Claims

1. An isolated antibody that specifically binds to human OX40, comprising:

(a) a heavy chain variable region comprising

a heavy chain complementarity determining region 1 (CDRl) comprising the amino acid sequence of GSAMH (SEQ ID NO: 4),

a heavy chain CDR2 comprising the amino acid sequence of RIRSKANSYATAYAASVKG (SEQ ID NO: 5),

and a heavy chain CDR3 comprising the amino acid sequence of GIYDSSGYDY (SEQ ID NO: 6); and

(b) a light chain variable region comprising

a light chain CDRl comprising the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 1),

a light chain CDR2 comprising the amino acid sequence of LGSNRAS (SEQ ID NO:2),

and a light chain CDR3 comprising the amino acid sequence of MQALQTPLT (SEQ ID NO: 3).

2. The antibody of claim 1, wherein

(a) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 16; and/or

(b) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 15.

3. The antibody of claim 1 or claim 2, wherein

(a) the antibody comprises a heavy chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-63; and/or

(b) the antibody comprises a light chain sequence comprising the amino acid sequence of SEQ ID NO: 20.

4. An isolated antibody that specifically binds to human OX40, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 16; and/or wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 15.

5. The antibody of claim 4, wherein the antibody comprises:

(a) (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 60; and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 20;

(b) (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 61; and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 20; or

(c) (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 or 63; and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 20.

6. The antibody of any one of claims 1, 2, or claim 4, further comprising a heavy chain constant region; optionally wherein the heavy chain constant region is selected from the group consisting of human immunoglobulins IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2; optionally wherein

(a) the IgG1 is non-fucosylated IgG_1;

(b) the amino acid sequence of the IgG_1 comprises a N297A mutation or a mutation selected from the group consisting of D265A, P329A, and a combination thereof;

(c) the amino acid sequence of the IgG_1 comprises a N297Q mutation;

(d) the amino acid sequence of the IgG_4 comprises a S228P mutation;

(e) the amino acid sequence of the IgG_2 comprises a Cl27S mutation;

(f) the heavy chain constant region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 64-71; or

(g) the amino acid sequence of the IgG_1 comprises a mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof or a mutation selected from the group consisting of D265A, P329A, and a combination thereof.

7. The antibody of any one of claims 1, 2, 4, or claim 6, further comprising a light chain constant region, optionally wherein the light chain constant region is selected from the group consisting of human immunoglobulins IgGκ and IgGλ.

8. The antibody of any one of claims 1-7, wherein the antibody is a human antibody.

9. An isolated antibody that binds to the same epitope of human OX40 as the antibody of any one of claims 1-8.

10. The antibody of any one of claims 1-9, wherein

(a) the antibody is agonistic;

(b) the antibody activates, enhances, or induces an activity of human OX40;

(c) the antibody induces production of TNFα, TNFβ, IFNγ, GM-CSF, IL-2, IL-4, IL-10, IL-13, or a combination thereof by anti-CD3-stimulated peripheral blood mononuclear cells (PBMCs); optionally where

(i) the production of TNFα, TNFβ, IFNγ, GM-CSF, IL-2, IL-10, or IL-13 is a substantially increasing function of the concentration of the antibody; or

(ii) wherein the production of TNFα, TNFβ, IFNγ, GM-CSF, IL-2, IL-10, or IL-13 shows a sigmoidal dose response curve;

(d) the antibody induces IL-2 production by SEA-stimulated PBMCs and suppresses IL-10 production by SEA-stimulated PBMCs;

(e) the antibody induces IL-2 production by SEA-stimulated PBMCs, wherein the IL-2 production is a substantially increasing function of the concentration of the antibody;

(f) the antibody induces IL-2 production by SEA-stimulated PBMCs, wherein the IL-2 production shows a sigmoidal dose response curve

(g) the antibody relieves suppression of T effector cells by T regulatory cells; and/or

(h) the antibody induces IL-2 production by a co-culture of T effector cells and T regulatory cells and suppresses IL-10 production by a co-culture of T effector cells and T regulatory cells.

11. The antibody of any one of claims 1-10, wherein the antibody induces CD4+ T cell

proliferation; optionally wherein

(a) the CD4+ T cell proliferation is a substantially increasing function of the concentration of the antibody; or

(b) wherein the CD4+ T cell proliferation shows a sigmoidal dose response curve.

12. The antibody of any one of claims 1-11, further comprising a detectable label.

13. An isolated antibody that specifically binds to human OX40, wherein:

(a) the binding between the antibody and a variant OX40 is substantially weakened relative to the binding between the antibody and a human OX40 sequence of SEQ ID NO: 55, wherein the variant OX40 comprises the sequence of SEQ ID NO: 55 except for an amino acid mutation selected from the group consisting of: N 60A, R62A, R80A, L88A, P93A, P99A, P115A, and a combination thereof;

(b) the binding between the antibody and a variant OX40 is substantially weakened relative to the binding between the antibody and a human OX40 sequence of SEQ ID NO: 55, wherein the variant OX40 comprises the sequence of SEQ ID NO: 55 except for the amino acid mutations W58A, N60A, R62A, R80A, L88A, P93A, P99A, and P115A;

(c) the antibody exhibits, as compared to binding to a human OX40 sequence of SEQ ID NO: 55, reduced or absent binding to a protein identical to SEQ ID NO: 55 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;

(d) the antibody exhibits, as compared to binding to a human OX40 sequence of SEQ ID NO: 55, reduced or absent binding to a protein identical to SEQ ID NO: 55 except for the presence of the amino acid mutations W58A, N60A, R62A, R80A, L88A, P93A, P99A, and P115A;

(e) the antibody specifically binds to an epitope of a human OX40 sequence comprising a residue of SEQ ID NO: 55 selected from the group consisting of: 60, 62, 80, 88, 93, 99, 115, and a combination thereof;

(f) the antibody specifically binds to an epitope of a human OX40 sequence comprising residues 58, 60, 62, 80, 88, 93, 99, and 115 of SEQ ID NO: 55;

(g) the antibody specifically binds to at least one residue of SEQ ID NO: 55 selected

from the group consisting of: 60, 62, 80, 88, 93, 99, 115, and a combination thereof; or

(h) the antibody specifically binds to residues 58, 60, 62, 80, 88, 93, 99, and 115 of SEQ ID NO: 55.

14. The antibody of claim 13, wherein the antibody comprises a human immunoglobulin IgG1 heavy chain constant region, and wherein the amino acid sequence of the IgG1 heavy chain constant region comprises a mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof or a mutation selected from the group consisting of D265A, P329A, and a combination thereof.

15. An isolated antibody that specifically binds to human OX40, comprising:

(a) a heavy chain variable region sequence and a light chain variable region sequence of any one of claims 1-8, wherein the antibody is selected from the group consisting of a Fab, Fab', F(ab')2, and scFv fragment; or

(b) one heavy chain and one light chain, wherein the heavy chain and light chain comprise the heavy chain variable region and the light chain variable region, respectively, of any one of claims 1-8.

16. The antibody of claim 15, further comprising a human immunoglobulin IgG1 heavy chain constant region, wherein the amino acid sequence of the IgG1 heavy chain constant region comprises a mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof or a mutation selected from the group consisting of D265A, P329A, and a combination thereof.

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

(a) (i) a first antigen-binding domain that specifically binds to human OX40; and
(ii) a second antigen-binding domain that does not specifically bind to an antigen expressed by a human immune cell; or

(b) (i) an antigen-binding domain that specifically binds to human OX40, comprising a first heavy chain and a light chain, and

(ii) a second heavy chain or a fragment thereof;

wherein the antigen-binding domain that specifically binds to human OX40 comprises:

(a) a first heavy chain variable domain (VH) comprising a VH complementarity determining region (CDR) 1 comprising the amino acid sequence of GSAMH (SEQ ID NO:4); a VH-CDR2 comprising the amino acid sequence of RIRSK.ANSYATAYAASVKG (SEQ ID NO:5); and a VH-CDR3 comprising the amino acid sequence of GIYDSSGYDY (SEQ ID NO:6); and

(b) a first light chain variable domain (VL) comprising a VL-CDR1 comprising the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 1); a VL-CDR2 comprising the amino acid sequence of LGSNRAS (SEQ ID NO:2); and a VL-CDR3 comprising the amino acid sequence of MQALQTPLT (SEQ ID NO:3).

18. The antibody of claim 17,

(a) wherein the antigen-binding domain that specifically binds to human OX40 specifically binds to the same epitope of human OX40 as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:16 and a VL comprising the amino acid sequence of SEQ ID NO:15;

(b) wherein the antigen-binding domain that specifically binds to human OX40 exhibits, as compared to binding to a human OX40 sequence of SEQ ID NO:55, reduced or absent binding to a protein identical to SEQ ID NO:55 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;

(c) wherein the 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:16; or

(d) wherein the 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:15.

19. The antibody of claim 17 or claim 18,

(a) wherein the second antigen-binding domain specifically binds to a non-human antigen;

(b) wherein the second antigen-binding domain specifically binds to a viral antigen; optionally wherein the viral antigen is a HIV antigen; or

(c) wherein the second antigen-binding domain specifically binds to chicken albumin or hen egg lysozyme.

20. An isolated antibody that specifically binds to OX40, wherein the antibody comprises:

(a) an antigen-binding domain that specifically binds to human OX40, comprising a first heavy chain and a light chain; and

(b) a second heavy chain or a fragment thereof;

wherein, the antigen-binding domain that specifically binds to human OX40 comprises:

(i) a first heavy chain variable domain (VH) comprising a VH complementarity determining region (CDR) 1 comprising the amino acid sequence of GSAMH (SEQ ID NO:4); a VH-CDR2 comprising the amino acid sequence of RIRSKANSYATAYAASVKG (SEQ ID NO:5); and a VH-CDR3 comprising the amino acid sequence of GIYDSSGYDY (SEQ ID NO:6); and a first light chain variable domain (VL) comprising a VL-CDR1 comprising the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: I); a VL-CDR2 comprising the amino acid sequence of LGSNRAS (SEQ ID NO:2); and a VL-CDR3 comprising the amino acid sequence of MQALQTPLT (SEQ ID NO:3);

(ii) the antigen-binding domain that specifically binds to human OX40 specifically binds to the same epitope of human OX40 as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 16 and a VL comprising the amino acid sequence of SEQ ID NO: 15;

(iii) the antigen-binding domain that specifically binds to human OX40 exhibits, as compared to binding to a human OX40 sequence of SEQ ID NO: 55, reduced or absent binding to a protein identical to SEQ ID NO: 55 except for the presence of an amino acid mutation selected from the group consisting of: N60A, R62A, R80A, L88A, P93A, P99A, Pll5A, and a combination thereof;

(iv) the 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: l6; or

(v) the 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: 15; optionally wherein the fragment of the second heavy chain is a Fe fragment.

21. The antibody of any one of claims 17-20, wherein:

(a) the 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: 16;

(b) the antigen-binding domain that specifically binds to human OX40 comprises a VH comprising the amino acid sequence of SEQ ID NO: 16;

(c) the 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;

(d) the antigen-binding domain that specifically binds to human OX40 comprises a VL 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:15;

(e) the antigen-binding domain that specifically binds to human OX40 comprises a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:3;

(f) the antigen-binding domain that specifically binds to human OX40 comprises a VL comprising the amino acid sequence of SEQ ID NO:15;

(g) the antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO:20;

(h) the antigen-binding domain that specifically binds to human OX40 comprises a light chain comprising the amino acid sequence of SEQ ID NO: 50;

(i) the 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

(j) the antigen-binding domain that specifically binds to human OX40 comprises the VH and VL sequences set forth in SEQ ID NOs: 16 and 15, respectively;

(k) the antigen-binding domain that specifically binds to human OX40 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 60;

(l) the first antigen-binding domain and the second antigen-binding domain comprise an identical mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof or an identical mutation selected from the group consisting of D265A, P329A, and a combination thereof; and/or

(m) the antigen-binding domain that specifically binds to human OX40 and the second heavy chain or fragment thereof comprise an identical mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof or an identical mutation selected from the group consisting of D265A, P329A, and a combination thereof.

22. The antibody of any one of claims 1, 2, 4, 6-9, or 12-21, wherein:

(a) the antibody is antagonistic to human OX40;

(b) the antibody deactivates, reduces, or inhibits an activity of human OX40;

(c) the antibody inhibits or reduces binding of human OX40 to human OX40 ligand;

(d) the antibody inhibits or reduces human OX40 signaling;

(e) the antibody inhibits or reduces human OX40 signaling induced by human OX40 ligand; and/or

(f) the antibody further comprises a detectable label.

23. An isolated nucleic acid molecule encoding (i) the heavy chain variable region or the heavy
chain of the antibody of any one of claims 1-22 and/or (ii) the light chain variable region or the light chain of the antibody of any one of claims 1-22.

24. The isolated nucleic acid molecule of claim 23, (i) wherein the nucleic acid molecule encodes a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 16; and/or (ii) wherein the nucleic acid molecule encodes a light chain variable region comprising the amino acid sequence of SEQ ID NO: 15.

25. An isolated vector comprising the nucleic acid molecule of claim 23 or claim 24.

26. A host cell comprising the nucleic acid molecule of claim 23 or claim 24, the vector of claim 25, or a first vector comprising the nucleic acid of claim 23(i) or claim 24(i) and a second vector comprising the nucleic acid of claim 23(ii) or claim 24(ii);

optionally wherein the host cell is selected from the group consisting of *E. coli, Pseudomonas, Bacillus, Streptomyces,* yeast, CHO, YB/20, NSO, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep 02, SP2/0, Rl.1, B-W, L-M, COS 1, COS 7, BSCl, BSC40, BMTl0 cell, plant cell, insect cell, and human cell in tissue culture.

27. A method of producing an antibody that binds to human OX40 comprising culturing the host cell of claim 26 so that the nucleic acid molecule is expressed and the antibody is produced.

28. An isolated antibody that specifically binds to human OX40 and is encoded by the isolated nucleic acid molecule of claim 23 or claim 24.

29. A pharmaceutical composition comprising:

(a) (i) the antibody of any one of claims 1-22 or claim 28;
(ii) the nucleic acid molecule of claim 23 or claim 24;
(iii) the vector of claim 25;
(iv) the host cell of claim 26; and

(b) a pharmaceutically acceptable excipient.

30. An effective amount of the antibody of any one of claims 1-22 or claim 28, the nucleic acid molecule of claim 23 or claim 24, the vector of claim 25, the host cell of claim 26, or the pharmaceutical composition of claim 29; for use in therapy by modulating an immune response in a subject;

optionally wherein modulating an immune response comprises enhancing or inducing the immune response of the subject.

31. An effective amount of the antibody of any one of claims 1-16, 22 or claim 28, the nucleic acid molecule of claim 23 or 24, the vector of claim 25, the host cell of claim 26, or the pharmaceutical composition of claim 29 for use in therapy by enhancing the expansion of T cells and T cell effector function in a subject.

32. Use of an effective amount of the antibody of any one of claims 1-16, 22 or claim 28, the nucleic acid molecule of claim 23 or claim 24, the vector of claim 25, the host cell of claim 26, or the pharmaceutical composition of claim 29 in the manufacture of a medicament for the treatment of cancer in a subject;

optionally wherein the cancer is selected from the group consisting of melanoma, renal cancer, prostate cancer, colon cancer, and lung cancer.

33. Use of an effective amount of the antibody of any one of claims 1, 2, 4, 6-9, 12-22, or claim 28, or the pharmaceutical composition of claim 29 in the manufacture of a medicament for the treatment of an autoimmune or inflammatory disease or disorder in a subject

optionally wherein the disease or disorder is selected from the group consisting of: transplant rejection, vasculitis, asthma, rheumatoid arthritis, dermatitis, inflammatory bowel disease, uveitis, and lupus.

34. An effective amount of the antibody of any one of claims 1-16, 22 or claim 28, the nucleic acid molecule of claim 23 or claim 24, the vector of claim 25, the host cell of claim 26, or the pharmaceutical composition of claim 29 for use in the treatment of an infectious disease in a subject.

35. The use of claim 32, wherein

(a) an inhibitor ofindoleamine-2,3-dioxygenase (IDO), optionally wherein the inhibitor is epacadostat, F001287, indoximod or NLG919;

(b) a vaccine;

optionally wherein the vaccine comprises a heat shock protein peptide complex (HSPPC) comprising a heat shock protein complexed with an antigenic peptide, optionally (i) wherein the heat shock protein is gp96 protein and is

complexed with a tumor associated antigeneic peptide, wherein the HSPPC is derived from a tumor obtained from a subject; or (ii) wherein the heat shock protein is hsp70 or hsc70 protein and is complexed with a tumor-associated antigenic peptide; or

(c) a checkpoint targeting agent;

optionally wherein the checkpoint targeting agent is selected from the group consisting of an antagonist anti-PD-1 antibody, an antagonist anti-PD-Ll 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, an agonist anti-CD137 antibody, and an agonist anti-OX40 antibody;

is to be administered as well as the medicament.

36. The use of any one of claims 32-35, wherein the subject is human.

37. A method for detecting OX40 in a sample comprising contacting the sample with the antibody of any one of claims 1-22 or claim 28.

38. A kit comprising the antibody of any one of claims 1-22 or claim 28 or the pharmaceutical composition of claim 29 and a) a detection reagent, b) an OX40 antigen, c) a notice that reflects approval for use or sale for human administration, or d) a combination thereof for use in therapy by modulating an immune response in a subject.

39. Use of a kit comprising the antibody of any one of claims 1-22 or claim 28 or the pharmaceutical composition of claim 29 and a) a detection reagent, b) an OX40 antigen, c) a notice that reflects approval for use or sale for human administration, or d) a combination thereof in the manufacture of a medicament for the treatment of cancer or an autoimmune or inflammatory disease or disorder.