

WHAT IS CLAIMED IS:

1. An isolated antibody or fragment thereof comprising a humanized heavy chain variable region (VH) and a humanized light chain variable region (VL);

wherein the VH comprises:

- (a) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8,
- (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 14, and
- (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 27, and

wherein the VL comprises:

- (d) a CDR1 comprising the amino acid sequence of residues 24-34 of SEQ ID NO: 29,
- (e) a CDR2 comprising the amino acid sequence of residues 50-56 of SEQ ID NO: 29, and
- (f) a CDR3 comprising the amino acid sequence of residues 89-97 of SEQ ID NO: 29,

wherein the antibody or fragment thereof can specifically bind to human OX40.

2. The antibody or fragment of claim 1, wherein the antigen-binding fragment is an Fv fragment, an Fab fragment, an F(ab')₂ fragment, an Fab' fragment, a dsFv fragment, an scFv fragment, or an sc(Fv)₂ fragment, or any combination thereof.

3. The antibody or fragment thereof of claim 1, which can induce dose-dependent proliferation of activated CD4⁺ T cells and dose-dependent cytokine release in primary activated human CD4⁺ T cells in a plate-based assay.

4. The antibody or fragment thereof of claim 3, wherein a 20% maximal proliferation response (EC₂₀) can be achieved in primary activated human CD4⁺ T cells at an antibody concentration of about 14 pM to about 28 pM, a 50% maximal proliferation response (EC₅₀) can be achieved in primary activated human CD4⁺ T cells at an antibody concentration of about 0.3 pM to about 130 pM, and a 90% maximal proliferation response (EC₉₀) can be achieved in primary activated human CD4⁺ T cells at an antibody concentration of about 50 pM to about 90 pM, all as measured by flow cytometry.

5. The antibody or fragment thereof of claim 4, wherein EC₂₀ is about 21 pM, EC₅₀ is about 28 pM, and EC₉₀ is about 72 pM.

6. The antibody or fragment thereof of claim 3, wherein the cytokine is IFN γ , TNF α , IL-5, IL-10, IL-2, IL-4, IL-13, IL-8, IL-12 p70, IL-1 β , or any combination thereof.

7. The antibody or fragment thereof of claim 6 wherein the cytokine is IFN γ , TNF α , IL-5, IL-10, IL-13, or any combination thereof.
8. The antibody or fragment thereof of claim 1, which can achieve CD4⁺ T cell proliferation and cytokine release in primary activated cynomolgus monkey CD4⁺ T cells and in primary activated rhesus monkey CD4⁺ T cells.
9. The antibody or fragment thereof of claim 1, which can activate the NF κ B pathway in OX40 expressing T cells in the presence of Fc γ R-expressing cells.
10. The antibody or fragment thereof of claim 9, wherein the OX40-expressing T cells are OX40-expressing Jurkat NF κ B-luciferase reporter cells that produce luciferase in response to stimulation of the NF κ B signaling pathway.
11. The antibody or fragment thereof of claim 1, which can trigger complement-dependent or antibody-dependent cellular cytotoxicity against OX40-expressing cells.
12. The antibody or fragment thereof of claim 11, which can bind to C1q and trigger NK-mediated antibody-dependent cellular cytotoxicity against the OX40-expressing cells.
13. A composition comprising the antibody or fragment thereof of claim 1, and a carrier.
14. An antibody or antigen-binding fragment thereof comprising a humanized heavy chain variable region (VH) and a humanized light chain variable region (VL), wherein the VH comprises the amino acid sequence SEQ ID NO: 59, wherein the VL comprises the amino acid sequence SEQ ID NO: 29, and wherein the antibody or fragment thereof can specifically bind to human OX40.
15. The antibody or fragment thereof of claim 14 comprising the heavy chain amino acid sequence SEQ ID NO: 71 and the light chain amino acid sequence SEQ ID NO: 30.
16. A polynucleotide comprising a nucleic acid that encodes the antibody or fragment thereof, of claim 14.

17. The polynucleotide of claim 16, comprising the nucleic acid of SEQ ID NO: 60, the nucleic acid of SEQ ID NO: 31, the nucleic acid of SEQ ID NO: 72, or any combination thereof.
18. A vector comprising the polynucleotide of claim 16.
19. A host cell comprising the polynucleotide of claim 16.
20. A method of producing an antibody or fragment thereof, comprising culturing the host cell of claim 19 under conditions in which the antibody or fragment thereof encoded by the polynucleotide is expressed, and recovering the antibody or fragment thereof.
21. A host cell comprising the vector of claim 18.
22. The antibody or fragment of claim 1 for use in therapy.
23. The antibody or fragment of claim 1 for use as a medicament.
24. The antibody or fragment of claim 1 for use in the treatment of cancer with a T cell infiltrate in a subject, wherein an effective amount of the antibody or fragment is to be administered to the subject.
25. The antibody or fragment for use of claim 24, wherein the cancer is a solid tumor.
26. The antibody or fragment for use of claim 24, wherein administration of the antibody or fragment can inhibit tumor growth, can promote tumor reduction, or both.
27. The antibody or fragment for use of claim 26, wherein tumor growth inhibition is achieved in the presence of T cells.
28. The antibody or fragment for use of claim 27, wherein tumor growth is inhibited by at least 10%, at least 20%, at least 30%, at least 40%, and least 50%, at least 60%, or at least 70% compared to administration of an isotype-matched control antibody or fragment thereof.
29. The antibody or fragment for use of claim 24, wherein the antibody or fragment comprises a humanized

heavy chain variable region (VH) and a humanized light chain variable region (VL), wherein the VH comprises the amino acid sequence SEQ ID NO: 59, wherein the VL comprises the amino acid sequence SEQ ID NO: 29, and wherein the antibody or fragment can specifically bind to human OX40.

30. The antibody or fragment for use of claim 29, wherein the antibody or fragment comprises the heavy chain amino acid sequence SEQ ID NO: 71 and the light chain amino acid sequence SEQ ID NO: 30.

31. The antibody or fragment for use of claim 24, wherein the antigen-binding fragment is an Fv fragment, an Fab fragment, an F(ab')₂ fragment, an Fab' fragment, a dsFv fragment, an scFv fragment, or an sc(Fv)₂ fragment, or any combination thereof.

32. A composition comprising the antibody or fragment of claim 1 for use in the treatment of cancer with a T cell infiltrate in a subject, wherein an effective amount of the composition is to be administered to the subject.

33. Use of the antibody or fragment of claim 1 in the manufacture of a medicament for the treatment of cancer with a T cell infiltrate in a subject, wherein an effective amount of the medicament is to be administered to the subject.

34. The use of claim 33, wherein the cancer is a solid tumor.

35. The use of claim 33, wherein administration of the antibody or fragment can inhibit tumor growth, can promote tumor reduction, or both.

36. The use of claim 35, wherein tumor growth inhibition is achieved in the presence of T cells.

37. The use of claim 36, wherein tumor growth is inhibited by at least 10%, at least 20%, at least 30%, at least 40%, and least 50%, at least 60%, or at least 70% compared to administration of an isotype-matched control antibody or fragment thereof.

38. The use of claim 33, wherein the antibody or fragment comprises a humanized heavy chain variable region (VH) and a humanized light chain variable region (VL), wherein the VH comprises the amino acid sequence SEQ ID NO: 59, wherein the VL comprises the amino acid sequence SEQ ID NO: 29, and wherein the antibody or fragment can specifically bind to human OX40.

39. The use of claim 38, wherein the antibody or fragment comprises the heavy chain amino acid sequence SEQ ID NO: 71 and the light chain amino acid sequence SEQ ID NO: 30.
40. The use of claim 33, wherein the antigen-binding fragment is an Fv fragment, an Fab fragment, an F(ab')₂ fragment, an Fab' fragment, a dsFv fragment, an scFv fragment, or an sc(Fv)₂ fragment, or any combination thereof.
41. Use of a composition comprising the antibody or fragment of claim 1 in the manufacture of a medicament in the treatment of cancer with a T cell infiltrate in a subject, wherein an effective amount of the medicament is to be administered to the subject.