[0007] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[0008] ~~In one aspect, p~~Provided are isolated antibodies that bind to human OX40.

[0009] ~~In another aspect, p~~Provided are anti-human OX40 agonist antibodies wherein the antibody is a depleting antibody. In ~~another~~ one aspect, provided are anti-human OX40 agonist antibodies wherein the antibody depletes cells that express human OX40 *in vitro* and binds human OX40 with an affinity of less than or equal to about 1 nM. In some embodiments, the antibodies deplete CD4+ effector T cells. In some embodiments the antibodies deplete regulatory T cells (Treg). In some embodiments, the depleting is by ADCC and/or phagocytosis. In some embodiments, the depleting is by ADCC.

[0010] ~~In another aspect, p~~Provided are anti-human OX40 agonist antibodies that bind human OX40 with an affinity of less than or equal to about 0.45 nM. In some embodiments, the antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some embodiments, antibody binding affinity is determined using radioimmunoassay. In some embodiments, the antibody binds human OX40 and cynomolgus OX40. In some embodiments, binding to human and cynomolgus OX40 is determined using a FACS assay. In some embodiments, binding to human OX40 has an EC50 of less than or equal to 0.2 ug/ml. In some embodiments, binding to human OX40 has an EC50 of less than or equal to 0.3 ug/ml or lower. In some embodiments, binding to cynomolgus OX40 has an EC50 of less than or equal to 1.5 ug/ml. In some embodiments, binding to cynomolgus OX40 has an EC50 of less than or equal to 1.4 ug/ml.

[0011] In another embodiment~~aspect~~, the disclosure~~invention~~ provides anti-human OX40 agonist antibodies that increase (are capable of increasing) CD4+ effector T cell proliferation and/or increasing cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with anti-human OX40 agonist antibody. In some embodiments, the cytokine is gamma interferon.

[0012] In another embodiment~~aspect~~, the disclosure~~invention~~ provides anti-human OX40 agonist antibodies that increase (are capable of increasing) memory T cell proliferation and/or increasing cytokine production by the memory cell. In some embodiments, the cytokine is gamma interferon.

[0013] In another embodiment~~aspect~~, the disclosure~~invention~~ provides anti-human OX40 agonist that inhibit (are capable of inhibiting) Treg function. In some embodiments, the antibodies inhibit Treg suppression of effector T cell function. In some embodiments, effector T cell function is effector T cell proliferation and/or cytokine production. In some embodiments, the effector T cell is a CD4+ effector T cell.

[0014] In another embodiment~~aspect~~, the disclosure~~invention~~ provides anti-human OX40 agonist antibodies that increase (are capable of increasing) OX40 signal transduction in a target cell that expresses OX40. In some

embodiments, OX40 signal transduction is detected by monitoring NFkB downstream signaling (e.g., in the OX40 expressing cell, e.g., CD4+ effector T cell, CD8+ effector T cell, CD4+ memory T cell).

[0015] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies that are stable after treatment at 40C for two weeks.

[0016] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein the antibodies comprise a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells, wherein the antibodies have diminished activity relative to anti-human OX40 agonist antibodies comprising native sequence IgG1 Fc portion. In some embodiments, the antibodies comprise a variant Fc portion comprising a mutation that eliminates binding to FcR (e.g., a DANA or N297G mutation). In some embodiments, the activity is one or more of: increasing CD4+ effector T cell proliferation and/or cytokine production, increasing CD4+ memory T cell proliferation and/or cytokine production, and/or depleting cells by ADCC and/or phagocytosis.

[0017] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein antibody cross-linking is required for anti-human OX40 agonist antibody function. In some embodiments, anti-human OX40 agonist antibody function is one or more of: increasing CD4+ effector T cell proliferation and/or cytokine production, increasing CD4+ memory T cell proliferation and/or cytokine production, and/or depleting cells by ADCC and/or phagocytosis.

[0018] In another aspect, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 4, 15, or 19; and (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28.

[0019] In another aspect, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:7.

[0020] In another aspect, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e)

HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:26.

[0021] In another aspect, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:27.

[0022] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 183, or 184.

[0023] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117.

[0024] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56. In some embodments, the VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40. In some embodiments, total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56. In some embodiments, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0025] In another embodiment~~aspect~~, provided are anti-human OX40 agonist antibodies, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57. In some embodiments, the VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains

the ability to bind to human OX40. In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57. In some embodiments, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0026] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO: 56.

[0027] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VL sequence of SEQ ID NO: 57.

[0028] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57.

[0029] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO: 94.

[0030] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VL sequence of SEQ ID NO: 95.

[0031] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95.

[0032] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO: 96.

[0033] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VL sequence of SEQ ID NO: 97.

[0034] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97.

[0035] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO: 180.

[0036] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VL sequence of SEQ ID NO: 179.

[0037] In another aspect, provided are agonist anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO:180 and a VL sequence of SEQ ID NO: 179.

[0038] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO: 182.

[0039] In another embodimentaspect, provided are anti-human OX40 agonist antibodies comprising a VL sequence of SEQ ID NO: 181.

[0040] In another aspect, provided are agonist anti-human OX40 agonist antibodies comprising a VH sequence of SEQ ID NO:182 and a VL sequence of SEQ ID NO: 181.

[0041] In some embodiments of any of the antibodies of the disclosure~~invention~~, the antibody is a full length human IgG1 antibody.

[0042] In some embodiments of any of the antibodies of the disclosure~~invention~~, the antibody is a human antibody. In some embodiments of any of the antibodies of the disclosure~~invention~~, the antibody is a humanized antibody. In some embodiments of any of the antibodies of the disclosure~~invention~~, the antibody is a chimeric antibody.

[0043] In some embodiments of any of the antibodies of the disclosure~~invention~~, the antibody is a naked antibody.

[0044] In another aspect, provided are isolated nucleic acids encoding any of the anti-human OX40 antibodies (e.g., agonist antibodies) provided herein.

[0045] In another aspect, provided are host cells comprising the nucleic acid encoding any of the anti-human OX40 antibodies (e.g., agonist antibodies) provided herein.

[0046] In another aspect, provided are methods of producing an antibody comprising culturing the host cell provided herein so that the antibody is produced. In some embodiments, the methods further comprise recovering the antibody from the host cell.

[0047] In another aspect, provided are immunoconjugates comprising any of the anti-human OX40 antibodies (e.g., agonist antibodies) provided herein and a cytotoxic agent.

[0048] In another aspect, provided are pharmaceutical formulations comprising any of the anti-human OX40 antibodies (e.g., agonist antibodies) provided herein and a pharmaceutically acceptable carrier. In ~~some embodiments~~yet another aspect, provided are~~the~~ pharmaceutical formulations comprise~~sing~~ (a) any of the anti-human OX40 agonist antibodies described herein at a concentration between about 10 mg/mL and about 100 mg/mL, (b) a polysorbate, wherein the polysorbate concentration is about 0.02% to about 0.06%; (c) a histidine buffer at about pH 5.0 to about pH 6.0; and (d) a saccharide, wherein the saccharide concentration is about 120mM to about 320 mM. In some embodiments, the histidine buffer is at pH 5.0 to 6.0. In some embodiments, the saccharide is sucrose. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 320 mM. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 5.5; and (d) sucrose, wherein the sucrose concentration is about 240 mM. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 120 mM. In some embodiments, the pharmaceutical

[0049] In another aspect, an anti-human OX0 agonist antibod~~ies~~y provided herein is for use as a medicament.

[0050] In another aspect, an anti-human OX0 agonist antibody provided herein is for use in treating cancer.

[0051] In another aspect, an anti-human OX0 agonist antibody provided herein is for use in one or more of: inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function, decrease tumor immunity, enhance T cell function and/or depleting OX-40 expressing cells.

[0052] In another aspect, provided is use of an anti-human OX0 agonist antibody provided herein in the manufacture of a medicament for treatment of cancer.

[0053] In another aspect, provided is use of an anti-human OX0 agonist antibody provided herein in the manufacture of a medicament for one or more of: inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function, decrease tumor immunity, enhance T cell function and/or depleting OX-40 expressing cells.

[0054] In another embodiment~~aspect~~, provided are methods of treating an individual having cancer comprising administering to the individual an effective amount of any of the anti-human OX40 agonist antibodies provided herein. In some embodiments, the methods further comprise administering an additional therapeutic agent. In some embodiments, the additional therapeutic agent comprises a chemotherapeutic agent. In some embodiments, the additional therapeutic agent comprises a PD-1 axis binding antagonist.

[0055] In another embodiment~~aspect~~, provided are methods of diagnosis or detection using any of the anti-human OX40 antibodies disclosed herein.

[0056] In another embodiment~~aspect~~, provided are kits or articles of manufacture comprising any of the anti-human OX40 antibodies disclosed herein. In some embodiments, the kits or articles of manufacture comprise a medicament comprising an anti-human OX40 agonist antibody described herein and an optional pharmaceutically acceptable carrier. In some embodiments, the kits or articles of manufacture further comprise instructions for administration of the medicament for treatment of cancer.

[0057] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure~~invention~~. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the disclosure~~invention~~ are further described by the detailed description that follows.

70. Use of the antibody of any one of claims 1-58 in the manufacture of a medicament for one or more of: inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function, decrease tumor immunity, enhance T cell function and/or depleting OX-40 expressing cells.
71. A method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody of any one of claims 1-58.
72. The method of claim 71, further comprising administering an additional therapeutic agent.
73. The method of claim 72, wherein the additional therapeutic agent comprises a chemotherapeutic agent.
74. The method of claim 72, wherein the additional therapeutic agent comprises a PD-1 axis binding antagonist.

70. Use of the antibody of any one of claims 1-58 in the manufacture of a medicament for one or more of: inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function, decrease tumor immunity, enhance T cell function and/or depleting OX-40 expressing cells.
71. The use of claim 69, where in the medicament is to be administered with an additional therapeutic agent.
72. The use of claim 71, wherein the additional therapeutic agent comprises a chemotherapeutic agent.
73. The use of claim 71, wherein the additional therapeutic agent comprises a PD-1 axis binding antagonist.