

CLAIMS

1. A multispecific antibody comprising:

(a) a first antigen-binding region that specifically binds to human OX40, the first antigen-binding region comprising a first VH comprising CDRs VH-CDR1, VH-CDR2, and VH-CDR3, and a first VL comprising CDRs VL-CDR1, VL-CDR2, and VL-CDR3, wherein the first VH comprises the VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences of the VH amino acid sequence of SEQ ID NO: 54, and the first VL comprises the VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences of the VL amino acid sequence of SEQ ID NO: 55; and

(b) a second antigen-binding region that specifically binds to human GITR, the second antigen-binding region comprising a second VH comprising CDRs VH-CDR1, VH-CDR2, and VH-CDR3, and a second VL comprising CDRs VL-CDR1, VL-CDR2, and VL-CDR3, wherein the second VH comprises the VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences of the VH amino acid sequence of SEQ ID NO: 18, and the second VL comprises the VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences of the VL amino acid sequence of SEQ ID NO: 19.

2. The multispecific antibody of claim 1, wherein:

(a) the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 of the first antigen-binding region comprise the amino acid sequences of SEQ ID NOs: 47, 48, 49, 50, 51, and 52, respectively; and

(b) the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 of the second antigen-binding region comprise the amino acid sequences of SEQ ID NOs: 7, 10, 3, 14, 5, and 16, respectively.

3. The multispecific antibody of claim 1, wherein the first VH comprises the amino acid sequence of SEQ ID NO: 54, and/or the first VL comprises the amino acid sequence of SEQ ID NO: 55.

4. The multispecific antibody of claim 1, wherein the first VH comprises the amino acid sequence of SEQ ID NO: 54, and the first VL comprises the amino acid sequence of SEQ ID NO: 55.

5. The multispecific antibody of claim 1, wherein the second VH comprises the amino acid sequence of SEQ ID NO: 18, and/or the second VL comprises the amino acid sequence of SEQ ID NO: 19.
6. The multispecific antibody of claim 1, wherein the second VH comprises the amino acid sequence of SEQ ID NO: 18, and the second VL comprises the amino acid sequence of SEQ ID NO: 19.
7. The multispecific antibody of claim 1, wherein the first antigen-binding region and/or the second antigen-binding region comprises a heavy chain constant region selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂.
8. The multispecific antibody of claim 7, wherein the heavy chain constant region is an IgG₁ heavy chain constant region.
9. The multispecific antibody of claim 8, wherein the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 126.
10. The multispecific antibody of claim 8, wherein:
 - (a) the first antigen-binding region comprises a first heavy chain constant region comprising serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively, and the second antigen-binding region comprises a second heavy chain constant region comprising tryptophan at amino acid position 366; or
 - (b) the first antigen-binding region comprises a first heavy chain constant region comprising tryptophan at amino acid position 366, and the second antigen-binding region comprises a second heavy chain constant region comprising serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively,
numbered according to the EU numbering system.
11. The multispecific antibody of claim 10, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

12. The multispecific antibody of claim 1, wherein the first antigen-binding region comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 54, and/or the second antigen-binding region comprises a second heavy chain comprising the amino acid sequence of SEQ ID NO:18.
13. The multispecific antibody of claim 1, wherein the first antigen-binding region and/or the second antigen-binding region comprises a light chain constant region selected from the group consisting of a human kappa light chain constant region or a human lambda light chain constant region.
14. The multispecific antibody of claim 1, wherein the first antigen-binding region comprises a first light chain comprising the amino acid sequence of SEQ ID NO: 55, and/or the second antigen-binding region comprises a second light chain comprising the amino acid sequence of SEQ ID NO: 19.
15. A multispecific antibody comprising:
- (a) a first antigen-binding region that specifically binds to human OX40, the first antigen-binding region comprising a first VH and a first VL, wherein the first VH comprises the amino acid sequence of SEQ ID NO: 54, and the first VL comprises the amino acid sequence of SEQ ID NO: 55; and
 - (b) a second antigen-binding region that specifically binds to human GITR, the second antigen-binding region comprising a second VH and a second VL, wherein the second VH comprises the amino acid sequence of SEQ ID NO: 18, and the second VL comprises the amino acid sequence of SEQ ID NO: 19.
16. The multispecific antibody of claim 15, wherein the first antigen-binding region and/or the second antigen-binding region comprises a heavy chain constant region selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂.
17. The multispecific antibody of claim 16, wherein the heavy chain constant region is an IgG₁ heavy chain constant region.
18. The multispecific antibody of claim 17, wherein the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 126.

19. The multispecific antibody of claim 17, wherein:
- (a) the first antigen-binding region comprises a first heavy chain constant region comprising serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively, and the second antigen-binding region comprises a second heavy chain constant region comprising tryptophan at amino acid position 366; or
 - (b) the first antigen-binding region comprises a first heavy chain constant region comprising tryptophan at amino acid position 366, and the second antigen-binding region comprises a second heavy chain constant region comprising serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively,
numbered according to the EU numbering system.
20. The multispecific antibody of claim 19, wherein the first heavy chain constant region and/or the second heavy chain constant region comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.
21. The multispecific antibody of claim 15, wherein the first antigen-binding region comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 54, and/or the second antigen-binding region comprises a second heavy chain comprising the amino acid sequence of SEQ ID NO: 18.
22. The multispecific antibody of claim 15, wherein the first and/or second antigen-binding region comprises a light chain constant region selected from the group consisting of a human light kappa chain constant region or a human lambda light chain constant region.
23. The multispecific antibody of claim 15, wherein the first antigen-binding region comprises a first light chain comprising the amino acid sequence of SEQ ID NO: 55, and/or the second antigen-binding region comprises a second light chain comprising the amino acid sequence of SEQ ID NO: 19.
24. A multispecific antibody comprising:
- (a) a first antigen-binding region that specifically binds to human OX40, the first antigen-binding region comprising a first IgG₁ heavy chain comprising the amino acid

sequence of SEQ ID NO: 54, and a first light chain comprising the amino acid sequence of SEQ ID NO: 67; and

(b) a second antigen-binding region that specifically binds to human GITR, the second antigen-binding region comprising a second IgG₁ heavy chain comprising the amino acid sequence of SEQ ID NO: 18, and a second light chain comprising the amino acid sequence of SEQ ID NO: 37.

25. The multispecific antibody of claim 24, wherein:

(a) the first IgG₁ heavy chain comprises serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively, and the second IgG₁ heavy chain comprises tryptophan at amino acid position 366; or

(b) the first IgG₁ heavy chain comprises tryptophan at amino acid position 366, and the second IgG₁ heavy chain comprises serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively,

numbered according to the EU numbering system.

26. The multispecific antibody of claim 25, wherein the first IgG₁ heavy chain and/or the second IgG₁ heavy chain comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

27. The multispecific antibody of claim 25, wherein the first IgG₁ heavy chain comprises serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively, and the second IgG₁ heavy chain comprises tryptophan at amino acid position 366, numbered according to the EU numbering system.

28. The multispecific antibody of claim 27, wherein the first IgG₁ heavy chain comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

29. The multispecific antibody of claim 27, wherein the second IgG₁ heavy chain comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

30. The multispecific antibody of claim 27, wherein the first IgG₁ heavy chain and the

second IgG1 heavy chain comprise aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

31. The multispecific antibody of claim 25, wherein the first IgG₁ heavy chain comprises tryptophan at amino acid position 366, and the second IgG₁ heavy chain comprises serine, alanine, and valine at amino acid positions 366, 368, and 407, respectively, numbered according to the EU numbering system.

32. The multispecific antibody of claim 31, wherein the first IgG₁ heavy chain comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

33. The multispecific antibody of claim 31, wherein the second IgG₁ heavy chain comprises aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

34. The multispecific antibody of claim 31, wherein the first IgG₁ heavy chain and the second IgG₁ heavy chain comprise aspartate, leucine, and glutamate at amino acid positions 239, 330, and 332, respectively, numbered according to the EU numbering system.

35. A pharmaceutical composition comprising the multispecific antibody of claim 1 and a pharmaceutically acceptable excipient.

36. A pharmaceutical composition comprising the multispecific antibody of claim 15 and a pharmaceutically acceptable excipient.

37. A pharmaceutical composition comprising the multispecific antibody of claim 24 and a pharmaceutically acceptable excipient.

38. A pharmaceutical composition comprising the multispecific antibody of claim 27 and a pharmaceutically acceptable excipient.

39. A pharmaceutical composition comprising the multispecific antibody of claim 28 and a pharmaceutically acceptable excipient.

40. A pharmaceutical composition comprising the multispecific antibody of claim 29 and a pharmaceutically acceptable excipient.
41. A pharmaceutical composition comprising the multispecific antibody of claim 30 and a pharmaceutically acceptable excipient.
42. A pharmaceutical composition comprising the multispecific antibody of claim 31 and a pharmaceutically acceptable excipient.
43. A pharmaceutical composition comprising the multispecific antibody of claim 32 and a pharmaceutically acceptable excipient.
44. A pharmaceutical composition comprising the multispecific antibody of claim 33 and a pharmaceutically acceptable excipient.
45. A pharmaceutical composition comprising the multispecific antibody of claim 34 and a pharmaceutically acceptable excipient.