding domain that specifically binds to human GITR comprises a VL comprising an amino acid sequence derived from a human IGKV4-1 germline sequence.
52. The antibody of any one of claims 6-12, 15-43 or 45-50, wherein the second antigen-binding domain that specifically binds to human GITR comprises VH and VL sequences set forth in SEQ ID NOs:18 and 19, SEQ ID NOs:20 and 21, SEQ ID NOs:22 and 23, or SEQ ID NOs:24 and 23, respectively.
53. The antibody of claim 52, wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH comprising the sequence set forth in SEQ ID NO:18 and a VL comprising the sequence set forth in SEQ ID NO:19.
54. The antibody of claim 53, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:29 and a light chain comprising the amino acid sequence of SEQ ID NO:37.
55. The antibody of claim 53, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:74 and a light chain comprising the amino acid sequence of SEQ ID NO:37.
56. The antibody of claim 53, wherein the second antigen-binding domain that specifically binds

- to human GITR comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:30 and a light chain comprising the amino acid sequence of SEQ ID NO:37.
57. The antibody of claim 53, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:75 and a light chain comprising the amino acid sequence of SEQ ID NO:37.
58. The antibody of claim 44 or 51, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV1-2 germline sequence and a light chain variable region having an amino acid sequence derived from a human IGKV4-1 germline sequence.
59. The antibody of any one of claims 1-5, 13, 14, 17-58, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 99% identical to the amino acid sequence of SEQ ID NO:54.
60. The antibody of claim 59, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH comprising the amino acid sequence of SEQ ID NO:54.
61. The antibody of claim 60, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:59, 60, and 66.
62. The antibody of claim 60, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:118, 119, and 125.
63. The antibody of any one of claims 1-3, 5, 13, 14, 17-28, 30-58, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH comprising an amino acid sequence derived from a human IGHV3-73 germline sequence.

64. The antibody of any one of claims 1-5, 13, 14, 17-63, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL comprising an amino acid sequence at least 75%, 80%, 85%, 90%, 95%, or 99% identical to the amino acid sequence of SEQ ID NO:55 or SEQ ID NO:56.
65. The antibody of any one of claims 1-5, 13, 14, 17-64, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:52.
66. The antibody of any one of claims 1-5, 13, 14, 17-65, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL comprising the amino acid sequence of SEQ ID NO:55.
67. The antibody of claim 66, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO:67.
68. The antibody of claim 66, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO:68.
69. The antibody of any one of claims 1-5, 13, 14, 17-64, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:53.
70. The antibody of any one of claims 1-5, 13, 14, 17-64, or 69, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL comprising the amino acid sequence of SEQ ID NO:56.
71. The antibody of claim 70, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO:69.
72. The antibody of claim 70, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO:70.

73. The antibody of any one of claims 1-4, 13, 14, 17-29, 31-63, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VL comprising an amino acid sequence derived from a human IGKV2-28 germline sequence.
74. The antibody of any one of claims 1-5, 13, 14, 17-62 or 64-72, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the VH and VL sequences set forth in SEQ ID NOs:54 and 55 or SEQ ID NOs:54 and 56, respectively.
75. The antibody of claim 74, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:59 and a light chain comprising the amino acid sequence of SEQ ID NO:67 or 69.
76. The antibody of claim 74, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:118 and a light chain comprising the amino acid sequence of SEQ ID NO:67 or 69.
77. The antibody of claim 63 or 73, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH comprising an amino acid sequence derived from a human IGHV3-73 germline sequence and a VL comprising an amino acid sequence derived from a human IGKV2-28 germline sequence.
78. The antibody of any one of claims 74-76, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the VH sequence set forth in SEQ ID NO:54 and the VL sequence set forth in SEQ ID NO:55 or 56, and wherein the second antigen-binding domain that specifically binds to human GITR comprises the VH sequence set forth in SEQ ID NO:18 and the VL sequence set forth in SEQ ID NO:19.
79. The antibody of claim 78, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the heavy chain sequence set forth in SEQ ID NO:59 and the light chain sequence set forth in SEQ ID NO:67 or 69, and wherein the second antigen-binding domain that specifically binds to human GITR comprises the heavy chain sequence set forth

in SEQ ID NO:29 and the light chain sequence set forth in SEQ ID NO:37.

80. The antibody of claim 78, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the heavy chain sequence set forth in SEQ ID NO:118 and the light chain sequence set forth in SEQ ID NO:67 or 69, and wherein the second antigen-binding domain that specifically binds to human GITR comprises the heavy chain sequence set forth in SEQ ID NO:74 and the light chain sequence set forth in SEQ ID NO:37.
81. The antibody of any one of claims 78-80, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the light chain sequence set forth in SEQ ID NO:67.
82. The antibody of any one of claims 78-80, wherein the first antigen-binding domain that specifically binds to human OX40 comprises the light chain sequence set forth in SEQ ID NO:69.
83. The antibody of claim 77, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a VH derived from a human IGHV3-73 germline sequence and a VL derived from a human IGKV2-28 germline sequence, and wherein the second antigen-binding domain that specifically binds to human GITR comprises a VH derived from a human IGHV1-2 germline sequence and a VL derived from a human IGKV4-1 germline sequence.
84. The antibody of any one of claims 1-12, 13-41, 44-48, 51-53, 58-60, 63-66, 69, 70, 73, 74, 77, 78, or 83, wherein the antibody is a kappa-lambda body, a dual-affinity re-targeting molecule (DART), a knob-in-hole antibody, or a strand-exchange engineered domain body (SEEDbody).
85. The antibody of any one of claims 1-12, 13-41, 44-48, 51-53, 58-60, 63-66, 69, 70, 73, 74, 77, 78, 83, or 84 wherein the first antigen-binding domain comprises a heavy chain constant region selected from the group consisting of human IgG₁, human IgG₂, human IgG₃, human IgG₄, human IgA₁, and human IgA₂, and wherein the second antigen-binding domain

comprises a heavy chain constant region selected from the group consisting of human IgG₁, human IgG₂, human IgG₃, human IgG₄, human IgA₁, and human IgA₂.

86. The antibody of claim 85, wherein the heavy chain constant region of the first antigen-binding domain is human IgG₁, and wherein the heavy chain constant region of the second antigen-binding domain is human IgG₁.
87. The antibody of claim 86, wherein the heavy chain constant region of the first antigen-binding domain is a human IgG₁.
88. The antibody of claim 86, wherein the heavy chain constant region of the second antigen-binding domain is a human IgG₁.
89. The antibody of any one of claims 1-12, 13-41, 44-48, 51-53, 58-60, 63-66, 69, 70, 73, 74, 77, 78, 83-88, , wherein the first antigen-binding domain comprises a light chain constant region selected from the group consisting of human IgG_κ and IgG_λ, and wherein the second antigen-binding domain comprises a light chain constant region selected from the group consisting of human IgG_κ and IgG_λ.
90. The antibody of any one of claims 10, 22-89, wherein the second antigen-binding domain exhibits, as compared to binding to a human GITR sequence of residues 26 to 241 of SEQ ID NO:41, reduced or absent binding to a protein identical to residues 26 to 241 of SEQ ID NO:41 except for the presence of a D60A substitution, numbered according to SEQ ID NO: 41.
91. The antibody of any one of claims 10, 22-89, wherein the second antigen-binding domain exhibits, as compared to binding to a human GITR sequence of residues 26 to 241 of SEQ ID NO:41, reduced or absent binding to a protein identical to residues 26 to 241 of SEQ ID NO:41 except for the presence of a G63A substitution, numbered according to SEQ ID NO: 41.

92. The antibody of any one of claims 8, 20-91, wherein the second antigen-binding domain that binds to human GITR binds to at least one residue selected from the group consisting of residues 60, 62, and 63 of SEQ ID NO:41.
93. The antibody of any one of claims 8, 20-91, wherein the second antigen-binding domain that binds to human GITR binds to at least one residue selected from the group consisting of residues 62 and 63 of SEQ ID NO:41.
94. The antibody of any one of claims 8, 20-91, wherein the second antigen-binding domain that binds to human GITR binds to at least one residue selected from the group consisting of residues 60 and 63 of SEQ ID NO:41.
95. The antibody of any one of claims 8, 20-91, wherein the second antigen-binding domain that binds to human GITR binds to an epitope comprising residues 60-63 of SEQ ID NO:41.
96. The antibody of any one of claims 17-95, wherein the antibody (i) shows increased binding to cells expressing human GITR and human OX40 as compared to a monospecific bivalent antibody that binds to human GITR and contains the same VH and VL as the second antigen-binding domain that binds to human GITR; and/or (ii) shows increased binding to cells expressing human GITR and human OX40 as compared to a monospecific bivalent antibody that binds to human OX40 and contains the same VH and VL as the first antigen-binding domain that binds to human OX40.
97. The antibody of any one of claims 17-96, wherein the antibody (i) shows decreased binding to GITR-positive, OX40-negative cells as compared to a monospecific bivalent antibody that binds to human GITR and contains the same VH and VL as the second antigen-binding domain that binds to human GITR; and/or (ii) shows decreased binding to GITR-negative, OX40-positive cells as compared to a monospecific bivalent antibody that binds to human OX40 and contains the same VH and VL as the first antigen-binding domain that binds to human OX40.

98. The antibody of any one of claims 17-97, wherein the antibody (i) induces stronger natural killer cell-mediated cytotoxicity towards regulatory T cells as compared to a monospecific bivalent antibody that binds to human GITR and contains the same VH and VL as the second antigen-binding domain that binds to human GITR; and/or (ii) induces stronger natural killer cell-mediated cytotoxicity towards regulatory T cells as compared to a monospecific bivalent antibody that binds to human OX40 and contains the same VH and VL as the first antigen-binding domain that binds to human OX40.
99. The antibody of any one of claims 6-12, 15-98, wherein the antibody inhibits binding of human GITR ligand to human GITR.
100. The antibody of any one of claims 1-5, 13, 14, 17-99, wherein the antibody inhibits binding of human OX40 ligand to human OX40.
101. The antibody of any one of claims 1-12, 13-100, wherein the antibody, when bound to activated regulatory T cells, binds to activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64 to a greater extent than the antibody, when bound to activated effector T cells, binds to the activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64.
102. The antibody of claim 101, wherein the activating Fc gamma receptor is expressed on a cell selected from the group consisting of myeloid-derived effector cells and lymphocyte-derived effector cells.
103. The antibody of any one of claims 1-12, 13-55, 58-102, wherein the antibody is agonistic to human GITR and/or human OX40.
104. The antibody of claim 103, wherein the antibody induces, activates, or enhances an activity of human GITR.
105. The antibody of claim 103 or 104, wherein the antibody induces, activates, or enhances an activity of human OX40.

106. The antibody of any one of claims 1-12, 13-48, 51-53, 58-60, 63-66, 69, 70, 73, 74, 77, 78, 83-102, wherein the first antigen-binding domain comprises a human IgG₁ heavy chain and the second antigen-binding domain comprises a human IgG₁ heavy chain constant region, and wherein the heavy chain constant regions comprise an identical mutation selected from the group consisting of a N297A, N297Q, D265A, and a combination thereof, numbered according to the EU numbering system.
107. The antibody of any one of claims 1-12, 13-53, 56-74, 77, 78, 81-102, wherein the antibody is antagonistic to human GITR and/or human OX40.
108. The antibody of claim 107, wherein the antibody deactivates, reduces, or inhibits an activity of human GITR.
109. The antibody of claim 107 or 108, wherein the antibody deactivates, reduces, or inhibits an activity of human OX40.
110. The antibody of any one of claims 107-109, wherein the antibody inhibits or reduces human GITR signaling.
111. The antibody of any one of claims 107-110, wherein the antibody inhibits or reduces human OX40 signaling.
112. The antibody of any one of claims 107-111, wherein the antibody inhibits or reduces human GITR signaling induced by human GITR ligand.
113. The antibody of any one of claims 107-112, wherein the antibody inhibits or reduces human OX40 signaling induced by human OX40 ligand.
114. The antibody of any one of claims 107-113, wherein the antibody decreases CD4⁺ T cell proliferation induced by synovial fluid from rheumatoid arthritis patients.
115. The antibody of any one of claims 107-114, wherein the antibody increases survival of NOG mice transplanted with human PBMCs

116. The antibody of any one of claims 107-115, wherein the antibody increases proliferation of regulatory T cells in a GVHD model.
117. The antibody of any one of claims 1-12, 13-116, further comprising a detectable label.
118. A composition comprising (i) a nucleic acid molecule encoding the light chain variable region or light chain of the first antigen-binding domain of the antibody of any one of claims 1-12, 13-116, (ii) a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the first antigen-binding domain of the antibody, (iii) a nucleic acid molecule encoding the light chain variable region or light chain of the second antigen-binding domain of the antibody, and (iv) a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the second antigen-binding domain of the antibody.
119. A host cell comprising (i) a nucleic acid molecule encoding the light chain variable region or light chain of the first antigen-binding domain of the antibody of any one of claims 1-12, 13-116, (ii) a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the first antigen-binding domain of the antibody, (iii) a nucleic acid molecule encoding the light chain variable region or light chain of the second antigen-binding domain of the antibody, and (iv) a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the second antigen-binding domain of the antibody.
120. The host cell of claim 119, which is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.
121. A method of producing an antibody that specifically binds to human GITR and human OX40 comprising culturing the host cell of claim 119 or 120 so that the nucleic acid molecules are expressed and the antibody is produced.
122. A method for detecting cells expressing GITR and OX40 in a sample comprising contacting said sample with the antibody of any one of claims 1-12, 13-117.

123. A pharmaceutical composition comprising the antibody of any one of claims 1-12, 13-117, and a pharmaceutically acceptable excipient.
124. A kit comprising the antibody of any one of claims 1-12, 13-117 or the pharmaceutical composition of claim 123 and a) a detection reagent, b) a GITR and/or OX40 antigen, c) a notice that reflects approval for use or sale for human administration, or d) a combination thereof.
125. A method of modulating an immune response in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-12, 13-116 or the pharmaceutical composition of claim 123.
126. A method for enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-12, 13-55, 58-105 or the pharmaceutical composition of claim 123.
127. A method of treating cancer in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-12, 13-55, 58-105 or the pharmaceutical composition of claim 123.
128. The method of claim 127, wherein the cancer is selected from the group consisting of melanoma, renal cancer, prostate cancer, colon cancer, and lung cancer.
129. The method of claim 127 or 128, further comprising administering to the subject an inhibitor of indoleamine-2,3-dioxygenase (IDO).
130. The method of claim 129, wherein the inhibitor is epacadostat.
131. The method of claim 129, wherein the inhibitor is F001287.
132. The method of claim 129, wherein the inhibitor is indoximod.
133. The method of claim 129, wherein the inhibitor is NLG919.

134. The method of claim 127 or 128, further comprising administering to the subject a vaccine.
135. The method of claim 134, wherein the vaccine comprises a heat shock protein peptide complex (HSPPC) comprising a heat shock protein complexed with an antigenic peptide.
136. The method of claim 135, wherein the heat shock protein is hsp70 or hsc70 and is complexed with a tumor-associated antigenic peptide.
137. The method of claim 136, wherein the heat shock protein is gp96 and is complexed with a tumor-associated antigenic peptide, wherein the HSPPC is derived from a tumor obtained from the subject.
138. The method of claim 127 or 128, further comprising administering to the subject a checkpoint targeting agent.
139. The method of claim 138, wherein the checkpoint targeting agent is selected from the group consisting of an antagonist anti-PD-1 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, an antagonist anti-CTLA-4 antibody, an antagonist anti-TIM-3 antibody, an antagonist anti-LAG-3 antibody, an antagonist anti-CEACAM1 antibody, an agonist anti-GITR antibody, and an agonist anti-OX40 antibody.
140. A method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-12, 13-116 or the pharmaceutical composition of claim 123.
141. A method for reducing or inhibiting an immune response in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-12, 13-116 or the pharmaceutical composition of claim 123.
142. A method for treating an autoimmune or inflammatory disease or disorder in a subject, the method comprising administering to the subject an effective amount of the antibody of

any one of claims 1-12, 13-116 or the pharmaceutical composition of claim 123.

143. The method of claim 142, wherein the autoimmune or inflammatory disease or disorder is selected from the group consisting of transplant rejection, graft-versus-host disease, vasculitis, asthma, rheumatoid arthritis, dermatitis, inflammatory bowel disease, uveitis, lupus, colitis, diabetes, multiple sclerosis, and airway inflammation.

144. The method of any one of claims 125-143, wherein the subject is human.