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Canadian Intellectual Property Office

CA 3041340 A1 2018/05/17

(21) 3 041 340

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2017/11/09
(87) Date publication PCT/PCT Publication Date: 2018/05/17
(85) Entrée phase nationale/National Entry: 2019/04/18
(86) N° demande PCT/PCT Application No.: US 2017/060854
(87) N° publication PCT/PCT Publication No.: 2018/089628
(30) Priorité/Priority: 2016/11/09 (US62/419,907)

(51) Cl.Int./Int.Cl. *A61K 39/395* (2006.01), *C07K 16/00* (2006.01), *C07K 16/28* (2006.01)

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(54) Titre : ANTICORPS ANTI-OX40, ANTICORPS ANTI-GITR, ET LEURS PROCEDES D'UTILISATION
(54) Title: ANTI-OX40 ANTIBODIES, ANTI-GITR ANTIBODIES, AND METHODS OF USE THEREOF

(57) Abrégé/Abstract:
The present disclosure provides antibodies that specifically bind to human OX40 receptor (OX40) and/or human GITR receptor (GITR), including multispecific antibodies that bind, e.g., to OX40 and GITR, and compositions comprising such antibodies. The antibodies disclosed herein modulate OX40 and/or GITR activity e.g., enhance, activate, induce, reduce, deactivate, or inhibit OX40 and/or GITR activity. The present disclosure also provides methods for treating disorders, such as cancer, autoimmune diseases or disorders, or inflammatory diseases or disorders, by administering an antibody that specifically binds to human OX40 and/or human GITR and modulates OX40 and/or GITR activity.

CA 3041340 A1 2018/05/17

(21) 3 041 340

(13) A1

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2018 (17.05.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/089628 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/00* (2006.01)
C07K 16/28 (2006.01)

(21) International Application Number:
PCT/US2017/060854

(22) International Filing Date:
09 November 2017 (09.11.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/419,907 09 November 2016 (09.11.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2018/089628 A1

(54) Title: ANTI-OX40 ANTIBODIES, ANTI-GITR ANTIBODIES, AND METHODS OF USE THEREOF

(57) Abstract: The present disclosure provides antibodies that specifically bind to human OX40 receptor (OX40) and/or human GITR receptor (GITR), including multispecific antibodies that bind, e.g., to OX40 and GITR, and compositions comprising such antibodies. The antibodies disclosed herein modulate OX40 and/or GITR activity e.g., enhance, activate, induce, reduce, deactivate, or inhibit OX40 and/or GITR activity. The present disclosure also provides methods for treating disorders, such as cancer, autoimmune diseases or disorders, or inflammatory diseases or disorders, by administering an antibody that specifically binds to human OX40 and/or human GITR and modulates OX40 and/or GITR activity.

ANTI-OX40 ANTIBODIES, ANTI-GITR ANTIBODIES, AND METHODS OF USE THEREOF

1. FIELD

[0001] The present disclosure relates to antibodies, including monospecific and multispecific (*e.g.*, bispecific) antibodies, that specifically bind to human OX40 receptor ("OX40"), compositions comprising such antibodies, and methods of producing and using those antibodies. Also provided are antibodies, including monospecific and multispecific (*e.g.*, bispecific) antibodies, that specifically bind to human glucocorticoid-induced TNFR family related receptor (GITR), compositions comprising such antibodies, and methods of producing and using those antibodies. Exemplary multispecific (*e.g.*, bispecific) antibodies provided herein bind to human OX40 and human GITR.

2. BACKGROUND

[0002] The contributions of the innate and adaptive immune response in the control of human tumor growth are well-characterized (Vesely MD *et al.*, (2011) Annu Rev Immunol 29: 235-271). As a result, antibody-based strategies have emerged that aim to enhance T cell responses for the purpose of cancer therapy, such as targeting T cell expressed stimulatory receptors with agonist antibodies, or inhibitory receptors with functional antagonists (Mellman I *et al.*, (2011) Nature 480: 480-489). Antibody-mediated agonist and antagonist approaches have shown preclinical, and more recently clinical, activity. An important stimulatory receptor that modulates T cell, Natural Killer T (NKT) cell, and NK cell function is the OX40 receptor (also known as OX40, CD134, TNFRSF4, TXGP1L, ACT35, and ACT-4) (Sugamura K *et al.*, (2004) Nat Rev Immunol 4: 420-431). OX40 is a member of the tumor necrosis factor receptor superfamily (TNFRSF) and signaling via OX40 can modulate important immune functions.

[0003] OX40 can be upregulated by antigen-specific T cells following T cell receptor (TCR) stimulation by professional antigen presenting cells (APCs) displaying MHC class I or II molecules loaded with a cognate peptide (Sugamura K *et al.*, (2004) Nat Rev Immunol 4: 420-431). Upon maturation APCs such as dendritic cells (DCs) upregulate stimulatory B7 family

members (*e.g.*, CD80 and CD86), as well as accessory co-stimulatory molecules including OX40 ligand (OX40L), which help to sculpt the kinetics and magnitude of the T cell immune response, as well as effective memory cell differentiation. Notably, other cell types can also express constitutive and/or inducible levels of OX40L such as B cells, vascular endothelial cells, mast cells, and in some instances activated T cells (Soroosh P *et al.*, (2006) J Immunol 176: 5975-5987). OX40:OX40L co-engagement is believed to drive the higher order clustering of receptor trimers and subsequent signal transduction (Compaan DM *et al.*, (2006) Structure 14: 1321-1330).

[0004] OX40 expression by T cells within the tumor microenvironment has been observed in murine and human tumor tissues (Bulliard Y *et al.*, (2014) Immunol Cell Biol 92: 475-480 and Piconese S *et al.*, (2014) Hepatology 60: 1494-1507). OX40 is highly expressed by intratumoral populations of regulatory T cells (Tregs) relative to conventional T cell populations, a feature attributed to their proliferative status (Waight JD *et al.*, (2015) J Immunol 194: 878-882 and Bulliard Y *et al.*, (2014) Immunol Cell Biol 92: 475-480). Early studies demonstrated that OX40 agonist antibodies were able to elicit tumor rejection in mouse models (Weinberg AD *et al.*, (2000) J Immunol 164: 2160-2169 and Piconese S *et al.*, (2008) J Exp Med 205: 825-839). A mouse antibody that agonizes human OX40 signaling has also been shown to enhance immune functions in cancer patients (Curti BD *et al.*, (2013) Cancer Res 73: 7189-7198).

[0005] OX40 and OX40L interactions also have been associated with immune responses in inflammatory and autoimmune diseases and disorders, including mouse models of asthma/atopy, encephalomyelitis, rheumatoid arthritis, colitis/inflammatory bowel disease, graft-versus-host disease (*e.g.*, transplant rejection), diabetes in non-obese diabetic mice, and atherosclerosis (Croft M *et al.*, (2009) Immunol Rev 229(1): 173-191, and references cited therein). Reduced symptomatology associated with the diseases and disorders has been reported in OX40- and OX40L-deficient mice, in mice receiving anti-OX40 liposomes loaded with a cytostatic drug, and in mice in which OX40 and OX40L interactions were blocked with an anti-OX40L blocking antibody or a recombinant OX40 fused to the Fc portion of human immunoglobulin (Croft M *et al.*; Boot EPJ *et al.*, (2005) Arthritis Res Ther 7: R604-615; Weinberg AD *et al.*, (1999) J Immunol 162: 1818-1826). Treatment with a blocking anti-OX40L antibody was also shown to inhibit Th2 inflammation in a rhesus monkey model of asthma (Croft M *et al.*, Seshasayee D *et al.*, (2007) J Clin Invest 117: 3868-3878). Additionally, polymorphisms in OX40L have been

associated with lupus (Croft M et al.).

[0006] Another important stimulator of immune responses is glucocorticoid-induced TNFR-related protein (GITR). GITR (also known as activation-inducible TNFR family receptor (AITR), GITR-D, CD357, and tumor necrosis factor receptor superfamily member 18 (TNFRSF18)), is expressed in many components of the innate and adaptive immune system and stimulates both acquired and innate immunity (Nocentini G *et al.*, (1994) PNAS 94: 6216-6221; Hanabuchi S *et al.*, (2006) Blood 107:3617-3623; Nocentini G & Riccardi C (2005) Eur J Immunol 35: 1016-1022; Nocentini G *et al.*, (2007) Eur J Immunol 37:1165-1169). It is expressed in several cells and tissues, including T, B, dendritic (DC) and Natural Killer (NK) cells and is activated by its ligand, GITRL, mainly expressed on antigen presenting cells (APCs), endothelial cells, and also tumor cells. The GITR/GITRL system participates in the development of autoimmune/inflammatory responses and potentiates response to infection and tumors. For example, treating animals with GITR-Fc fusion protein ameliorates autoimmune/inflammatory diseases while GITR triggering is effective in treating viral, bacterial, and parasitic infections, as well in boosting immune response against tumors (Nocentini G *et al.*, (2012) Br J Pharmacol 165: 2089-99). These effects are due to several concurrent mechanisms including: co-activation of effector T cells, inhibition of regulatory T (Treg) cells, NK-cell co-activation, activation of macrophages, modulation of dendritic cell function and regulation of the extravasation process. The membrane expression of GITR is increased following T cell activation (Hanabuchi S *et al.*, (2006) *supra*; Nocentini G & Riccardi C *supra*). Its triggering coactivates effector T lymphocytes (McHugh RS *et al.*, (2002) Immunity 16: 311-323; Shimizu J *et al.*, (2002) Nat Immunol 3: 135-142; Roncheti S *et al.*, (2004) Eur J Immunol 34: 613-622; Tone M *et al.*, (2003) PNAS 100: 15059-15064). GITR activation increases resistance to tumors and viral infections, is involved in autoimmune/inflammatory processes and regulates leukocyte extravasation (Nocentini G & Riccardi C (2005) *supra*; Cuzzocrea S *et al.*, (2004) J Leukoc Biol 76: 933-940; Shevach EM & Stephens GL (2006) Nat Rev Immunol 6: 613-618; Cuzzocrea S *et al.*, (2006) J Immunol 177: 631-641; Cuzzocrea S *et al.*, (2007) FASEB J 21: 117-129).

[0007] Human GITR is expressed at very low levels in peripheral (non-activated) T cells. After T cell activation, GITR is strongly up-regulated for several days in both $CD4^+$ and $CD8^+$ cells (Kwon B *et al.*, (1999) J Biol Chem 274: 6056-6061; Gurney AL *et al.*, (1999) Curr Biol 9: 215-218; Ronchetti S *et al.*, (2004) *supra*; Shimizu J *et al.*, (2002) *supra*; Ji HB *et al.*, (2004)

supra; Ronchetti S *et al.*, (2002) Blood 100: 350-352; Li Z *et al.*, (2003) J Autoimmun 21: 83-92), with $CD4^+$ cells having a higher GITR expression than $CD8^+$ cells (Kober J *et al.*, (2008) Eur J Immunol 38(10): 2678-88; Bianchini R *et al.*, (2011) Eur J Immunol 41(8): 2269-78).

[0008] Given the role of human OX40 and GITR in modulating immune responses, provided herein are antibodies that specifically bind to OX40 or GITR. Such antibodies include multispecific antibodies, for example bispecific antibodies that specifically bind to OX40 and/or GITR. Thus use of such antibodies to modulate OX40 activity and/or GITR activity are also provided herein.

3. SUMMARY

[0009] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein: (a) CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein X_1 is G, Q, H, or E, X_2 is S, E, or Y, and X_3 is A, S, or G; (b) CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein X_1 is A, S, or Y, X_2 is N, E, or Y, X_3 is S, Q, or G, X_4 is Y, E, or Q, and X_5 is A, E, or L; (c) CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein X_1 is Y or A, X_2 is D or A, X_3 is S, T, or W, X_4 is S, E, or L, X_5 is G or A, X_6 is Y or A, and X_7 is D or A; (d) CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); (e) CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and (f) CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein X_1 is A or G, X_2 is L or S, X_3 is Q or K, and X_4 is T or W, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

[0010] In one embodiment, CDRH2 comprises the amino acid sequence of RIRSKAXSYATAYAASVKG (SEQ ID NO: 44), wherein: X is N or Y. In one embodiment, CDRH3 comprises the amino acid sequence of $GIX_1X_2SSGX_3X_4Y$ (SEQ ID NO: 45), wherein: X_1 is Y or A; X_2 is D or A; X_3 is Y or A; and X_4 is D or A.

[0011] In one embodiment, CDRH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-20. In one embodiment, CDRH2 comprises an amino acid

sequence selected from the group consisting of SEQ ID NOs: 21-24. In one embodiment, CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-31. In one embodiment, CDRL3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-38.

[0012] In one embodiment, CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively.

[0013] In one embodiment, CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively.

[0014] In one embodiment, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16, 21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively.

[0015] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34, respectively.

[0016] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 37, respectively.

[0017] In one embodiment, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 47 or 48.

[0018] In one embodiment, the antibody comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.

[0019] In one embodiment, the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.

[0020] In one embodiment, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 49.

[0021] In one embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15. In one embodiment, the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15.

[0022] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-10.

[0023] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-14.

[0024] In one embodiment, provided herein is an isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.

[0025] In one embodiment, the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11, respectively. In one embodiment, the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively.

[0026] In one embodiment, the antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence.

[0027] In one embodiment, the antibody comprises a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence.

[0028] In one embodiment, the antibody comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2.

[0029] In one embodiment, the heavy chain constant region is IgG_1. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 88, 89, 90, or 91. In one embodiment, the amino acid sequence of IgG_1 comprises S239D and I332E mutations, numbered according to the EU numbering system. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 107. In one embodiment, the amino acid sequence of IgG_1 comprises S239D, A330L, and I332E mutations, numbered according to the EU numbering system. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 108. In one embodiment, the amino acid sequence of IgG_1 comprises L235V, F243L, R292P, Y300L, and P396L mutations, numbered according to the EU numbering system. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 109. In one embodiment, the IgG_1 is non-fucosylated IgG_1. In one embodiment, the amino acid sequence of IgG_1 comprises a N297A or N297Q mutation, numbered according to the EU numbering system. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 92.

[0030] In one embodiment, the heavy chain constant region is IgG_4. In one embodiment, the amino acid sequence of IgG_4 comprises a S228P mutation, numbered according to the EU numbering system. In one embodiment, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 93.

[0031] In one embodiment, the antibody comprises a light chain constant region selected from the group consisting of human IgGκ and IgGλ. In one embodiment, the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 94.

[0032] In one embodiment, provided herein is an isolated antibody that comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody cross-competes for binding to human OX40 with an anti-OX40 antibody provided herein.

[0033] In one embodiment, provided herein is an isolated antibody that comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody binds to the same epitope of human OX40 as an antibody provided herein.

[0034] In one embodiment, the antibody is human.

[0035] In one embodiment, the antibody is conjugated to a cytotoxic agent, cytostatic agent, toxin, radionuclide, or detectable label.

[0036] In any antibody embodiments as disclosed herein, the N-terminal amino acid residue of a heavy chain variable region of the antibody has been converted to pyroglutamate (e.g., as a result of post-translational cyclization of the free amino group of the N-terminal glutamic acid or glutamine residue of the heavy chain variable region). In any antibody embodiments as disclosed herein, the N-terminal amino acid residue of a heavy chain of the antibody has been converted to pyroglutamate (e.g., as a result of post-translational cyclization of the free amino group of the N-terminal glutamic acid or glutamine residue of the heavy chain).

[0037] In one embodiment, provided herein is an isolated multispecific antibody comprising a first antigen-binding domain of an antibody provided herein, wherein the first antigen-binding domain specifically binds to human OX40 and comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[0038] In one embodiment, CDRH1, CDRH2, and CDRH3 of the first antigen-binding domain that specifically binds to human OX40 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively.

[0039] In one embodiment, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically binds to human OX40 comprise the CDRL1, CDRL2, and CDRL3

amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively.

[0040] In one embodiment, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16, 21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively.

[0041] In one embodiment, the heavy chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.

[0042] In one embodiment, the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15.

[0043] In one embodiment, the heavy chain variable region and the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.

[0044] In one embodiment, the second antigen-binding domain specifically binds to human GITR. In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein: (a) CDRH1 comprises the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 76), wherein X_1 is D, E or G, X_2 is A or V, and X_3 is Y or H; (b) CDRH2 comprises the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO: 77), 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; (c) CDRH3 comprises the amino acid sequence of SGTVXGFAY (SEQ ID NO: 99), wherein; X is R or A; (d) CDRL1 comprises the amino acid sequence of $KSSQSLLNSX_1NQKNYLX_2$ (SEQ ID NO: 80), wherein X_1 is G or S, and X_2 is T or S; (e) CDRL2 comprises the amino acid sequence of WASTRES (SEQ ID NO: 71); and (f) CDRL3 comprises the amino acid sequence of QNX_1YSX_2PYT (SEQ ID NO: 81),

wherein X_1 is D, E, or A; and X_2 is Y, F, or S.

[0045] In one embodiment, CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of X_1YAMX_2 (SEQ ID NO: 78), wherein: X_1 is D, G, or E; and X_2 is Y or H.

[0046] In one embodiment, CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of $X_1IRTYSGX_2VX_3YNQKFX_4X_5$ (SEQ ID NO: 79), 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.

[0047] In one embodiment, CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of KSSQSLLNSXNQKNYLT (SEQ ID NO: 82), wherein: X is G or S.

[0048] In one embodiment, CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of QNX_1YSX_2PYT (SEQ ID NO: 83), wherein: X_1 is D, E, or A; and X_2 is Y or F.

[0049] In one embodiment, CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-62. In one embodiment, CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-67. In one embodiment, CDRH3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 68 and 97. In one embodiment, CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 69 and 70. In one embodiment, CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 73, and 98.

[0050] In one embodiment, CDRH1, CDRH2, and CDRH3 of the second antigen-binding domain that specifically binds to human GITR comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 60, 63, and 68; 60, 64, and 68; 60, 63, and 97; 61, 65, and 68; 62, 66, and 68; or 62, 67, and 68, respectively.

[0051] In one embodiment, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the CDRL1, CDRL2, and CDRL3

amino acid sequences set forth in SEQ ID NOs: 69, 71, and 72; 69, 71, and 98; 70, 71, and 73; or 69, 71, and 72, respectively.

[0052] In one embodiment, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 60, 63, 68, 69, 71, and 72; 60, 64, 68, 69, 71, and 72; 60, 63, 97, 69, 71, and 72; 60, 63, 68, 69, 71, and 98; 61, 65, 68, 70, 71, and 73; 62, 66, 68, 69, 71, and 72; or 62, 67, 68, 69, 71, and 72, respectively.

[0053] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 84.

[0054] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-56, and 95.

[0055] In one embodiment, the heavy chain variable region of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-56, and 95.

[0056] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85.

[0057] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-59, and 96.

[0058] In one embodiment, the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-59, and 96.

[0059] In one embodiment, the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 52 and 57; 53 and 57; 95 and 57; 52 and 96; 54 and 58; 55 and 59; or 56 and 59, respectively.

[0060] In one embodiment, 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.

[0061] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region having an amino acid sequence derived from a human IGKV4-1 germline sequence.

[0062] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2.

[0063] In one embodiment, the heavy chain constant region of the second antigen-binding domain that specifically binds to human GITR is IgG_1.

[0064] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 88, 89, 90, or 91.

[0065] In one embodiment, the amino acid sequence of IgG_1 comprises S239D and I332E mutations, numbered according to the EU numbering system.

[0066] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 107.

[0067] In one embodiment, the amino acid sequence of IgG_1 comprises S239D, A330L, and I332E mutations, numbered according to the EU numbering system.

[0068] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 108.

[0069] In one embodiment, the amino acid sequence of IgG_1 comprises L235V, F243L, R292P, Y300L, and P396L mutations, numbered according to the EU numbering system.

[0070] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 109.

[0071] In one embodiment, the IgG_1 is non-fucosylated IgG_1.

[0072] In one embodiment, the amino acid sequence of IgG_1 of the second antigen-binding

domain that specifically binds to human GITR comprises a N297A or N297Q mutation, numbered according to the EU numbering system.

[0073] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 92.

[0074] In one embodiment, the heavy chain constant region of the second antigen-binding domain that specifically binds to human GITR is IgG_4.

[0075] In one embodiment, the amino acid sequence of IgG_4 of the second antigen-binding domain that specifically binds to human GITR comprises a S228P mutation, numbered according to the EU numbering system.

[0076] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 93.

[0077] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a light chain constant region selected from the group consisting of human IgGκ and IgGλ.

[0078] In one embodiment, the second antigen-binding domain that specifically binds to human GITR comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 94.

[0079] In one embodiment, the second antigen-binding domain that specifically binds to human GITR is humanized.

[0080] In one embodiment, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically binds to human OX40 and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences listed in a single row of Table 12.

[0081] In one embodiment, provided herein is an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain that specifically binds to human GITR, wherein the first antigen-binding domain comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising CDRL1, CDRL2, and CDRL3, and wherein the second antigen-binding domain comprises a heavy chain variable region comprising CDRH1, CDRH2,

and CDRH3 and a light chain variable region comprising CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 12.

[0082] In one embodiment, the heavy chain variable region and the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 and the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences listed in a single row of Table 13.

[0083] In one embodiment, provided here in is an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain that specifically binds to human GITR, wherein the first antigen-binding domain comprises a heavy chain variable region and a light chain variable region, and wherein the second antigen-binding domain comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain and the heavy chain variable region and the light chain variable region of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 13.

[0084] In one embodiment, provided herein is an isolated antibody that specifically binds to human GITR, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 60, 64, 68, 69, 71, and 72, respectively.

[0085] In one embodiment, the heavy chain variable region and the light chain variable region of the antibody comprise the amino acid sequences set forth in SEQ ID NOs: 53 and 57, respectively.

[0086] In one embodiment, provided herein is an isolated antibody that specifically binds to human GITR, the antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53.

[0087] In one embodiment, provided herein is an isolated multispecific antibody comprising

a first antigen-binding domain and a second antigen-binding domain, wherein the second antigen-binding domain specifically binds to human GITR and comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 60, 64, 68, 69, 71, and 72, respectively.

[0088] In one embodiment, the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 53 and 57, respectively.

[0089] In one embodiment, provided herein is an isolated multispecific antibody comprising a first antigen-binding domain and a second antigen-binding domain, wherein the second antigen-binding domain specifically binds to human GITR and comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53.

[0090] In one embodiment, the first antigen-binding domain specifically binds to human OX40.

[0091] In one embodiment, the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein: (a) CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein X_1 is G, Q, H, or E, X_2 is S, E, or Y, and X_3 is A, S, or G; (b) CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein X_1 is A, S, or Y, X_2 is N, E, or Y, X_3 is S, Q, or G, X_4 is Y, E, or Q, and X_5 is A, E, or L; (c) CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein X_1 is Y or A, X_2 is D or A, X_3 is S, T, or W, X_4 is S, E, or L, X_5 is G or A, X_6 is Y or A, and X_7 is D or A; (d) CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); (e) CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and (f) CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein X_1 is A or G, X_2 is L or S, X_3 is Q or K, and X_4 is T or W.

[0092] In one embodiment, the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3

regions of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively.

[0093] In one embodiment, the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively.

[0094] In any multispecific antibody embodiments as disclosed herein, the N-terminal amino acid residues of one or more heavy chain variable regions of the antibody (e.g., the heavy chain variable regions of a first antigen-binding domain and/or of a second antigen-binding domain) has been converted to pyroglutamate (e.g., as a result of post-translational cyclization of the free amino group of the N-terminal glutamic acid or glutamine residue of the heavy chain variable region). In any multispecific antibody embodiments as disclosed herein, the N-terminal amino acid residue of one or more heavy chains of the antibody has been converted to pyroglutamate (e.g., as a result of post-translational cyclization of the free amino group of the N-terminal glutamic acid or glutamine residue of the heavy chain).

[0095] In one embodiment, provided herein is a pharmaceutical composition comprising an antibody or a multispecific antibody provided herein and a pharmaceutically acceptable carrier or excipient.

[0096] In one embodiment, provided herein is an isolated polynucleotide encoding a heavy and/or light chain of an antibody or a multispecific antibody provided herein.

[0097] In one embodiment, provided herein is an isolated polynucleotide encoding an antibody or a multispecific antibody provided herein.

[0098] In one embodiment, provided herein is a vector comprising a polynucleotide provided herein.

[0099] In one embodiment, provided herein is a recombinant host cell comprising a polynucleotide or vector provided herein.

[00100] In one embodiment, provided herein is a method of producing an antibody that specifically binds to human OX40, a multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain, an antibody that specifically binds to human GITR, or a multispecific antibody comprising a first antigen-binding domain and a second antigen-binding domain that specifically binds to human GITR, the method comprising culturing a host cell provided herein so that the polynucleotide is

expressed and the antibody or the multispecific antibody is produced.

[00101] In one embodiment, provided herein is a method of modulating an immune response in a subject, the method comprising administering to the subject an effective amount of an antibody, a multispecific antibody, or a pharmaceutical composition provided herein.

[00102] In one embodiment, provided herein is a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of an antibody, a multispecific antibody, or a pharmaceutical composition provided herein.

[00103] In one embodiment, provided herein is a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an antibody, a multispecific antibody, or a pharmaceutical composition provided herein.

[00104] In one embodiment, the cancer is selected from the group consisting of melanoma, renal cancer, prostate cancer, colon cancer, and lung cancer.

[00105] In one embodiment, the method further comprises administering an additional therapeutic agent to the subject. In one embodiment, the additional therapeutic agent is a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent. In one embodiment, 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. In one embodiment, the additional therapeutic agent is an inhibitor of indoleamine-2,3-dioxygenase (IDO). In one embodiment, the inhibitor is selected from the group consisting of epacadostat, F001287, indoximod, and NLG919. In one embodiment, the additional therapeutic agent is a vaccine. In one embodiment, the vaccine comprises a heat shock protein peptide complex (HSPPC) comprising a heat shock protein complexed with an antigenic peptide. In one embodiment, the heat shock protein is hsc70 and is complexed with a tumor-associated antigenic peptide. In one embodiment, 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 a subject.

[00106] In one embodiment, provided herein is a method for reducing or inhibiting an immune response in a subject, the method comprising administering to the subject an effective amount of an antibody, a multispecific antibody, or a pharmaceutical composition provided

herein.

[00107] In one embodiment, provided herein is 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 an antibody, a multispecific antibody, or a pharmaceutical composition provided herein.

[00108] In one embodiment, 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.

[00109] In one embodiment, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody) of the invention, or a pharmaceutical composition of the invention, or a polynucleotide of the invention, or a vector of the invention, or a recombinant host cell of the invention for use as a medicament.

[00110] In one embodiment, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody) of the invention, or a pharmaceutical composition of the invention, or a polynucleotide of the invention, or a vector of the invention, or a recombinant host cell of the invention for use as a diagnostic.

[00111] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for increasing an immune response.

[00112] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for increasing an immune response in a subject comprising administering to the subject an effective amount of an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the invention.

[00113] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for the treatment of cancer.

[00114] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical

composition of the present invention for use in a method for the treatment of cancer in a subject comprising administering to the subject an effective amount of an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the invention.

[00115] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for the treatment of an infectious disease.

[00116] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for the treatment of an infectious disease in a subject comprising administering to the subject an effective amount of an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the invention.

[00117] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for inhibiting an immune response.

[00118] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for inhibiting an immune response in a subject comprising administering to the subject an effective amount of an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the invention.

[00119] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for the treatment of an autoimmune or inflammatory disease or disorder.

[00120] In one aspect, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention for use in a method for the treatment of an autoimmune or inflammatory disease or disorder in a subject comprising administering to the subject an

effective amount of an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the invention.

[00121] In one aspect, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent for use as a medicament.

[00122] In one aspect, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent for use in a method for the treatment of cancer.

[00123] In one aspect, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent for use in a method for the treatment of an infectious disease.

[00124] In one aspect, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent for use in a method for the treatment of an autoimmune or inflammatory disease or disorder.

[00125] In one aspect, the present invention relates to a pharmaceutical composition, kit or kit-of-parts comprising (a) an antibody (*e.g.*, a monospecific or multispecific antibody), polynucleotide, vector, recombinant host cell, and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent.

4. BRIEF DESCRIPTION OF THE FIGURES

[00126] **Figures 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, and 1J** are a set of flow cytometry plots showing the binding of anti-OX40 antibodies or an isotype control antibody to Jurkat cells expressing human OX40. The anti-OX40 antibodies tested include pab1949, pab2049, heavy chain variants of pab1949 (pab1949 N56Y, pab1949 Y103A, pab1949 D104A, pab1949 Y108A, and pab1949 D109A), and light chain variants of pab1949 (pab1949 A96G/L97S, pab1949 Q98K, and pab1949 T99W). All the anti-OX40 antibodies tested are IgG_1 antibodies. MFI values are plotted over a range of antibody concentrations.

[00127] **Figures 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, and 2I** are results from an assay where

Jurkat-huOX40-NF-κB-luciferase reporter cells were pre-incubated with anti-OX40 antibodies or an isotype control antibody before activated by multimeric OX40L. The anti-OX40 antibodies tested include pab2049, heavy chain variants of pab1949 (pab1949 N56Y, pab1949 Y103A, pab1949 D104A, pab1949 Y108A, and pab1949 D109A), and light chain variants of pab1949 (pab1949 A96G/L97S, pab1949 Q98K, and pab1949 T99W). All the anti-OX40 antibodies tested are IgG_1 antibodies. The % OX40L activity is plotted against a range of antibody concentrations.

[00128] **Figures 3A, 3B, 3C, 3D, 3E, 3F, and 3G** are a set of flow cytometry plots showing the binding of anti-GITR antibodies or an isotype control antibody to Jurkat cells expressing human GITR. The anti-GITR antibodies tested include pab1876 (IgG_1), heavy chain variants of pab1876 (pab1876 D57G (IgG_1) and pab1876 R103A (IgG_1)), a light chain variant of pab1876 (pab1876 D97A (IgG_1)), pab1967 (IgG_1), pab1967 (IgG_1 N297A), pab1975 (IgG_1), pab1975 (IgG_1 N297A), pab1979 (IgG_1), and pab1979 (IgG_1 N297A). MFI values are plotted over a range of antibody concentrations.

5. DETAILED DESCRIPTION

[00129] Provided herein is an antibody (*e.g.*, a monospecific antibody) that specifically binds to OX40 (*e.g.*, human OX40) and modulates OX40 activity. For example, in one aspect, provided herein is an antibody that specifically binds to OX40 and enhances, induces, or increases one or more OX40 activities. For example, in another aspect, provided herein is an antibody that specifically binds to OX40 (*e.g.*, human OX40) and deactivates, reduces, or inhibits one or more OX40 activities. In a specific embodiment, the antibody is isolated.

[00130] Also provided is an antibody (*e.g.*, a monospecific antibody) that specifically binds to GITR (*e.g.*, human GITR) and modulates GITR activity. For example, in one aspect, provided herein is an antibody that specifically binds to GITR and enhances, induces, or increases one or more GITR activities. For example, in another aspect, provided herein is an antibody that specifically binds to GITR (*e.g.*, human GITR) and deactivates, reduces, or inhibits one or more GITR activities. In a specific embodiment, the antibody is isolated.

[00131] Further provided is a multispecific (*e.g.*, bispecific) antibody that specifically binds to OX40 (*e.g.*, human OX40) and/or GITR (*e.g.*, human GITR). For example, in one aspect, a multispecific (*e.g.*, bispecific) antibody provided herein can contain a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding

domain. The second antigen-binding domain can be distinct from the first antigen-binding domain. The second antigen-binding domain can bind to a different antigen (*i.e.*, an antigen that is not OX40) than the first antigen-binding domain. The second antigen-binding domain can bind to a different epitope than the first antigen-binding domain. In one instance, a multispecific (*e.g.*, bispecific) antibody provided herein contains a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR). In a specific embodiment, the multispecific antibody is isolated.

[00132] In another example, a multispecific (*e.g.*, bispecific) antibody provided herein can contain a first antigen-binding domain and a second antigen-binding domain that binds to GITR. The first antigen-binding domain can be distinct from the second antigen-binding domain. The first antigen-binding domain can bind to a different antigen (*i.e.*, an antigen that is not GITR) than the first antigen-binding domain. The second antigen-binding domain can bind to a different epitope than the first antigen-binding domain. In one instance, a multispecific (*e.g.*, bispecific) antibody provided herein contains a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR). In a specific embodiment, the multispecific antibody is isolated.

[00133] In one aspect, provided herein is a multispecific (*e.g.*, bispecific) antibody that specifically binds to OX40 and GITR and enhances, induces, or increases one or more OX40 and/or GITR activities. In another aspect, provided herein is a multispecific (*e.g.*, bispecific) antibody that specifically binds to OX40 and GITR and reduces, inhibits, or decreases one or more OX40 or GITR activities. In a specific embodiment, the multispecific antibody is isolated.

Also provided are isolated nucleic acids (polynucleotides), such as complementary DNA (cDNA), encoding such antibodies (*e.g.*, monospecific or multispecific antibodies). Further provided are vectors (*e.g.*, expression vectors) and cells (*e.g.*, host cells) comprising nucleic acids (polynucleotides) encoding such antibodies (*e.g.*, monospecific or multispecific antibodies). Also provided are methods of making such antibodies (*e.g.*, monospecific or multispecific antibodies). In other aspects, provided herein are methods and uses for inducing, increasing, or enhancing OX40 and/or GITR activity, and treating certain conditions, such as cancer. Further provided are methods and uses for inhibiting, decreasing, or reducing OX40 and/or GITR activity, and treating certain conditions, such as inflammatory or autoimmune

diseases and disorders. Related compositions (*e.g.*, pharmaceutical compositions), kits, and detection methods are also provided.

5.1 Definitions

[00134] As used herein, the terms "about" and "approximately," when used to modify a numeric value or numeric range, indicate that deviations of 5% to 10% above (*e.g.*, up to 5% to 10% above) and 5% to 10% below (*e.g.*, up to 5% to 10% below) the value or range remain within the intended meaning of the recited value or range.

[00135] As used herein, B is a "substantially increasing function" of A over a specified domain of A values if B substantially increases as A increases over the specified domain, *e.g.*, in a given experiment, or using mean values from multiple experiments. This definition allows for a value of B corresponding to a specified value of A to be up to 1%, 2%, 3%, 4%, 5%, 10%, 15%, or 20% lower relative to a value of B corresponding to any lower value of A.

[00136] As used herein, B is a "substantially decreasing function" of A over a specified domain of A values if B substantially decreases as A increases over the specified domain, *e.g.*, in a given experiment, or using mean values from multiple experiments. This definition allows for a value of B corresponding to a specified value of A to be up to 1%, 2%, 3%, 4%, 5%, 10%, 15%, or 20% higher relative to a value of B corresponding to any lower value of A.

[00137] As used herein, the terms "antibody" and "antibodies" are terms of art and can be used interchangeably herein and refer to a molecule with an antigen-binding site that specifically binds an antigen.

[00138] As used herein, the terms "antibody" and "antibodies" include full length antibodies, antigen-binding fragments of full length antibodies, and molecules comprising antibody CDRs, VH regions or VL regions. Examples of antibodies include monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, $F(ab')_2$ fragments, disulfide-linked Fvs (sdFv),

anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 or IgA_2), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG_1 or IgG_4) or subclass thereof. In a specific embodiment, the antibody is a humanized monoclonal antibody. In another specific embodiment, the antibody is a human monoclonal antibody.

[00139] "Multispecific" antibodies are antibodies with at least two different antigen-binding sites. Multispecific antibodies include bispecific antibodies that contain two different antigen-binding sites (exclusive of the Fc region). Examples of multispecific antibodies include recombinantly produced antibodies, human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain-antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, $F(ab')_2$ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), and antigen-binding fragments of any of the above. Multispecific antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 or IgA_2), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, multispecific antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG_1 or IgG_4) or subclass thereof.

[00140] As used herein, the terms "antigen-binding domain," "antigen-binding region," "antigen-binding site," and similar terms refer to the portion of antibody molecules which comprises the amino acid residues that confer on the antibody molecule its specificity for the antigen (*e.g.*, the complementarity determining regions (CDR)). The antigen-binding region can be derived from any animal species, such as rodents (*e.g.*, mouse, rat, or hamster) and humans.

[00141] As used herein, the term "anti-OX40/GITR" antibody refers to a multispecific antibody (*e.g.*, a bispecific antibody) that contains an antigen-binding domain that binds to OX40

(*e.g.*, human OX40) and an antigen-binding domain that binds to GITR (*e.g.*, human GITR).

[00142] As used herein, the terms "variable region" and "variable domain" are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[00143] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[00144] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[00145] The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding portion thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (see, *e.g.*, Kabat EA & Wu TT (1971) Ann NY Acad Sci 190: 382-391 and Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, each of which is herein incorporated by reference in its entirety). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the

Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[00146] As used herein, the terms "constant region" and "constant domain" are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[00147] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG_1, IgG_2, IgG_3, and IgG_4.

[00148] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[00149] As used herein, the term "EU numbering system" refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman, G.M. *et al.*, Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat *et al.*, Sequences of Proteins of Immunological Interest, U.S. Dept. Health and Human Services, 5th edition, 1991, each of which is herein incorporated by reference in its entirety.

[00150] "Binding affinity" generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant

(K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on}, whereas K_A is calculated from the quotient of k_{on}/k_{off}. k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation rate constant of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIAcore® or KinExA. As used herein, a "lower affinity" refers to a larger K_D.

[00151] As used herein, a "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). In certain embodiments, one or more amino acid residues within a CDR(s) or within a framework region(s) of an antibody can be replaced with an amino acid residue with a similar side chain.

[00152] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays (*e.g.*, constraining peptides using CLIPS (Chemical Linkage of Peptides onto Scaffolds) to map discontinuous or conformational epitopes), and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-

6303, each of which is herein incorporated by reference in its entirety). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see*, *e.g.*, Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.*,; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323), each of which is herein incorporated by reference in its entirety. Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See*, *e.g.*, Champe M *et al.*, (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085, each of which is herein incorporated by reference in its entirety, for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. CLIPS (Chemical Linkage of Peptides onto Scaffolds) is a technology to present one or more peptides in a structurally constrained configuration to behave as functional mimics of complex protein domains. *See*, *e.g.*, U.S. Publication Nos. US 2008/0139407 A1 and US 2007/099240 A1, and US Patent No. 7,972,993, each of which is herein incorporated by reference in its entirety. In a specific embodiment, the epitope of an antibody is determined using alanine scanning mutagenesis studies. In a specific embodiment, the epitope of an antibody is determined using hydrogen/deuterium exchange coupled with mass spectrometry. In a specific embodiment, the epitope of an antibody is determined using CLIPS Epitope Mapping Technology from Pepscan Therapeutics.

[00153] As used herein, the terms "immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen can bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIAcore®, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that immunospecifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind non-specifically to another antigen. In the context of multispecific (*e.g.*, bispecific) antibodies, the terms

"immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" refer to antibodies that have distinct specificities for more than one antigen or for more than one epitope on a single antigen. For example, a bispecific antibody may, *e.g.*, specifically bind each of human OX40 and human GITR, *e.g.*, with distinct antigen-binding domains.

[00154] In another specific embodiment, antigen-binding domains that immunospecifically bind to an antigen do not cross react with other proteins under similar binding conditions. In another specific embodiment, antigen-binding domains that immunospecifically bind to OX40 antigen do not cross react with other non-OX40 proteins. In another specific embodiment, antigen-binding domains that immunospecifically bind to GITR antigen do not cross react with other non-GITR proteins. In a specific embodiment, provided herein is an antibody containing an antigen-binding domain that binds to OX40 or GITR with higher affinity than to another unrelated antigen. In certain embodiments, provided herein is an antibody containing an antigen-binding domain that binds to OX40 or GITR (*e.g.*, human OX40 or human GITR) with a 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or higher affinity than to another, unrelated antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, the extent of binding of an anti-OX40 antigen-binding domain described herein to an unrelated, non-OX40 protein is less than 10%, 15%, or 20% of the binding of the antigen-binding domain to OX40 protein as measured by, *e.g.*, a radioimmunoassay. In a specific embodiment, the extent of binding of an anti-GITR antigen-binding domain described herein to an unrelated, non-GITR protein is less than 10%, 15%, or 20% of the binding of the antigen-binding domain to GITR protein as measured by, *e.g.*, a radioimmunoassay.

[00155] In a specific embodiment, provided herein is an antibody containing an antigen-binding domain that binds to human OX40 with higher affinity than to another species of OX40 and/or an antigen-binding domain that binds to human GITR with higher affinity than to another species of GITR. In certain embodiments, provided herein is an antibody containing an antigen-binding domain that binds to human OX40 with a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or higher affinity than to another species of OX40 as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay and/or that binds to human GITR with a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%,

65%, 70% or higher affinity than to another species of GITR as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, an antibody described herein, which binds to human OX40 and human GITR, will bind to another species of OX40 and/or GITR protein with less than 10%, 15%, or 20% of the binding of the antibody to the human OX40 and/or GITR protein as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay.

[00156] As used herein, the term "OX40 receptor" or "OX40" refers to tumor necrosis factor receptor superfamily member 4 (TNFRSF4) (also known as CD134). As used herein, the term "human OX40" refers to a human OX40 protein encoded by a wild type human OX40 gene, *e.g.*, GenBank™ accession number BC105070. An exemplary immature amino acid sequence of human OX40 is provided as SEQ ID NO: 101. An exemplary mature amino acid sequence of human OX40 is provided as SEQ ID NO: 100.

[00157] As used herein, the term "OX40 ligand" or "OX40L" refers to tumor necrosis factor ligand superfamily member 4 (TNFSF4). OX40L is otherwise known as CD252, GP34, TXGP1, and CD134L. As used herein, the term "human OX40L" refers to a human OX40L protein encoded by a wild type human OX40L gene, *e.g.*, GenBank™ accession number D90224.1. RefSeq number NP_003317.1 and Swiss-Prot accession number P23510-1 provide exemplary human OX40L amino acid sequences for isoform 1. RefSeq number NP_001284491.1 and Swiss-Prot accession number P23510-2 provide exemplary human OX40L amino acid sequences for isoform 2. Human OX40L is designated GeneID: 7292 by Entrez Gene.

[00158] As used herein, the term "GITR" refers to glucocorticoid-induced TNFR family related receptor (also known as tumor necrosis factor receptor superfamily member 18 (TNFRSF18), activation-inducible TNFR family receptor (AITR), GITR-D, or CD357). As used herein, the term "human GITR" refers to a human GITR protein encoded by a wild type human GITR gene, *e.g.*, GenBank™ accession numbers BC152381 and BC152386. Exemplary immature amino acid sequences of human GITR are provided as SEQ ID NOs: 103, 104, and 105. An exemplary mature amino acid sequence of human GITR is provided as SEQ ID NO: 102. An exemplary immature amino acid sequence of cynomolgus GITR is provided as SEQ ID NO: 106.

[00159] As used herein, the terms "GITR ligand" and "GITRL" refer to glucocorticoid-induced TNFR-related protein ligand. GITRL is otherwise known as activation-induced TNF-

related ligand (AITRL) and tumor necrosis factor ligand superfamily member 18 (TNFSF18). As used herein, the term "human GITRL" refers to a human GITRL protein encoded by a wild type human GITRL gene, *e.g.*, GenBank™ accession number AF125303. GenBank™ accession number NP_005083 and Swiss-Prot accession number Q9UNG2 provide exemplary human GITRL amino acid sequences.

Table 1. Exemplary OX40 and GITR sequences.

SEQ ID NO:	Description	Amino acid Sequence
100	Mature human OX40 sequence	LHCVGDTYPSNDRCCHECRPGNGMVSRCSRSQNTVCRPCGP GFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCR AGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAG KHTLQPASNSSDAICEDRDPPATQPQETQGPPARPITVQPT EAWPRTSQGPSTRPVEVPGGRAVAAILGLGLVLGLLGPLAI LLALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTL AKI
101	Immature human OX40 sequence	MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDR CCHECRPGNGMVSRCSRSQNTVCRPCGPGFYNDVVSSKPCK PCTWCNLRSGSERKQLCTATQDTVCRCRAGTQPLDSYKPGV DCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQPASNSSDA ICEDRDPPATQPQETQGPPARPITVQPTEAWPRTSQGPSTR PVEVPGGRAVAAILGLGLVLGLLGPLAILLALYLLRRDQRL PPDAHKPPGGGSFRTPIQEEQADAHSTLAKI
102	Mature human GITR sequence (Isoform 1)	QRPTGGPGCGPGRLLLGTGTDARCCRVHTTRCCRDYPGEEC CSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGVQSQGKFS FGFQCIDCASGTFSGGHEGHCKPWTDCTQFGFLTVFPGNKT HNAVCVPGSPPAEPLGWLTVVLLAVAACVLLLTSAQLGLHI WQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSA EEKGRLGDLWV
103	Immature human GITR sequence (Isoform 1)	MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLL GTGTDARCCRVHTTRCCRDYPGEECCSEWDCMCVQPEFHCG DPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDCASGTFSGG HEGHCKPWTDCTQFGFLTVFPGNKTHNAVCVPGSPPAEPLG WLTVVLLAVAACVLLLTSAQLGLHIWQLRSQCMWPRETQLL LEVPPSTEDARSCQFPEEERGERSAEEKGRLGDLWV
104	Immature human GITR sequence (Isoform 2)	MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLL GTGTDARCCRVHTTRCCRDYPGEECCSEWDCMCVQPEFHCG DPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDCASGTFSGG HEGHCKPWTDCCWRCRRRPKTPEAASSPRKSGASDRQRRRG GWETCGCEPGRPPGPPTAASPSPGAPQAAGALRSALGRALL PWQQKWVQEGGSDQRPGPCSSAAAAGPCRRERETQSWPPSS LAGPDGVGS

SEQ ID NO:	Description	Amino acid Sequence
105	Immature human GITR sequence (Isoform 3)	MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLL GTGTDARCCRVHTTRCCRDYPGEECCSEWDCMCVQPEFHCG DPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDCASGTFSGG HEGHCKPWTDCTQFGFLTVFPGNKTHNAVCVPGSPPAEPLG WLTVVLLAVAACVLLLTSAQLGLHIWQLRKTQLLLEVPPST EDARSCQFPEEERGERSAEEKGRLGDLWV
106	Immature cynomolgus GITR sequence	VARHGAMCACGTLCCLALLCAASLGQRPTGGPGCGPGRLLL GTGKDARCCRVHPTRCCRDYQSEECCSEWDCVCVQPEFHCG NPCCTTCQHHPCPSGQGVQPQGKFSFGFRCVDCALGTFSRG HDGHCKPWTDCTQFGFLTVFPGNKTHNAVCVPGSPPAEPPG WLTIVLLAVAACVLLLTSAQLGLHIWQLGKTQLLLEVPPST EDASSCQFPEEERGERLAEEKGRLGDLWV

[00160] As used herein, the term “host cell” can be any type of cell, *e.g.*, a primary cell, a cell in culture, or a cell from a cell line. In specific embodiments, the term “host cell” refers to a cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell are not necessarily identical to the parent cell transfected with the nucleic acid molecule, *e.g.*, due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[00161] As used herein, the term “effective amount” in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect.

[00162] As used herein, the terms “subject” and “patient” are used interchangeably. The subject can be an animal. In some embodiments, the subject is a mammal such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat, etc.) or a primate (*e.g.*, monkey or human), for example a human. In some embodiments, the subject is a cynomolgus monkey. In certain embodiments, such terms refer to a non-human animal (*e.g.*, a non-human animal such as a pig, horse, cow, cat, or dog). In some embodiments, such terms refer to a pet or farm animal. In specific embodiments, such terms refer to a human.

[00163] The determination of “percent identity” between two sequences (*e.g.*, amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87: 2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90: 5873-5877, each of which is herein incorporated by

reference in its entirety. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul SF *et al.*, (1990) J Mol Biol 215: 403, which is herein incorporated by reference in its entirety. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul SF *et al.*, (1997) Nuc Acids Res 25: 3389 3402, which is herein incorporated by reference in its entirety. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (*see*, *e.g.*, National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another specific, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17, which is herein incorporated by reference in its entirety. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[00164] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

5.2 Antibodies

5.2.1 Anti-OX40 Antibodies

[00165] In a specific aspect, provided herein is an antibody (*e.g.*, a monoclonal antibody, such as a chimeric, humanized, or human antibody) that specifically binds to OX40 (*e.g.*, human OX40). Also provided herein is a multispecific antibody that comprises a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and, optionally, a second antigen-binding domain that does not specifically bind to OX40 (*e.g.*, human OX40).

[00166] The amino acid sequences of exemplary antibodies are set forth in Tables 2-5, herein.

Table 2. Amino acid sequences of exemplary anti-OX40 antibodies.*

SEQ ID NO:	Description	Amino acid Sequence
1	pab1949 VH	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGYDYWGQGTLVTVSS
2	pab1949 VH N56Y	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKAYSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGYDYWGQGTLVTVSS
3	pab1949 VH Y103A	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIADSSGYDYWGQGTLVTVSS
4	pab1949 VH D104A	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYASSGYDYWGQGTLVTVSS
5	pab1949 VH Y108A	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGADYWGQGTLVTVSS
6	pab1949 VH D109A	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGYAYWGQGTLVTVSS
7	pab1949 VH AM-1	EVQLVESGGGLVQPGGSLKLSCAASGFTFSQEGMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSENTAY LQMNSLKTEDTAVYYCTSGIYDTLAYDYWGQGTLVTVSS
8	pab1949 VH AM-2	EVQLVESGGGLVQPGGSLKLSCAASGFTFSHEGMHWVRQAS GKGLEWVGRIRSKYYQEETAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGYDYWGQGTLVTVSS
9	pab1949 VH AM-3	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGYSMHWVRQAS GKGLEWVGRIRSKSEGQLTAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDSSGYDYWGQGTLVTVSS
10	pab1949 VH AM-4	EVQLVESGGGLVQPGGSLKLSCAASGFTFSEESMHWVRQAS GKGLEWVGRIRSKANSYATAYAASVKGRFTISRDDSKNTAY LQMNSLKTEDTAVYYCTSGIYDWEGYDYWGQGTLVTVSS
11	pab1949 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQALQTPLTFGGGTKVEIK
12	pab1949 VL A96G/L97S	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQGSQTPLTFGGGTKVEIK
13	pab1949 VL Q98K	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQALKTPLTFGGGTKVEIK
14	pab1949 VL T99W	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQALQWPLTFGGGTKVEIK

SEQ ID NO:	Description	Amino acid Sequence
15	pab2049 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNY LDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGAGT DFTLKISRVEAEDVGIYYCMQGSKWPLTFGGGTKLEI K
16	VH CDR1	GSAMH
17	VH CDR1	QEGMH
18	VH CDR1	HEGMH
19	VH CDR1	GYSMH
20	VH CDR1	EESMH
21	VH CDR2	RIRSKANSYATAYAASVKG
22	VH CDR2	RIRSKAYSYATAYAASVKG
23	VH CDR2	RIRSKYYQEETAYAASVKG
24	VH CDR2	RIRSKSEGQLTAYAASVKG
25	VH CDR3	GIYDSSGYDY
26	VH CDR3	GIADSSGYDY
27	VH CDR3	GIYASSGYDY
28	VH CDR3	GIYDSSGADY
29	VH CDR3	GIYDSSGYAY
30	VH CDR3	GIYDTLAYDY
31	VH CDR3	GIYDWEGYDY
32	VL CDR1	RSSQSLLHSNGYNYLD
33	VL CDR2	LGSNRAS
34	VL CDR3	MQALQTPLT
35	VL CDR3	MQGSQTPLT
36	VL CDR3	MQALKTPLT
37	VL CDR3	MQALQWPLT
38	VL CDR3	MQGSKWPLT
39	OX40 VH germline IGHV3-73*01	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWV RQASGKGLEWVGRIRSKANSYATAYAASVKGRFTISR DDSKNTAYLQMNSLKTEDTAVYYCTR
40	OX40 VL germline IGKV2-28*01	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNY LDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCMQALQTP
41	CDRH1 consensus sequence 1	$X_1X_2X_3$MH, wherein: X_1 is G, Q, H, or E; X_2 is S, E, or Y; and X_3 is A, S, or G
42	CDRH2 consensus sequence 1	RIRSK$X_1X_2X_3X_4X_5$TAYAASVKG, wherein: X_1 is A, S, or Y; X_2 is N, E, or Y; X_3 is S, Q, or G; X_4 is Y, E, or Q; and X_5 is A, E, or L

SEQ ID NO:	Description	Amino acid Sequence
43	CDRH3 consensus sequence 1	GIX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$Y, wherein: X$_1$ is Y or A; X$_2$ is D or A; X$_3$ is S, T, or W; X$_4$ is S, E, or L; X$_5$ is G or A; X$_6$ is Y or A; and X$_7$ is D or A
44	CDRH2 consensus sequence 2	RIRSKAXSYATAYAASVKG, wherein X is N or Y
45	CDRH3 consensus sequence 2	GIX$_1$X$_2$SSGX$_3$X$_4$Y, wherein X$_1$ is Y or A; X$_2$ is D or A; X$_3$ is Y or A; and X$_4$ is D or A
46	CDRL3 consensus sequence	MQX$_1$X$_2$X$_3$X$_4$PLT, wherein X$_1$ is A or G; X$_2$ is L or S; X$_3$ is Q or K; and X$_4$ is T or W
47	VH consensus sequence 1	EVQLVESGGGLVQPGGSLKLSCAASGFTFSX$_1$X$_2$X$_3$MH WVRQASGKGLEWVGRIRSKX$_4$X$_5$X$_6$X$_7$X$_8$TAYAASVKGR FTISRDDSX$_9$NTAYLQMNSLKTEDTAVYYCTSGIX$_{10}$X$_{11}$X$_{12}$X$_{13}$X$_{14}$X$_{15}$X$_{16}$YWGQGTLVTVSS, wherein X$_1$ is G, Q, H, or E; X$_2$ is S, E, or Y; X$_3$ is A, S, or G; X$_4$ is A, S, or Y; X$_5$ is N, E, or Y; X$_6$ is S, Q, or G; X$_7$ is Y, E, or Q; X$_8$ is A, E, or L; X$_9$ is K or E; X$_{10}$ is Y or A; X$_{11}$ is D or A; X$_{12}$ is S, T, or W; X$_{13}$ is S, E, or L; X$_{14}$ is G or A; X$_{15}$ is Y or A; and X$_{16}$ is D or A

SEQ ID NO:	Description	Amino acid Sequence
48	VH consensus sequence 2	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWV RQASGKGLEWVGRIRSKAX$_1$SYATAYAASVKGRFTISR DDSKNTAYLQMNSLKTEDTAVYYCTSGIX$_2$X$_3$SSGX$_4$X$_5$ YWGQGTLVTVSS, wherein X$_1$ is N or Y; X$_2$ is Y or A; X$_3$ is D or A; X$_4$ is Y or A; and X$_5$ is D or A
49	VL consensus sequence	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNY LDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGX$_1$GT DFTLKISRVEAEDVGX$_2$YYCMQX$_3$X$_4$X$_5$X$_6$PLTFGGGTK X$_7$EIK, wherein X$_1$ is S or A; X$_2$ is V or I; X$_3$ is A or G; X$_4$ is L or S; X$_5$ is Q or K; X$_6$ is T or W; and X$_7$ is V or L
50	pab1949/pab2049 heavy chain (IgG1)	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSAMHWV RQASGKGLEWVGRIRSKANSYATAYAASVKGRFTISR DDSKNTAYLQMNSLKTEDTAVYYCTSGIYDSSGYDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG
51	pab1949 light chain	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNY LDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

*CDRs are defined according to the Kabat numbering system.

Table 3. Heavy chain CDR amino acid sequences of exemplary anti-OX40 antibodies.*

VH (SEQ ID NO:)	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)

VH (SEQ ID NO:)	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
pab1949 VH (1)	GSAMH (16)	RIRSKANSYATAYAASVKG (21)	GIYDSSGYDY (25)
pab1949 VH N56Y (2)	GSAMH (16)	RIRSKAYSYATAYAASVKG (22)	GIYDSSGYDY (25)
pab1949 VH Y103A (3)	GSAMH (16)	RIRSKANSYATAYAASVKG (21)	GIADSSGYDY (26)
pab1949 VH D104A (4)	GSAMH (16)	RIRSKANSYATAYAASVKG (21)	GIYASSGYDY (27)
pab1949 VH Y108A (5)	GSAMH (16)	RIRSKANSYATAYAASVKG (21)	GIYDSSGADY (28)
pab1949 VH D109A (6)	GSAMH (16)	RIRSKANSYATAYAASVKG (21)	GIYDSSGYAY (29)
pab1949 VH AM-1 (7)	QEGMH (17)	RIRSKANSYATAYAASVKG (21)	GIYDTLAYDY (30)
pab1949 VH AM-2 (8)	HEGMH (18)	RIRSKYYQEETAYAASVKG (23)	GIYDSSGYDY (25)
pab1949 VH AM-3 (9)	GYSMH (19)	RIRSKSEGQLTAYAASVKG (24)	GIYDSSGYDY (25)
pab1949 VH AM-4 (10)	EESMH (20)	RIRSKANSYATAYAASVKG (21)	GIYDWEGYDY (31)

*Defined according to the Kabat numbering system.

Table 4. Light chain CDR amino acid sequences of exemplary anti-OX40 antibodies.*

VL (SEQ ID NO:)	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
pab1949 VL (11)	RSSQSLLHSNGYNYLD (32)	LGSNRAS (33)	MQALQTPLT (34)
pab1949 VL A96G/L97S (12)	RSSQSLLHSNGYNYLD (32)	LGSNRAS (33)	MQGSQTPLT (35)
pab1949 VL Q98K (13)	RSSQSLLHSNGYNYLD (32)	LGSNRAS (33)	MQALKTPLT (36)
pab1949 VL T99W (14)	RSSQSLLHSNGYNYLD (32)	LGSNRAS (33)	MQALQWPLT (37)
pab2049 VL (15)	RSSQSLLHSNGYNYLD (32)	LGSNRAS (33)	MQGSKWPLT (38)

*Defined according to the Kabat numbering system.

Table 5. Heavy chain variable region (VH) and light chain variable region (VL) sequences of exemplary anti-OX40 antibodies.

Antibody	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:

Antibody	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
pab1949	pab1949 VH	1	pab1949 VL	11
pab1949 N56Y	pab1949 VH N56Y	2	pab1949 VL	11
pab1949 Y103A	pab1949 VH Y103A	3	pab1949 VL	11
pab1949 D104A	pab1949 VH D104A	4	pab1949 VL	11
pab1949 Y108A	pab1949 VH Y108A	5	pab1949 VL	11
pab1949 D109A	pab1949 VH D109A	6	pab1949 VL	11
pab1949 AM-1	pab1949 VH AM-1	7	pab2049 VL	15
pab1949 AM-2	pab1949 VH AM-2	8	pab2049 VL	15
pab1949 AM-3	pab1949 VH AM-3	9	pab2049 VL	15
pab1949 AM-4	pab1949 VH AM-4	10	pab2049 VL	15
pab2049	pab1949 VH	1	pab2049 VL	15
pab1949 A96G/L97S	pab1949 VH	1	pab1949 VL A96G/L97S	12
pab1949 Q98K	pab1949 VH	1	pab1949 VL Q98K	13
pab1949 T99W	pab1949 VH	1	pab1949 VL T99W	14

Table 6. Closest germline genes for exemplary anti-OX40 antibodies.

Closest germline gene	SEQ ID NO:
IGHV3-73*01	39
IGKV2-28*01	40

[00167] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 2 herein. In certain embodiments, the antibody comprises the CDRH1 of one of heavy chain variable regions set forth in Table 2. In certain embodiments, the antibody comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 2. In certain embodiments, the antibody comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 2.

[00168] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 2 herein. In certain embodiments, the antibody comprises the CDRL1 of one of light chain variable regions set forth in Table 2. In certain embodiments, the antibody comprises the CDRL2 of one of the light chain variable regions set forth in Table 2. In certain embodiments,

the antibody comprises the CDRL3 of one of the light chain variable regions set forth in Table 2.

[00169] In certain embodiments, the CDRs of an antibody can be determined according to Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[00170] In certain embodiments, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see*, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol Biol 227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties). Typically, when using the Kabat numbering convention, the Chothia CDRH1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDRH2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDRH3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDRL1 loop is present at light chain amino acids 24 to 34, the Chothia CDRL2 loop is present at light chain amino acids 50 to 56, and the Chothia CDRL3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDRH1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34).

[00171] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising the Chothia VH CDRs of a VH disclosed in Table 2 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising the Chothia VL CDRs of a VL disclosed in Table 2 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 2 herein. In certain embodiments, antibodies that specifically bind to OX40 (*e.g.*, human OX40) comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40) and comprises combinations of

Kabat CDRs and Chothia CDRs.

[00172] In certain embodiments, the CDRs of an antibody can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) The Immunologist 7: 132-136 and Lefranc M-P *et al.*, (1999) Nucleic Acids Res 27: 209-212, each of which is herein incorporated by reference in its entirety. In certain embodiments, the instant disclosure provides antibodies that specifically bind to OX40 (*e.g.*, human OX40) and comprise CDRs of an antibody disclosed in Table 2 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*.

[00173] In certain embodiments, the CDRs of an antibody can be determined according to the AbM numbering scheme, which refers to AbM hypervariable regions, which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to OX40 (*e.g.*, human OX40) and comprise CDRs of an antibody disclosed in Table 2 herein as determined by the AbM numbering scheme.

[00174] In certain embodiments, the CDRs of an antibody can be determined according to MacCallum RM *et al.*, (1996) J Mol Biol 262: 732-745, herein incorporated by reference in its entirety. *See also*, *e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in *Antibody Engineering*, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to OX40 (*e.g.*, human OX40) and comprise CDRs of an antibody disclosed in Table 2 herein as determined by the MacCallum numbering scheme.

[00175] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein each CDR is defined in accordance with the MacCallum definition, the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT

numbering system, or the AbM definition of CDR.

[00176] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively.

[00177] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively.

[00178] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), the antibody comprising:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3$MH (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of RIRSK$X_1X_2X_3X_4X_5$TAYAASVKG (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of GI$X_1X_2X_3X_4X_5X_6X_7$Y (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of MQ$X_1X_2X_3X_4$PLT (SEQ ID NO: 46),

wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

In certain embodiments, CDRH2 comprises the amino acid sequence of RIRSKAXSYATAYAASVKG (SEQ ID NO: 44), wherein: X is N or Y. In certain embodiments, CDRH3 comprises the amino acid sequence of $GIX_1X_2SSGX_3X_4Y$ (SEQ ID NO: 45), wherein: X_1 is Y or A; X_2 is D or A; X_3 is Y or A; and X_4 is D or A. In certain embodiments, CDRH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-20. In certain embodiments, CDRH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 21-24. In certain embodiments, CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-31. In certain embodiments, CDRL3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-38.

[00179] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively.

[00180] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the

antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively.

[00181] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

[00182] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively.

[00183] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively.

[00184] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

[00185] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable

region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16, 21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively.

[00186] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID

NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 2. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 3. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 4. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 6. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 7. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 8. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 9. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 10.

[00187] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2,

CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO:

13. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 14. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 15.

[00188] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an

amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 2 and 11, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 3 and 11, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 4 and 11, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 5 and 11, respectively.

In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 6 and 11, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 7 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 8 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 9 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 10 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 12, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 13, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 14, respectively.

[00189] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence

of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39). In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39).

[00190] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40). In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40).

[00191] In certain embodiments, the instant disclosure provides an isolated antibody that

specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to OX40 (*e.g.*, human OX40), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

[00192] In certain embodiments, the instant disclosure provides an isolated antibody, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody cross-competes for binding to OX40 (*e.g.*, human OX40) with an antibody described herein., e.g., an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.

[00193] In certain embodiments, the instant disclosure provides an isolated antibody, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not

respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody binds to the same or an overlapping epitope of OX40 (*e.g.*, an epitope of human OX40) as an antibody described herein, *e.g.*, an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.

[00194] As further provided herein, antibodies that bind to OX40 can increase OX40 activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40). For instance, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can increase OX40 (*e.g.*, human OX40) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 (*e.g.*, human OX40) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40). Non-limiting examples of OX40 (*e.g.*, human OX40) activity can include OX40 (*e.g.*, human OX40) signaling, OX40 (*e.g.*, human OX40) binding to OX40 (*e.g.*, human OX40) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

[00195] As further provided herein, antibodies that bind to OX40 can agonize OX40 function, for example, by stimulating T cell activation. For instance, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can stimulate T cell activation, optionally wherein T cell activation is a substantially increasing function of antibody

concentrations.

[00196] As further provided herein, antibodies that bind to OX40 can agonize OX40 function, for example, by stimulating IL-2 release in an SEA assay. For instance, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can, in combination with Staphylococcus Enterotoxin A (SEA) (*e.g.*, 100 ng/ml), induce IL-2 production in, *e.g.*, PBMCs upon stimulation for, *e.g.*, 5 days at, *e.g.*, 37°C, 5% CO_2, and 97% humidity, as measured by, *e.g.*, electrochemiluminescence. In some embodiments, the IL-2 production is a substantially increasing function of antibody concentrations. In certain embodiments, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can, in combination with Staphylococcus Enterotoxin A (SEA), induce IL-2 production in, *e.g.*, PBMCs, optionally wherein the IL-2 production is a substantially increasing function of antibody concentrations as assessed in, *e.g.*, an assay comprising the following steps: (a) culturing the PBMCs (*e.g.*, 10^5 cells in a well) in the absence or presence of varying concentrations of the antibody and, *e.g.*, 100 ng/ml of SEA for, *e.g.*, 5 days at, *e.g.*, 37°C, 5% CO_2, and 97% humidity; and (b) collecting clarified supernatant and measuring the titer of IL-2 by, *e.g.*, electrochemiluminescence.

[00197] As further provided herein, antibodies that bind to OX40 can agonize OX40 function, for example, by stimulating NF-κB signaling. For instance, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can stimulate NF-κB signaling, *e.g.*, in a Jurkat-huOX40-NF-κB-luciferase reporter assay as described in the examples herein, optionally wherein the NF-κB signaling is a substantially increasing function of antibody concentrations.

[00198] As further provided herein, antibodies that bind to OX40 can decrease OX40 activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40). For instance, an antibody that binds to OX40, *e.g.*, an antibody that binds to OX40 and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can decrease OX40 (*e.g.*, human OX40) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 (*e.g.*, human OX40) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40). Non-limiting examples of OX40 (*e.g.*, human OX40) activity can include OX40 (*e.g.*, human OX40) signaling, OX40 (*e.g.*, human OX40) binding to OX40 (*e.g.*, human OX40) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

5.2.2 Anti-GITR Antibodies

[00199] In a specific aspect, provided herein is an antibody (*e.g.*, a monoclonal antibody, such as a chimeric, humanized, or human antibody) that specifically binds to GITR (*e.g.*, human GITR). Also provided herein is a multispecific antibody that comprises a first antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) and, optionally, a second antigen-binding domain that does not specifically bind to GITR (*e.g.*, human GITR).

[00200] The amino acid sequences of exemplary antibodies are set forth in Tables 7-10, herein.

Table 7. Amino acid sequences of exemplary anti-GITR antibodies.*

SEQ ID NO:	Description*	Amino acid Sequence

SEQ ID NO:	Description*	Amino acid Sequence
52	pab1876 VH	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTDYAMYWV RQAPGQGLEWIGVIRTYSGDVTYNQKFKDRATMTVDK SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLVTVSS
53	pab1876 VH D57G	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTDYAMYWV RQAPGQGLEWIGVIRTYSGGVTYNQKFKDRATMTVDK SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLVTVSS
95	pab1876 VH R103A	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTDYAMYWV RQAPGQGLEWIGVIRTYSGDVTYNQKFKDRATMTVDK SISTAYMELSRLRSDDTAVYYCAKSGTVAGFAYWGQG TLVTVSS
54	pab1967 VH	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTGYAMHWV RQAPGQGLEWMGLIRTYSGGVSYNQKFRERATMTVDT SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLITVSS
55	pab1975 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYAMHWV RQAPGQGLEWMGLIRTYSGGVSYNQKFQGRATMTVDT SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLVTVSS
56	pab1979 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYAMHWV RQAPGQGLEWMGVIRTYSGGVSYNQKFQERVTMTVDT SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLVTVSS
57	pab1876 VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYHCQNDYSYPYTFGQGTKLE IK
96	pab1876 VL D97A	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYHCQNAYSYPYTFGQGTKLE IK
58	pab1967 VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSSNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSG TDFTLTISSVQAEDVAVYHCQNEYSFPYTFGQGTKLE IK
59	pab1975/pab1979 VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQNDYSYPYTFGQGTKLE IK
60	VH CDR1	DYAMY
61	VH CDR1	GYAMH
62	VH CDR1	EYAMH
63	VH CDR2	VIRTYSGDVTYNQKFKD
64	VH CDR2	VIRTYSGGVTYNQKFKD

SEQ ID NO:	Description*	Amino acid Sequence
65	VH CDR2	LIRTYSGGVSYNQKFRE
66	VH CDR2	LIRTYSGGVSYNQKFQG
67	VH CDR2	VIRTYSGGVSYNQKFQE
68	VH CDR3	SGTVRGFAY
97	VH CDR3	SGTVAGFAY
69	VL CDR1	KSSQSLLNSGNQKNYLT
70	VL CDR1	KSSQSLLNSSNQKNYLT
71	VL CDR2	WASTRES
72	VL CDR3	QNDYSYPYT
98	VL CDR3	QNAYSYPYT
73	VL CDR3	QNEYSFPYT
74	GITR VH germline	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWV RQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDT SISTAYMELSRLRSDDTAVYYCAR
75	GITR VL germline	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKN YLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQQYYSTP
76	CDRH1 consensus sequence 1	$X_1YX_2MX_3$, wherein X_1 is D, E or G; X_2 is A or V; and X_3 is Y or H
77	CDRH2 consensus sequence 1	$X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$, 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
99	CDRH3 consensus sequence 1	SGTVXGFAY, wherein X is R or A
78	CDRH1 consensus sequence 2	X_1YAMX_2, wherein X_1 is D, G, or E, and X_2 is Y or H
79	CDRH2 consensus sequence 2	$X_1IRTYSGX_2VX_3YNQKFX_4X_5$, 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
80	CDRL1 consensus sequence 1	$KSSQSLLNSX_1NQKNYLX_2$, wherein X_1 is G or S; and X_2 is T or S

SEQ ID NO:	Description*	Amino acid Sequence
81	CDRL3 consensus sequence 1	QNX$_1$YSX$_2$PYT, wherein X$_1$ is D, E, or A; and X$_2$ is Y, F, or S
82	CDRL1 consensus sequence 2	KSSQSLLNSXNQKNYLT, wherein X is G or S
83	CDRL3 consensus sequence 2	QNX$_1$YSX$_2$PYT, wherein X$_1$ is D, E, or A; and X$_2$ is Y or F
84	VH consensus	QVQLVQSGAEVKKPGASVKVSCKX$_1$SGYTFTX$_2$YAMX$_3$ WVRQAPGQGLEWX$_4$GX$_5$IRTYSGX$_6$VX$_7$YNQKFX$_8$X$_9$RX$_1$ $_0$TMTVDX$_{11}$SISTAYMELSRLRSDDTAVYYCAKSGTVX$_1$ $_2$GFAYWGQGTLX$_{13}$TVSS X$_1$ is G or A; X$_2$ is D, G, or E; X$_3$ is Y or H; X$_4$ is I or M; X$_5$ is V or L; X$_6$ is D or G; X$_7$ is T or S; X$_8$ is K, R, or Q; X$_9$ is D, E, or G; X$_{10}$ is A or V; X$_{11}$ is K or T; X$_{12}$ is R or A; and X$_{13}$ is V or I
85	VL consensus	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSX$_1$NQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFX$_2$GSGSG TDFTLTISSX$_3$QAEDVAVYX$_4$CQNX$_5$YSX$_6$PYTFGQGTK LEIK X$_1$ is G or S; X$_2$ is S or T; X$_3$ is L or V; X$_4$ is H or Y; X$_5$ is D, E, or A; and X$_6$ is Y or F

SEQ ID NO:	Description*	Amino acid Sequence
86	pab1876 heavy chain (IgG1)	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTDYAMYWV RQAPGQGLEWIGVIRTYSGDVTYNQKFKDRATMTVDK SISTAYMELSRLRSDDTAVYYCAKSGTVRGFAYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG
87	pab1876 light chain	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKN YLTWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSG TDFTLTISSLQAEDVAVYHCQNDYSYPYTFGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

*CDRs are defined according to the Kabat numbering system.

Table 8. Heavy chain CDR amino acid sequences of exemplary anti-GITR antibodies.*

VH (SEQ ID NO:)	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
pab1876 VH (52)	DYAMY (60)	VIRTYSGDVTYNQKFKD (63)	SGTVRGFAY (68)
pab1876 VH D57G (53)	DYAMY (60)	VIRTYSGGVTYNQKFKD (64)	SGTVRGFAY (68)
pab1876 VH R103A (95)	DYAMY (60)	VIRTYSGDVTYNQKFKD (63)	SGTVAGFAY (97)
pab1967 VH (54)	GYAMH (61)	LIRTYSGGVSYNQKFRE (65)	SGTVRGFAY (68)
pab1975 VH (55)	EYAMH (62)	LIRTYSGGVSYNQKFQG (66)	SGTVRGFAY (68)
pab1979 VH (56)	EYAMH (62)	VIRTYSGGVSYNQKFQE (67)	SGTVRGFAY (68)

*Defined according to the Kabat numbering system.

Table 9. Light chain CDR amino acid sequences of exemplary anti-GITR antibodies.*

VL (SEQ ID NO:)	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
pab1876 VL (57)	KSSQSLLNSGNQKNYLT (69)	WASTRES (71)	QNDYSYPYT (72)
pab1876 VL D97A (96)	KSSQSLLNSGNQKNYLT (69)	WASTRES (71)	QNAYSYPYT (98)

VL (SEQ ID NO:)	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
pab1967 VL (58)	KSSQSLLNSSNQKNYLT (70)	WASTRES (71)	QNEYSFPYT (73)
pab1975/pab1979 VL (59)	KSSQSLLNSGNQKNYLT (69)	WASTRES (71)	QNDYSYPYT (72)

*Defined according to the Kabat numbering system.

Table 10. Heavy chain variable region (VH) and light chain variable region (VL) sequences of exemplary anti-GITR antibodies.

Antibody	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
pab1876	pab1876 VH	52	pab1876 VL	57
pab1876 D57G	pab1876 VH D57G	53	pab1876 VL	57
pab1876 R103A	pab1876 VH R103A	95	pab1876 VL	57
pab1876 D97A	pab1876 VH	52	pab1876 VL D97A	96
pab1967	pab1967 VH	54	pab1967 VL	58
pab1975	pab1975 VH	55	pab1975 VL	59
pab1979	pab1979 VH	56	pab1979 VL	59

Table 11. Closest germline genes for exemplary anti-GITR antibodies.

Closest germline gene	SEQ ID NO:
IGHV1-2*02	74
IGKV4-1*01	75

[00201] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), the antibody comprising a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 7 herein. In certain embodiments, the antibody comprises the CDRH1 of one of heavy chain variable regions set forth in Table 7. In certain embodiments, the antibody comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 7. In certain embodiments, the antibody comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 7.

[00202] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), the antibody comprising a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in

Table 7 herein. In certain embodiments, the antibody comprises the CDRL1 of one of light chain variable regions set forth in Table 7. In certain embodiments, the antibody comprises the CDRL2 of one of the light chain variable regions set forth in Table 7. In certain embodiments, the antibody comprises the CDRL3 of one of the light chain variable regions set forth in Table 7.

[00203] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), the antibody comprising the Chothia VH CDRs of a VH disclosed in Table 7 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), the antibody comprising the Chothia VL CDRs of a VL disclosed in Table 7 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), the antibody comprising the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 7 herein. In certain embodiments, antibodies that specifically bind to GITR (*e.g.*, human GITR) comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR) and comprises combinations of Kabat CDRs and Chothia CDRs.

[00204] In certain embodiments, the instant disclosure provides antibodies that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of an antibody disclosed in Table 7 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*.

[00205] In certain embodiments, the instant disclosure provides antibodies that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of an antibody disclosed in Table 7 herein as determined by the AbM numbering scheme.

[00206] In certain embodiments, the instant disclosure provides antibodies that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of an antibody disclosed in Table 7 herein as determined by the MacCallum numbering scheme.

[00207] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a

light chain variable region set forth in SEQ ID NO: 57, 58, 59, or 96, wherein each CDR is defined in accordance with the MacCallum definition, the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, or the AbM definition of CDR.

[00208] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 60, 63, and 68; 60, 64, and 68; 60, 63, and 97; 61, 65, and 68; 62, 66, and 68; or 62, 67, and 68, respectively.

[00209] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 69, 71, and 72; 69, 71, and 98; 70, 71, and 73; or 69, 71, and 72, respectively.

[00210] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 60, 64, 68, 69, 71, and 72; 60, 63, 97, 69, 71, and 72; 60, 63, 68, 69, 71, and 98, respectively.

[00211] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 53. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 95.

[00212] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 57. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 96.

[00213] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to GITR (*e.g.*, human GITR), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 53 and 57; 95 and 57; 52 and 96, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 53 and 57, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 95 and 57, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 52 and 96, respectively.

[00214] As further provided herein, antibodies that bind to GITR can increase GITR activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5

fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to GITR activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to GITR). For instance, an antibody that binds to GITR, *e.g.*, an antibody that binds to GITR and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can increase GITR (*e.g.*, human GITR) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to GITR (*e.g.*, human GITR) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to GITR). Non-limiting examples of GITR (*e.g.*, human GITR) activity can include GITR (*e.g.*, human GITR) signaling, GITR (*e.g.*, human GITR) binding to GITR (*e.g.*, human GITR) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

[00215] As further provided herein, antibodies that bind to GITR can decrease GITR activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to GITR activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to GITR). For instance, an antibody that binds to GITR, *e.g.*, an antibody that binds to GITR and comprises a combination of CDR sequences specified herein, a VH and/or VL sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with VH and/or VL sequences specified herein, or heavy and/or light chains specified herein, can decrease GITR (*e.g.*, human GITR) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to GITR (*e.g.*, human GITR) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to GITR). Non-limiting examples of GITR (*e.g.*, human GITR) activity can

include GITR (*e.g.*, human GITR) signaling, GITR (*e.g.*, human GITR) binding to GITR (*e.g.*, human GITR) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

5.2.3 Multispecific Antibodies that Bind to OX40 and/or GITR

[00216] In a specific aspect, provided herein are multispecific antibodies (*e.g.*, bispecific antibodies) which specifically bind to OX40 and/or GITR (*e.g.*, human OX40 and/or human GITR). For instance, a multispecific (*e.g.*, bispecific) antibody provided herein can comprise a first antigen-binding domain that binds to OX40 and a second antigen-binding domain. A multispecific (*e.g.*, bispecific) antibody provided herein can also comprise a first antigen-binding domain and a second antigen-binding domain that binds to GITR. Such multispecific antibodies advantageously show greater specificity for certain subsets of immune cells containing the combination of target proteins than monospecific bivalent antibodies that only bind to OX40 or GITR.

[00217] In one instance, an antibody provided herein that specifically binds to OX40 and GITR contains a combination of CDRs shown in a single row of Table 12 below.

Table 12. CDR sequences of exemplary anti-OX40/GITR antibodies.*

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human OX40						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human GITR					
VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3	VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3
16	21	25	32	33	34	60	64	68	69	71	72
16	21	25	32	33	34	60	63	97	69	71	72
16	21	25	32	33	34	60	63	68	69	71	98
16	21	25	32	33	38	60	64	68	69	71	72
16	21	25	32	33	38	60	63	97	69	71	72
16	21	25	32	33	38	60	63	68	69	71	98
16	22	25	32	33	34	60	63	68	69	71	72
16	22	25	32	33	34	60	64	68	69	71	72
16	22	25	32	33	34	60	63	97	69	71	72

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human OX40						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human GITR					
VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3	VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3
16	22	25	32	33	34	60	63	68	69	71	98
16	22	25	32	33	34	61	65	68	70	71	73
16	22	25	32	33	34	62	66	68	69	71	72
16	22	25	32	33	34	62	67	68	69	71	72
16	21	26	32	33	34	60	63	68	69	71	72
16	21	26	32	33	34	60	64	68	69	71	72
16	21	26	32	33	34	60	63	97	69	71	72
16	21	26	32	33	34	60	63	68	69	71	98
16	21	26	32	33	34	61	65	68	70	71	73
16	21	26	32	33	34	62	66	68	69	71	72
16	21	26	32	33	34	62	67	68	69	71	72
16	21	27	32	33	34	60	63	68	69	71	72
16	21	27	32	33	34	60	64	68	69	71	72
16	21	27	32	33	34	60	63	97	69	71	72
16	21	27	32	33	34	60	63	68	69	71	98
16	21	27	32	33	34	61	65	68	70	71	73
16	21	27	32	33	34	62	66	68	69	71	72
16	21	27	32	33	34	62	67	68	69	71	72
16	21	28	32	33	34	60	63	68	69	71	72
16	21	28	32	33	34	60	64	68	69	71	72
16	21	28	32	33	34	60	63	97	69	71	72
16	21	28	32	33	34	60	63	68	69	71	98
16	21	28	32	33	34	61	65	68	70	71	73
16	21	28	32	33	34	62	66	68	69	71	72
16	21	28	32	33	34	62	67	68	69	71	72
16	21	29	32	33	34	60	63	68	69	71	72

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human OX40						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human GITR					
VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3	VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3
16	21	29	32	33	34	60	64	68	69	71	72
16	21	29	32	33	34	60	63	97	69	71	72
16	21	29	32	33	34	60	63	68	69	71	98
16	21	29	32	33	34	61	65	68	70	71	73
16	21	29	32	33	34	62	66	68	69	71	72
16	21	29	32	33	34	62	67	68	69	71	72
17	21	30	32	33	38	60	63	68	69	71	72
17	21	30	32	33	38	60	64	68	69	71	72
17	21	30	32	33	38	60	63	97	69	71	72
17	21	30	32	33	38	60	63	68	69	71	98
17	21	30	32	33	38	61	65	68	70	71	73
17	21	30	32	33	38	62	66	68	69	71	72
17	21	30	32	33	38	62	67	68	69	71	72
18	23	25	32	33	38	60	63	68	69	71	72
18	23	25	32	33	38	60	64	68	69	71	72
18	23	25	32	33	38	60	63	97	69	71	72
18	23	25	32	33	38	60	63	68	69	71	98
18	23	25	32	33	38	61	65	68	70	71	73
18	23	25	32	33	38	62	66	68	69	71	72
18	23	25	32	33	38	62	67	68	69	71	72
19	24	25	32	33	38	60	63	68	69	71	72
19	24	25	32	33	38	60	64	68	69	71	72
19	24	25	32	33	38	60	63	97	69	71	72
19	24	25	32	33	38	60	63	68	69	71	98
19	24	25	32	33	38	61	65	68	70	71	73
19	24	25	32	33	38	62	66	68	69	71	72

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human OX40						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human GITR					
VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3	VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3
19	24	25	32	33	38	62	67	68	69	71	72
20	21	31	32	33	38	60	63	68	69	71	72
20	21	31	32	33	38	60	64	68	69	71	72
20	21	31	32	33	38	60	63	97	69	71	72
20	21	31	32	33	38	60	63	68	69	71	98
20	21	31	32	33	38	61	65	68	70	71	73
20	21	31	32	33	38	62	66	68	69	71	72
20	21	31	32	33	38	62	67	68	69	71	72
16	21	25	32	33	35	60	63	68	69	71	72
16	21	25	32	33	35	60	64	68	69	71	72
16	21	25	32	33	35	60	63	97	69	71	72
16	21	25	32	33	35	60	63	68	69	71	98
16	21	25	32	33	35	61	65	68	70	71	73
16	21	25	32	33	35	62	66	68	69	71	72
16	21	25	32	33	35	62	67	68	69	71	72
16	21	25	32	33	36	60	63	68	69	71	72
16	21	25	32	33	36	60	64	68	69	71	72
16	21	25	32	33	36	60	63	97	69	71	72
16	21	25	32	33	36	60	63	68	69	71	98
16	21	25	32	33	36	61	65	68	70	71	73
16	21	25	32	33	36	62	66	68	69	71	72
16	21	25	32	33	36	62	67	68	69	71	72
16	21	25	32	33	37	60	63	68	69	71	72
16	21	25	32	33	37	60	64	68	69	71	72
16	21	25	32	33	37	60	63	97	69	71	72
16	21	25	32	33	37	60	63	68	69	71	98

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human OX40						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human GITR					
VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3	VH CDR1	VH CDR2	VH CDR3	VL CDR1	VL CDR2	VL CDR3
16	21	25	32	33	37	61	65	68	70	71	73
16	21	25	32	33	37	62	66	68	69	71	72
16	21	25	32	33	37	62	67	68	69	71	72

*Defined according to the Kabat numbering system.

[00218] In one instance, an antibody provided herein that specifically binds to OX40 and GITR contains a combination of two heavy chain variable domains and two light chain variable domains shown in a single row of Table 13 below.

Table 13. Heavy chain variable region (VH) and light chain variable region (VL) sequences of exemplary anti-OX40/GITR antibodies.

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human OX40		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human GITR	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
1	11	53	57
1	11	95	57
1	11	52	96
1	15	53	57
1	15	95	57
1	15	52	96
2	11	52	57
2	11	53	57
2	11	95	57
2	11	52	96
2	11	54	58

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human OX40		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human GITR	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
2	11	55	59
2	11	56	59
3	11	52	57
3	11	53	57
3	11	95	57
3	11	52	96
3	11	54	58
3	11	55	59
3	11	56	59
4	11	52	57
4	11	53	57
4	11	95	57
4	11	52	96
4	11	54	58
4	11	55	59
4	11	56	59
5	11	52	57
5	11	53	57
5	11	95	57
5	11	52	96
5	11	54	58
5	11	55	59
5	11	56	59
6	11	52	57
6	11	53	57
6	11	95	57

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human OX40		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human GITR	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
6	11	52	96
6	11	54	58
6	11	55	59
6	11	56	59
7	15	52	57
7	15	53	57
7	15	95	57
7	15	52	96
7	15	54	58
7	15	55	59
7	15	56	59
8	15	52	57
8	15	53	57
8	15	95	57
8	15	52	96
8	15	54	58
8	15	55	59
8	15	56	59
9	15	52	57
9	15	53	57
9	15	95	57
9	15	52	96
9	15	54	58
9	15	55	59
9	15	56	59
10	15	52	57

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human OX40		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human GITR	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
10	15	53	57
10	15	95	57
10	15	52	96
10	15	54	58
10	15	55	59
10	15	56	59
1	12	52	57
1	12	53	57
1	12	95	57
1	12	52	96
1	12	54	58
1	12	55	59
1	12	56	59
1	13	52	57
1	13	53	57
1	13	95	57
1	13	52	96
1	13	54	58
1	13	55	59
1	13	56	59
1	14	52	57
1	14	53	57
1	14	95	57
1	14	52	96
1	14	54	58
1	14	55	59

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human OX40		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human GITR	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
1	14	56	59

[00219] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 2 herein. In certain embodiments, the first antigen-binding domain comprises the CDRH1 of one of heavy chain variable regions set forth in Table 2. In certain embodiments, the first antigen-binding domain comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 2. In certain embodiments, the first antigen-binding domain comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 2.

[00220] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 2 herein. In certain embodiments, the first antigen-binding domain comprises the CDRL1 of one of light chain variable regions set forth in Table 2. In certain embodiments, the first antigen-binding domain comprises the CDRL2 of one of the light chain variable regions set forth in Table 2. In certain embodiments, the first antigen-binding domain comprises the CDRL3 of one of the light chain variable regions set forth in Table 2.

[00221] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises the Chothia VH CDRs of a VH disclosed in Table 2 herein. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises the Chothia VL CDRs of a VL disclosed in Table 2 herein. In certain embodiments, the instant disclosure

provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 2 herein. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises combinations of Kabat CDRs and Chothia CDRs.

[00222] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises CDRs of an antibody disclosed in Table 2 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*.

[00223] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises CDRs of an antibody disclosed in Table 2 herein as determined by the AbM numbering scheme.

[00224] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises CDRs of an antibody disclosed in Table 2 herein as determined by the MacCallum numbering scheme.

[00225] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein each CDR is defined in accordance with the MacCallum definition, the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT

numbering system, or the AbM definition of CDR.

[00226] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively,

and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00227] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO:

32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively,

and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00228] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises:

(a) a CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G; and/or

(b) a CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L; and/or

(c) a CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A; and/or

(d) a CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32); and/or

(e) a CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and/or

(f) a CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38,

and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00229] In certain embodiments, CDRH2 of the first antigen-binding domain that specifically binds to human OX40 comprises the amino acid sequence of RIRSKAXSYATAYAASVKG (SEQ ID NO: 44), wherein: X is N or Y. In certain embodiments, CDRH3 of the first antigen-binding domain that specifically binds to human OX40 comprises the amino acid sequence of $GIX_1X_2SSGX_3X_4Y$ (SEQ ID NO: 45), wherein: X_1 is Y or A; X_2 is D or A; X_3 is Y or A; and X_4 is D or A. In certain embodiments, CDRH1 of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-20. In certain embodiments, CDRH2 of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 21-24. In certain embodiments, CDRH3 of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-31. In certain embodiments, CDRL3 of the first

antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-38.

[00230] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00231] In certain embodiments, the instant disclosure provides an isolated multispecific

antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00232] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the first antigen-binding domain that specifically binds to OX40

(*e.g.*, human OX40) comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16, 21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00233] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00234] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region

comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region

having the amino acid sequence set forth in SEQ ID NO: 2. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 3. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 4. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 6. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 7. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 8. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 9. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 10.

[00235] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to

human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00236] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region comprising an amino acid

sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 13. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 14. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 15.

[00237] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an

amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 47 or 48, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 49, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00238] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in

SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 13, 14, or 15. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 2 and 11, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and

light chain variable region having the amino acid sequences set forth in SEQ ID NO: 3 and 11, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 4 and 11, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 5 and 11, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 6 and 11, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 7 and 15, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 8 and 15, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 9 and 15, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 10 and 15, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 12, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 13, respectively. In certain embodiments, the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 1 and 14, respectively.

[00239] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain

specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) of the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) can be derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39). In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 of the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) are all derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39).

[00240] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five of these regions) of the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) can be derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40). In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 of the first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) are all derived from a human

IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40).

[00241] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence (*e.g.*, IGHV3-73*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 39), and a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence (*e.g.*, IGKV2-28*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 40), wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively

either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00242] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and cross-competes for binding to OX40 (*e.g.*, human OX40) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00243] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain, wherein the first antigen-binding domain specifically binds to OX40 (*e.g.*, human OX40) and binds to the same or an overlapping epitope of OX40 (*e.g.*, an epitope of human OX40) as an antibody described herein, *e.g.*, an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the first antigen-binding domain that specifically binds to human OX40 are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.

[00244] In some embodiments, the second antigen-binding domain of an isolated multispecific antibody disclosed herein specifically binds to human GITR.

[00245] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 7 herein. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the CDRH1 of one of heavy chain variable regions set forth in Table 7. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*,

human GITR) comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 7. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 7.

[00246] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 7 herein. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the CDRL1 of one of light chain variable regions set forth in Table 7. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the CDRL2 of one of the light chain variable regions set forth in Table 7. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the CDRL3 of one of the light chain variable regions set forth in Table 7.

[00247] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the Chothia VH CDRs of a VH disclosed in Table 7 herein. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the Chothia VL CDRs of a VL disclosed in Table 7 herein. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 7 herein. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises combinations of Kabat CDRs and Chothia CDRs.

[00248] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprise CDRs of an antibody disclosed in Table 7 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*.

[00249] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises CDRs of an antibody disclosed in Table 7 herein as

determined by the AbM numbering scheme.

[00250] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 57, 58, 59, or 96, wherein each CDR is defined in accordance with the MacCallum definition, the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, or the AbM definition of CDR.

[00251] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 57, 58, 59, or 96, wherein each CDR is defined in accordance with the MacCallum definition, the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, or the AbM definition of CDR.

[00252] In certain embodiments, the second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR) comprises:

(a) a CDRH1 comprises the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 76), wherein

X_1 is D, E or G,

X_2 is A or V, and

X_3 is Y or H; and/or

(b) a CDRH2 comprises the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO: 77), 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; and/or

(c) a CDRH3 comprises the amino acid sequence of SGTVXGFAY (SEQ ID NO: 99), wherein

X is R or A; and/or

(d) a CDRL1 comprises the amino acid sequence of KSSQSLLNSX_1NQKNYLX_2 (SEQ ID NO: 80), wherein

X_1 is G or S, and

X_2 is T or S; and/or

(e) a CDRL2 comprises the amino acid sequence of WASTRES (SEQ ID NO: 71); and/or

(f) a CDRL3 comprises the amino acid sequence of QNX_1YSX_2PYT (SEQ ID NO: 81), wherein

X_1 is D, E, or A; and

X_2 is Y, F, or S.

[00253] In certain embodiments, CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of X_1YAMX_2 (SEQ ID NO: 78), wherein: X_1 is D, G, or E; and X_2 is Y or H. In certain embodiments, CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of X_1IRTYSGX_2VX_3YNQKFX_4X_5 (SEQ ID NO: 79), 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. In certain embodiments, CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of KSSQSLLNSXNQKNYLT (SEQ ID NO: 82), wherein: X is G or S. In certain embodiments, CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of QNX_1YSX_2PYT (SEQ ID NO: 83), wherein: X_1 is D, E, or A; and X_2 is Y or F. In certain embodiments, CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-62. In certain embodiments, CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-67. In certain embodiments, CDRH3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 68 and 97. In

certain embodiments, CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 69 and 70. In certain embodiments, CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 73, and 98.

[00254] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising the CDRH1, CDRH2 and CDRH3 amino acid sequences set forth in SEQ ID NOs: 60, 63, and 68; 60, 64, and 68; 60, 63, and 97; 61, 65, and 68; 62, 66, and 68; or 62, 67, and 68, respectively.

[00255] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising the CDRL1, CDRL2 and CDRL3 amino acid sequences set forth in SEQ ID NOs: 69, 71, and 72; 69, 71, and 98; 70, 71, and 73; or 69, 71, and 72, respectively.

[00256] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 60, 63, 68, 69, 71, and 72; 60, 64, 68, 69, 71, and 72; 60, 63, 97, 69, 71, and 72; 60, 63, 68, 69, 71, and 98; 61, 65, 68, 70, 71, and 73; 62, 66, 68, 69, 71, and 72; or 62, 67, 68, 69, 71, and 72, respectively.

[00257] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 84. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52. In certain

embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 53. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 95.

[00258] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 85. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 57. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 96.

[00259] In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 84, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 85. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 52, 53, 54, 55, 56, or 95, and a light chain variable region having the amino acid sequence

set forth in SEQ ID NO: 57, 58, 59, or 96. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 53 and 57; 95 and 57; 52 and 96, respectively. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 53 and 57, respectively. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 95 and 57, respectively. In certain embodiments, the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NO: 52 and 96, respectively.

[00260] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 12. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 21, 25, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 21, 25, 32, 33, 38, 60, 64, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 38, 60, 63, 97, 69, 71, and 72; 16, 21, 25, 32, 33, 38, 60, 63, 68, 69, 71, and 98; 16, 22, 25, 32, 33, 34, 60, 63, 68, 69, 71, and 72; 16, 22, 25, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 22, 25, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 22, 25, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 22, 25, 32, 33, 34, 61, 65, 68, 70, 71, and 73; 16, 22, 25, 32, 33, 34, 62, 66, 68, 69, 71, and 72; 16, 22, 25, 32, 33, 34, 62, 67, 68, 69, 71, and 72; 16, 21, 26, 32, 33, 34, 60, 63, 68, 69, 71,

and 72; 16, 21, 26, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 21, 26, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 21, 26, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 21, 26, 32, 33, 34, 61, 65, 68, 70, 71, and 73; 16, 21, 26, 32, 33, 34, 62, 66, 68, 69, 71, and 72; 16, 21, 26, 32, 33, 34, 62, 67, 68, 69, 71, and 72; 16, 21, 27, 32, 33, 34, 60, 63, 68, 69, 71, and 72; 16, 21, 27, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 21, 27, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 21, 27, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 21, 27, 32, 33, 34, 61, 65, 68, 70, 71, and 73; 16, 21, 27, 32, 33, 34, 62, 66, 68, 69, 71, and 72; 16, 21, 27, 32, 33, 34, 62, 67, 68, 69, 71, and 72; 16, 21, 28, 32, 33, 34, 60, 63, 68, 69, 71, and 72; 16, 21, 28, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 21, 28, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 21, 28, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 21, 28, 32, 33, 34, 61, 65, 68, 70, 71, and 73; 16, 21, 28, 32, 33, 34, 62, 66, 68, 69, 71, and 72; 16, 21, 28, 32, 33, 34, 62, 67, 68, 69, 71, and 72; 16, 21, 29, 32, 33, 34, 60, 63, 68, 69, 71, and 72; 16, 21, 29, 32, 33, 34, 60, 64, 68, 69, 71, and 72; 16, 21, 29, 32, 33, 34, 60, 63, 97, 69, 71, and 72; 16, 21, 29, 32, 33, 34, 60, 63, 68, 69, 71, and 98; 16, 21, 29, 32, 33, 34, 61, 65, 68, 70, 71, and 73; 16, 21, 29, 32, 33, 34, 62, 66, 68, 69, 71, and 72; 16, 21, 29, 32, 33, 34, 62, 67, 68, 69, 71, and 72; 17, 21, 30, 32, 33, 38, 60, 63, 68, 69, 71, and 72; 17, 21, 30, 32, 33, 38, 60, 64, 68, 69, 71, and 72; 17, 21, 30, 32, 33, 38, 60, 63, 97, 69, 71, and 72; 17, 21, 30, 32, 33, 38, 60, 63, 68, 69, 71, and 98; 17, 21, 30, 32, 33, 38, 61, 65, 68, 70, 71, and 73; 17, 21, 30, 32, 33, 38, 62, 66, 68, 69, 71, and 72; 17, 21, 30, 32, 33, 38, 62, 67, 68, 69, 71, and 72; 18, 23, 25, 32, 33, 38, 60, 63, 68, 69, 71, and 72; 18, 23, 25, 32, 33, 38, 60, 64, 68, 69, 71, and 72; 18, 23, 25, 32, 33, 38, 60, 63, 97, 69, 71, and 72; 18, 23, 25, 32, 33, 38, 60, 63, 68, 69, 71, and 98; 18, 23, 25, 32, 33, 38, 61, 65, 68, 70, 71, and 73; 18, 23, 25, 32, 33, 38, 62, 66, 68, 69, 71, and 72; 18, 23, 25, 32, 33, 38, 62, 67, 68, 69, 71, and 72; 19, 24, 25, 32, 33, 38, 60, 63, 68, 69, 71, and 72; 19, 24, 25, 32, 33, 38, 60, 64, 68, 69, 71, and 72; 19, 24, 25, 32, 33, 38, 60, 63, 97, 69, 71, and 72; 19, 24, 25, 32, 33, 38, 60, 63, 68, 69, 71, and 98; 19, 24, 25, 32, 33, 38, 61, 65, 68, 70, 71, and 73; 19, 24, 25, 32, 33, 38, 62, 66, 68, 69, 71, and 72; 19, 24, 25, 32, 33, 38, 62, 67, 68, 69, 71, and 72; 20, 21, 31, 32, 33, 38, 60, 63, 68, 69, 71, and 72; 20, 21, 31, 32, 33, 38, 60, 64, 68, 69, 71, and 72; 20, 21, 31, 32, 33, 38, 60, 63, 97, 69, 71, and 72; 20, 21, 31, 32, 33, 38, 60, 63, 68, 69, 71, and 98; 20, 21, 31, 32, 33, 38, 61, 65, 68, 70, 71, and 73; 20, 21, 31, 32, 33, 38, 62, 66, 68, 69, 71, and 72; 20, 21, 31, 32, 33, 38, 62, 67, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 35, 60, 63, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 35, 60, 64, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 35, 60, 63, 97, 69, 71, and 72; 16, 21, 25, 32, 33, 35, 60, 63, 68, 69, 71, and 98; 16, 21, 25, 32, 33, 35,

61, 65, 68, 70, 71, and 73; 16, 21, 25, 32, 33, 35, 62, 66, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 35, 62, 67, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 36, 60, 63, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 36, 60, 64, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 36, 60, 63, 97, 69, 71, and 72; 16, 21, 25, 32, 33, 36, 60, 63, 68, 69, 71, and 98; 16, 21, 25, 32, 33, 36, 61, 65, 68, 70, 71, and 73; 16, 21, 25, 32, 33, 36, 62, 66, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 36, 62, 67, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 37, 60, 63, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 37, 60, 64, 68, 69, 71, and 72; 16, 21, 25, 32, 33, 37, 60, 63, 97, 69, 71, and 72; 16, 21, 25, 32, 33, 37, 60, 63, 68, 69, 71, and 98; 16, 21, 25, 32, 33, 37, 61, 65, 68, 70, 71, and 73; 16, 21, 25, 32, 33, 37, 62, 66, 68, 69, 71, and 72; or 16, 21, 25, 32, 33, 37, 62, 67, 68, 69, 71, and 72, respectively.

[00261] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR), wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain and the heavy chain variable region and the light chain variable region of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 13. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to OX40 (*e.g.*, human OX40) and a second antigen-binding domain that specifically binds to GITR (*e.g.*, human GITR), wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain and the heavy chain variable region and the light chain variable region of the second antigen-binding domain comprise the amino acid sequences set forth in SEQ ID NOs: 1, 11, 53, and 57; 1, 11, 95, and 57; 1, 11, 52, and 96; 1, 15, 53, and 57; 1, 15, 95, and 57; 1, 15, 52, and 96; 2, 11, 52, and 57; 2, 11, 53, and 57; 2, 11, 95, and 57; 2, 11, 52, and 96; 2, 11, 54, and 58; 2, 11, 55, and 59; 2, 11, 56, and 59; 3, 11, 52, and 57; 3, 11, 53, and 57; 3, 11, 95, and 57; 3, 11, 52, and 96; 3, 11, 54, and 58; 3, 11, 55, and 59; 3, 11, 56, and 59; 4, 11, 52, and 57; 4, 11, 53, and 57; 4, 11, 95, and 57; 4, 11, 52, and 96; 4, 11, 54, and 58; 4, 11, 55, and 59; 4, 11, 56, and 59; 5, 11, 52, and 57; 5, 11, 53, and 57; 5, 11, 95, and 57; 5, 11, 52, and 96; 5, 11, 54, and 58; 5, 11, 55, and 59; 5, 11, 56, and 59; 6, 11, 52, and 57; 6, 11, 53, and 57; 6, 11, 95, and 57; 6, 11, 52, and 96; 6, 11, 54, and 58; 6, 11, 55, and 59; 6, 11, 56, and 59; 7, 15, 52, and 57; 7, 15, 53, and 57; 7, 15, 95, and 57; 7, 15, 52, and 96; 7, 15, 54, and 58; 7, 15, 55, and 59; 7, 15, 56, and 59; 8, 15, 52, and 57; 8, 15, 53, and 57; 8, 15, 95, and 57; 8, 15, 52, and 96; 8, 15, 54, and

58; 8, 15, 55, and 59; 8, 15, 56, and 59; 9, 15, 52, and 57; 9, 15, 53, and 57; 9, 15, 95, and 57; 9, 15, 52, and 96; 9, 15, 54, and 58; 9, 15, 55, and 59; 9, 15, 56, and 59; 10, 15, 52, and 57; 10, 15, 53, and 57; 10, 15, 95, and 57; 10, 15, 52, and 96; 10, 15, 54, and 58; 10, 15, 55, and 59; 10, 15, 56, and 59; 1, 12, 52, and 57; 1, 12, 53, and 57; 1, 12, 95, and 57; 1, 12, 52, and 96; 1, 12, 54, and 58; 1, 12, 55, and 59; 1, 12, 56, and 59; 1, 13, 52, and 57; 1, 13, 53, and 57; 1, 13, 95, and 57; 1, 13, 52, and 96; 1, 13, 54, and 58; 1, 13, 55, and 59; 1, 13, 56, and 59; 1, 14, 52, and 57; 1, 14, 53, and 57; 1, 14, 95, and 57; 1, 14, 52, and 96; 1, 14, 54, and 58; 1, 14, 55, and 59; or 1, 14, 56, and 59, respectively.

[00262] As further provided herein, antibodies that bind to OX40 and GITR can increase OX40 and/or GITR activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 and/or GITR activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40 or GITR). For instance, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can increase OX40 (*e.g.*, human OX40) and/or GITR (*e.g.*, human GITR) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 (*e.g.*, human OX40) and/or GITR (*e.g.*, human GITR) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40 or GITR). Non-limiting examples of OX40 (*e.g.*, human OX40) activity can include OX40 (*e.g.*, human OX40) signaling, OX40 (*e.g.*, human OX40) binding to OX40 (*e.g.*, human OX40) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13). Non-limiting examples of GITR (*e.g.*, human GITR) activity can include GITR (*e.g.*, human GITR) signaling, GITR (*e.g.*, human GITR) binding to GITR (*e.g.*, human GITR) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

[00263] As further provided herein, antibodies that bind to OX40 and GITR can agonize OX40 and/or GITR function, for example, by stimulating T cell activation. For instance, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can stimulate T cell activation, optionally wherein T cell activation is a substantially increasing function of antibody concentrations.

[00264] As further provided herein, antibodies that bind to OX40 and GITR can agonize OX40 and/or GITR function, for example, by stimulating IL-2 release in an SEA assay. For instance, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can, in combination with Staphylococcus Enterotoxin A (SEA) (*e.g.*, 100 ng/ml), induce IL-2 production in, *e.g.*, PBMCs upon stimulation for, *e.g.*, 5 days at, *e.g.*, 37°C, 5% CO_2, and 97% humidity, as measured by, *e.g.*, electrochemiluminescence. In some embodiments, the IL-2 production is a substantially increasing function of antibody concentrations. In certain embodiments, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can, in combination with Staphylococcus Enterotoxin A (SEA), induce IL-2 production in, *e.g.*, PBMCs, wherein the IL-2 production is a substantially increasing function of antibody concentrations as assessed in, *e.g.*, an assay comprising the following steps: (a) culturing the PBMCs (*e.g.*, 10^5 cells in a well) in the absence or presence of varying concentrations of the antibody and, *e.g.*, 100 ng/ml of SEA for, *e.g.*, 5 days at, *e.g.*, 37°C, 5% CO_2, and 97% humidity; and (b) collecting clarified supernatant and measuring the titer of IL-2

by, *e.g.*, electrochemiluminescence.

[00265] As further provided herein, antibodies that bind to OX40 and GITR can agonize OX40 and/or GITR function, for example, by stimulating NF-κB signaling. For instance, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can stimulate NF-κB signaling, *e.g.*, in a Jurkat-huOX40-NF-κB-luciferase reporter assay as described in the examples herein, optionally wherein the NF-κB signaling is a substantially increasing function of antibody concentrations.

[00266] As further provided herein, antibodies that bind to OX40 and GITR can decrease OX40 and/or GITR activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 and/or GITR activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40 or GITR). For instance, an antibody that binds to OX40 and GITR, *e.g.*, an antibody that binds to OX40 and GITR and comprises a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can decrease OX40 (*e.g.*, human OX40) and/or GITR (*e.g.*, human GITR) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to OX40 (*e.g.*, human OX40) and/or GITR (*e.g.*, human GITR) activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not bind to OX40 or GITR). Non-limiting examples of OX40 (*e.g.*, human OX40) activity can include OX40 (*e.g.*, human OX40) signaling, OX40 (*e.g.*, human OX40) binding to OX40 (*e.g.*, human OX40) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13). Non-limiting examples of GITR (*e.g.*, human GITR)

activity can include GITR (*e.g.*, human GITR) signaling, GITR (*e.g.*, human GITR) binding to GITR (*e.g.*, human GITR) ligand, cell proliferation, cell survival, and cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13).

[00267] A multispecific antibody, *e.g.*, a bispecific antibody, that binds to OX40 and/or GITR as provided herein can be prepared by chemically linking two different monoclonal antibodies or by fusing two hybridoma cell lines to produce a hybrid-hybridoma. Other multivalent formats that can be used include, for example, Kλ-bodies, dAbs, diabodies, TandAbs, nanobodies, SMIPs, DNLs, strand-exchange engineered domain bodies (SEEDbodies), Affibodies, Fynomers, Kunitz Domains, Albu-dabs, DARTs, DVD-IG, Covx-bodies, peptibodies, scFv-Igs, SVD-Igs, dAb-Igs, Knobs-in-Holes, and triomAbs. Exemplary bispecific formats are discussed in Garber *et al.*, *Nature Reviews Drug Discovery 13*:799-801 (2014), which is herein incorporated by reference in its entirety.

[00268] Exemplary bispecific antibody molecules of the invention comprise (i) a single antibody that has two arms comprising different antigen-binding regions, one with a specificity to a first antigen such as OX40 and one with a specificity to a second antigen such as GITR, (ii) a single antibody that has one antigen-binding region or arm specific to a first antigen such as OX40 and a second antigen-binding region or arm specific to a second antigen such as GITR, (iii) a single chain antibody that has a first specificity to a first antigen such as OX40 and a second specificity to a second antigen such as GITR, *e.g.*, via two scFvs linked in tandem by an extra peptide linker; (iv) a dual-variable-domain antibody (DVD-Ig), where each light chain and heavy chain contains two variable domains in tandem through a short peptide linkage (Wu et al., Generation and Characterization of a Dual Variable Domain Immunoglobulin (DVD-Ig.TM.) Molecule, In: Antibody Engineering, Springer Berlin Heidelberg (2010)); (v) a chemically-linked bispecific $(Fab')_2$ fragment; (vi) a Tandab, which is a fusion of two single chain diabodies resulting in a tetravalent bispecific antibody that has two binding sites for each of the target antigens; (vii) a flexibody, which is a combination of scFvs with a diabody resulting in a multivalent molecule; (viii) a so called "dock and lock" molecule, based on the "dimerization and docking domain" in Protein Kinase A, which, when applied to Fabs, can yield a trivalent bispecific binding protein consisting of two identical Fab fragments linked to a different Fab fragment; (ix) a so-called Scorpion molecule, comprising, e.g., two scFvs fused to both termini of a human Fab-arm; and (x) a diabody.

[00269] Examples of different classes of bispecific antibodies include but are not limited to IgG-like molecules with complementary CH3 domains to force heterodimerisation; recombinant IgG-like dual targeting molecules, wherein the two sides of the molecule each contain the Fab fragment or part of the Fab fragment of at least two different antibodies; IgG fusion molecules, wherein full length IgG antibodies are fused to extra Fab fragment or parts of Fab fragment; Fc fusion molecules, wherein single chain Fv molecules or stabilized diabodies are fused to heavy-chain constant-domains, Fc-regions or parts thereof; Fab fusion molecules, wherein different Fab-fragments are fused together; ScFv- and diabody-based and heavy chain antibodies (e.g., domain antibodies, nanobodies) wherein different single chain Fv molecules or different diabodies or different heavy-chain antibodies (e.g. domain antibodies, nanobodies) are fused to each other or to another protein or carrier molecule.

[00270] Examples of Fab fusion bispecific antibodies include but are not limited to $F(ab)_2$ (Medarex/AMGEN), Dual-Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech). Examples of ScFv-, diabody-based and domain antibodies include but are not limited to Bispecific T Cell Engager (BITE) (Micromet, Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-like Antibodies (AIT, ReceptorLogics), Human Serum Albumin ScFv Fusion (Merrimack) and COMBODY (Epigen Biotech), dual targeting nanobodies (Ablynx), and dual targeting heavy chain only domain antibodies.

5.2.4 Constant regions

[00271] Any heavy chain or light chain constant region can be used in the antibodies (*e.g.*, monospecific or multispecific antibodies) disclosed herein. In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) disclosed herein comprise an Ig region that is a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule. Exemplary constant region sequences that can be used in the antibodies (*e.g.*, monospecific or multispecific antibodies) disclosed herein are disclosed in Table 14.

Table 14. Exemplary constant region sequences.

SEQ ID NO:	Description	Amino acid Sequence
88	Human IgG1 constant region consensus sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKX$_1$VEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRX$_2$EX$_3$TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEX$_4$LHNHYTQKSLSLSPG, wherein X$_1$ is K or R X$_2$ is D or E X$_3$ is L or M X$_4$ is G or A
89	Human IgG1 G1m3 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
90	Human IgG1 G1m17,1 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
91	Human IgG1, G1m17,1,2 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEGLHNHYTQKSLSLSPG

SEQ ID NO:	Description	Amino acid Sequence
92	Human IgG1 G1m3 allotype N297A	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
107	Human IgG1 S239D/I332E	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPDVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPEEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
108	Human IgG1 S239D/A330L/I332E	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPDVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPLPEEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
109	Human IgG1 L235V/F243L/R292P /Y300L/P396L	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELVGGPSVFLLPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPPEEQYNSTLRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPLVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
93	Human IgG4 S228P	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLSLG

SEQ ID NO:	Description	Amino acid Sequence
94	Human kappa light chain constant region IGKC*01 Km3 allotype	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[00272] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) disclosed herein comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc gamma receptors with higher affinity than the wild type human IgG heavy chain constant region binds to the human Fc gamma receptors.

[00273] In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S239D and I332E. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S239D and I332E. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E.

[00274] In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L.

[00275] In certain embodiments, the variant human IgG heavy chain constant region

comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: G236A, S239D, F243L, T256A, K290A, R292P, S298A, Y300L, V305I, A330L, I332E, E333A, K334A, A339T, and P396L. In certain embodiments, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S239D; T256A; K290A; S298A; I332E; E333A; K334A; A339T; S239D and I332E; S239D, A330L, and I332E; S298A, E333A, and K334A; G236A, S239D, and I332E; and F243L, R292P, Y300L, V305I, and P396L, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises S267E or L328F amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S267E and L328F. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S267E and L328F. In certain embodiments, the variant human IgG heavy chain constant region comprises P238D amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising P238D amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region comprises C127S amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_2 heavy chain constant region comprising C127S amino acid mutation, numbered according to the EU numbering system.

[00276] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific

antibodies) provided herein comprise an afucosylated Fc region.

[00277] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) disclosed herein comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc gamma receptors with lower affinity than the wild type human IgG heavy chain constant region binds to the human Fc gamma receptors. In certain embodiments, the variant human IgG heavy chain constant region comprises a mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises a mutation selected from the group consisting of D265A, P329A, and a combination thereof, numbered according to the EU numbering system.

[00278] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein (*e.g.*, CH2 domain (residues 231-340 of human IgG_1) and/or CH3 domain (residues 341-447 of human IgG_1) and/or the hinge region numbered according to the EU numbering system to alter one or more functional properties of the antibody (*e.g.*, a monospecific or multispecific antibody), such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular cytotoxicity.

[00279] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, *e.g.*, U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody (*e.g.*, a monospecific or multispecific antibody).

[00280] In some embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein (*e.g.*, CH2 domain (residues 231-340 of human IgG_1) and/or CH3 domain (residues 341-447 of human IgG_1) and/or the hinge region numbered according to the EU numbering system to increase or decrease the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an

effector cell. Mutations in the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) that decrease or increase the affinity of an antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody (*e.g.*, a monospecific or multispecific antibody) that can be made to alter the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor are described in, *e.g.*, Smith P *et al.*, (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[00281] In a specific embodiment, one, two, or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of an antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. *See, e.g.*, International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions, or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to decrease the half-life of the antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In other embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In a specific embodiment, the antibodies (*e.g.*, monospecific or multispecific antibodies) may have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG_1) and/or the third constant (CH3) domain (residues 341-447 of human IgG_1), numbered according to the EU numbering system. In a specific embodiment, the constant region of the IgG_1 of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU

numbering system. *See* U.S. Patent No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (*see* Dall'Acqua WF *et al.*, (2006) J Biol Chem 281: 23514-24). In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU numbering system.

[00282] In certain embodiments, one or more amino acids selected from amino acid residues 329, 331, and 322 in the constant region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein, numbered according to the EU numbering system, can be replaced with a different amino acid residue such that the antibody (*e.g.*, a monospecific or multispecific antibody) has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 (Idusogie *et al*). In some embodiments, one or more amino acid residues within amino acid positions 231 to 238 in the N-terminal region of the CH2 domain of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein are altered to thereby alter the ability of the antibody (*e.g.*, a monospecific or multispecific antibody) to fix complement. This approach is described further in International Publication No. WO 94/29351. In certain embodiments, the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein is modified to increase the ability of the antibody (*e.g.*, a monospecific or multispecific antibody) to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fcγ receptor by mutating one or more amino acids (*e.g.*, introducing amino acid substitutions) at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 328, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438, or 439, numbered according to the EU numbering system. This approach is described further in International Publication No. WO 00/42072.

[00283] In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises the constant region of an IgG_4 antibody and the serine at amino acid residue 228 of the heavy chain, numbered according to the EU numbering system, is substituted

for proline.

[00284] In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises the constant region of an IgG_2 antibody and the cysteine at amino acid residue 127 of the heavy chain, numbered according to the EU numbering system, is substituted for serine.

[00285] Antibodies with reduced fucose content have been reported to have an increased affinity for Fc receptors, such as, *e.g.*, FcγRIIIa. Accordingly, in certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) described herein have reduced fucose content or no fucose content. Such antibodies (*e.g.*, monospecific or multispecific antibodies) can be produced using techniques known to one skilled in the art. For example, the antibodies (*e.g.*, monospecific or multispecific antibodies) can be expressed in cells deficient or lacking the ability of fucosylation. In a specific example, cell lines with a knockout of both alleles of α1,6-fucosyltransferase can be used to produce antibodies (*e.g.*, monospecific or multispecific antibodies) with reduced fucose content. The Potelligent® system (Lonza) is an example of such a system that can be used to produce antibodies (*e.g.*, monospecific or multispecific antibodies) with reduced fucose content. Alternatively, antibodies (*e.g.*, monospecific or multispecific antibodies) with reduced fucose content or no fucose content can be produced by, *e.g.*: (i) culturing cells under conditions which prevent or reduce fucosylation; (ii) posttranslational removal of fucose (*e.g.*, with a fucosidase enzyme); (iii) post-translational addition of the desired carbohydrate, *e.g.*, after recombinant expression of a non-glycosylated glycoprotein; or (iv) purification of the glycoprotein so as to select for antibodies (e.g., monospecific or multispecific antibodies) thereof which are not fucsoylated. *See*, *e.g.*, Longmore GD & Schachter H (1982) Carbohydr Res 100: 365-92 and Imai-Nishiya H *et al.*, (2007) BMC Biotechnol. 7: 84 for methods for producing antibodies (*e.g.*, monospecific or multispecific antibodies) with no fucose content or reduced fucose content.

[00286] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Methods for generating engineered glycoforms in an antibody (*e.g.*, a monospecific or multispecific antibody) described herein include but are not limited to those disclosed, *e.g.*, in Umaña P *et al.*, (1999) Nat Biotechnol 17: 176-180; Davies J *et al.*, (2001) Biotechnol Bioeng 74: 288-294; Shields RL *et al.*, (2002) J Biol Chem 277: 26733-26740; Shinkawa T *et al.*, (2003) J Biol Chem 278: 3466-3473; Niwa R *et al.*,

(2004) Clin Cancer Res 1: 6248-6255; Presta LG *et al.*, (2002) Biochem Soc Trans 30: 487-490; Kanda Y *et al.*, (2007) Glycobiology 17: 104-118; U.S. Patent Nos. 6,602,684; 6,946,292; and 7,214,775; U.S. Patent Publication Nos. US 2007/0248600; 2007/0178551; 2008/0060092; and 2006/0253928; International Publication Nos. WO 00/61739; WO 01/292246; WO 02/311140; and WO 02/30954; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb® glycosylation engineering technology (Glycart biotechnology AG, Zurich, Switzerland). *See also*, *e.g.*, Ferrara C *et al.*, (2006) Biotechnol Bioeng 93: 851-861; International Publication Nos. WO 07/039818; WO 12/130831; WO 99/054342; WO 03/011878; and WO 04/065540.

[00287] In certain embodiments, the technology used to engineer the Fc domain of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein is the Xmab® Technology of Xencor (Monrovia, CA). *See*, *e.g.*, U.S. Patent Nos. 8,367,805; 8,039,592; 8,124,731; 8,188,231; U.S. Patent Publication No. 2006/0235208; International Publication Nos. WO 05/077981; WO 11/097527; and Richards JO *et al.*, (2008) Mol Cancer Ther 7: 2517-2527.

[00288] In certain embodiments, any of the constant region mutations or modifications described herein can be introduced into one or both heavy chain constant regions of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein having two heavy chain constant regions.

5.3 Antibody Production

[00289] Antibodies, including monospecific or multispecific (*e.g.*, bispecific) antibodies, that immunospecifically bind to OX40 and/or GITR, (*e.g.*, human OX40 and/or GITR) can be produced by any method known in the art for the synthesis of antibodies, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employ, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. *See*, *e.g.*, Maniatis T *et al.*, (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.*, Current Protocols in Molecular Biology, John Wiley &

Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B *et al.*, (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00290] In a specific embodiment, an antibody described herein is an antibody (*e.g.*, a recombinant antibody) prepared, expressed, created or isolated by any means that involves creation, *e.g.*, via synthesis, genetic engineering of DNA sequences. In certain embodiments, such antibody comprises sequences (*e.g.*, DNA sequences or amino acid sequences) that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.*, human) *in vivo*.

[00291] In a certain aspect, provided herein is a method of making an antibody which immunospecifically binds to OX40 and/or GITR (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or human GITR) comprising culturing a cell or host cell described herein. In a certain aspect, provided herein is a method of making an antibody which immunospecifically binds to OX40 and/or GITR (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or human GITR) comprising expressing (*e.g.*, recombinantly expressing) the antibody using a cell or host cell described herein (*e.g.*, a cell or a host cell comprising polynucleotides encoding an antibody described herein). In a particular embodiment, the cell is an isolated cell. In a particular embodiment, the exogenous polynucleotides have been introduced into the cell. In a particular embodiment, the method further comprises the step of purifying the antibody obtained from the cell or host cell.

[00292] Methods for producing polyclonal antibodies are known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.,* eds., John Wiley and Sons, New York).

[00293] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow E & Lane D, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ *et al.,* in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier,

N.Y., 1981). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. For example, monoclonal antibodies can be produced recombinantly from host cells exogenously expressing an antibody described herein.

[00294] In specific embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single cell (*e.g.*, hybridoma or host cell producing a recombinant antibody), wherein the antibody immunospecifically binds to OX40 and/or GITR (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) as determined, *e.g.*, by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. In particular embodiments, a monoclonal antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a monoclonal antibody is a monovalent antibody or multivalent (*e.g.*, bivalent) antibody. In certain embodiments, a monoclonal antibody can be a Fab fragment or a $F(ab')_2$ fragment. Monoclonal antibodies described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495 or can, *e.g.*, be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al., supra*).

[00295] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. For example, in the hybridoma method, a mouse or other appropriate host animal, such as a sheep, goat, rabbit, rat, hamster or macaque monkey, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein (*e.g.*, OX40 or GITR (*e.g.*, human OX40 or GITR)) used for immunization. Alternatively, lymphocytes can be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilpatrick KE *et al.*, (1997) Hybridoma 16:381-9, incorporated by reference in its entirety).

[00296] In some embodiments, mice (or other animals, such as rats, monkeys, donkeys, pigs, sheep, hamster, or dogs) can be immunized with an antigen (*e.g.*, OX40 or GITR (*e.g.*, human

OX40 or GITR)) and once an immune response is detected, *e.g.*, antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well-known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the American Type Culture Collection (ATCC®) (Manassas, VA), to form hybridomas. Hybridomas are selected and cloned by limited dilution. In certain embodiments, lymph nodes of the immunized mice are harvested and fused with NS0 myeloma cells.

[00297] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that optionally contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00298] Specific embodiments employ myeloma cells that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these myeloma cell lines are murine myeloma lines, such as NS0 cell line or those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8.653 cells available from the American Type Culture Collection, Rockville, MD, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor D (1984) J Immunol 133: 3001-5; Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[00299] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against OX40 and/or GITR (*e.g.*, human OX40 and/or GITR). The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by methods known in the art, for example, immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

[00300] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, *supra*).

Suitable culture media for this purpose include, for example, D-MEM or RPMI 1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00301] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00302] Antibodies described herein can be generated by any technique known to those of skill in the art. For example, Fab and $F(ab')_2$ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). A Fab fragment corresponds to one of the two identical arms of a tetrameric antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A $F(ab')_2$ fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[00303] Further, the antibodies or antigen-binding fragments described herein can also be generated using various phage display methods known in the art. In phage display methods, proteins are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding heavy and light chain variable regions are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of affected tissues). The DNA encoding the heavy and light chain variable regions are recombined together with a scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13, and the heavy and light chain variable regions are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antibody that binds to a particular antigen can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies described herein include those disclosed in Brinkman U *et al.*, (1995) J Immunol Methods 182: 41-50; Ames RS *et al.*, (1995) J Immunol Methods 184: 177-186; Kettleborough CA *et al.*, (1994) Eur J Immunol 24: 952-958; Persic L *et al.*, (1997) Gene 187: 9-18; Burton DR & Barbas CF (1994) Advan Immunol 57: 191-280; PCT Application No. PCT/GB91/001134; International Publication Nos. WO 90/02809, WO

91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO 97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743, and 5,969,108.

[00304] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate antibodies, including human antibodies, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce antibodies such as Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax RL *et al.*, (1992) BioTechniques 12(6): 864-9; Sawai H *et al.*, (1995) Am J Reprod Immunol 34: 26-34; and Better M *et al.*, (1988) Science 240: 1041-1043.

[00305] In one aspect, to generate antibodies, PCR primers including heavy or light chain variable region nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the heavy or light chain variable region sequences from a template, *e.g.*, scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified heavy chain variable regions can be cloned into vectors expressing a heavy chain constant region, and the PCR amplified light chain variable regions can be cloned into vectors expressing a light chain constant region, *e.g.*, human kappa or lambda constant regions. The heavy and light chain variable regions can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00306] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. For example, a chimeric antibody can contain a variable region of a mouse or rat monoclonal antibody fused to a constant region of a human antibody. Methods for producing chimeric antibodies are known in the art. *See*, *e.g.*, Morrison SL (1985) Science 229: 1202-7; Oi VT & Morrison SL (1986) BioTechniques 4: 214-221; Gillies SD *et al.*, (1989) J Immunol Methods 125: 191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415.

[00307] A humanized antibody is capable of binding to a predetermined antigen and which

comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and CDRs having substantially the amino acid sequence of a non-human immunoglobulin (*e.g.*, a murine immunoglobulin). In particular embodiments, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The antibody also can include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. A humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG_1, IgG_2, IgG_3 and IgG_4. Humanized antibodies can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592106 and EP 519596; Padlan EA (1991) Mol Immunol 28(4/5): 489-498; Studnicka GM *et al.,* (1994) Prot Engineering 7(6): 805-814; and Roguska MA *et al.,* (1994) PNAS 91: 969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.,* U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 93/17105; Tan P *et al.,* (2002) J Immunol 169: 1119-25; Caldas C *et al.,* (2000) Protein Eng. 13(5): 353-60; Morea V *et al.,* (2000) Methods 20(3): 267-79; Baca M *et al.,* (1997) J Biol Chem 272(16): 10678-84; Roguska MA *et al.,* (1996) Protein Eng 9(10): 895 904; Couto JR *et al.,* (1995) Cancer Res. 55 (23 Supp): 5973s-5977s; Couto JR *et al.,* (1995) Cancer Res 55(8): 1717-22; Sandhu JS (1994) Gene 150(2): 409-10 and Pedersen JT *et al.,* (1994) J Mol Biol 235(3): 959-73. See also U.S. Application Publication No. US 2005/0042664 A1 (Feb. 24, 2005), which is incorporated by reference herein in its entirety.

[00308] Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well known in the art. See Riechmann L & Muyldermans S (1999) J Immunol 231: 25-38; Nuttall SD *et al.,* (2000) Curr Pharm Biotechnol 1(3): 253-263; Muyldermans S, (2001) J Biotechnol 74(4): 277-302; U.S. Patent No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591 and WO 01/44301.

[00309] Further, antibodies that immunospecifically bind to an OX40 and/or GITR antigen can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" an antigen using techniques well known to those skilled in the art. (See, *e.g.,* Greenspan NS & Bona CA (1989) FASEB J 7(5): 437-444; and Nissinoff A (1991) J Immunol 147(8): 2429-2438).

[00310] In particular embodiments, an antibody or antigen-binding fragment thereof described

herein, which binds to the same epitope of OX40 and/or GITR (*e.g.*, human OX40 and/or GITR) as an anti-OX40 or GITR antibody or antigen-binding fragment thereof described herein, is a human antibody. In particular embodiments, an antibody described herein, which competitively blocks (*e.g.*, in a dose-dependent manner) any one of the antibodies described herein, from binding to OX40 or GITR (*e.g.*, human OX40 or GITR), is a human antibody. Human antibodies can be produced using any method known in the art. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, can be used. In particular, the human heavy and light chain immunoglobulin gene complexes can be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region can be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes can be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of an antigen (*e.g.*, OX40 or GITR). Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg N & Huszar D (1995) Int Rev Immunol 13:65-93. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see*, *e.g.*, International Publication Nos. WO 98/24893, WO 96/34096 and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318 and 5,939,598. Examples of mice capable of producing human antibodies include the Xenomouse™ (Abgenix, Inc.; U.S. Patent Nos. 6,075,181 and 6,150,184), the HuAb-Mouse™ (Mederex, Inc./Gen Pharm; U.S. Patent Nos. 5,545,806 and 5,569, 825), the Trans

Chromo Mouse™ (Kirin) and the KM Mouse™ (Medarex/Kirin).

[00311] Human antibodies or antigen-binding fragments which specifically bind to OX40 and/or GITR (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. *See* also U.S. Patent Nos. 4,444,887, 4,716,111, and 5,885,793; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[00312] In some embodiments, human antibodies can be produced using mouse–human hybridomas. For example, human peripheral blood lymphocytes transformed with Epstein-Barr virus (EBV) can be fused with mouse myeloma cells to produce mouse–human hybridomas secreting human monoclonal antibodies, and these mouse–human hybridomas can be screened to determine ones which secrete human monoclonal antibodies that immunospecifically bind to a target antigen (*e.g.*, OX40 or GITR, *e.g.*, human OX40 or GITR). Such methods are known and are described in the art, see, *e.g.*, Shinmoto H *et al.*, (2004) Cytotechnology 46: 19-23; Naganawa Y *et al.*, (2005) Human Antibodies 14: 27-31.

[00313] Bispecific, bivalent antibodies, and methods of making them, are described, for instance in U.S. Pat. Nos. 5,731,168, 5,807,706, 5,821,333, and U.S. Appl. Publ. Nos. 2003/020734 and 2002/0155537; each of which is herein incorporated by reference in its entirety. Bispecific tetravalent antibodies, and methods of making them are described, for instance, in Int. Appl. Publ. Nos. WO02/096948 and WO00/44788, the disclosures of both of which are herein incorporated by reference in its entirety. See generally, Int. Appl. Publ. Nos. WO93/17715, WO92/08802, WO91/00360, and WO92/05793; Tutt *et al.*, J. Immunol. 147:60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; and 5,601,819; and Kostelny *et al.*, J. Immunol. 148:1547-1553 (1992); each of which is herein incorporated by reference in its entirety.

[00314] One method for generating bispecific antibodies has been termed the “knobs-into-holes” strategy (see, *e.g.*, Intl. Publ. WO2006/028936). The mispairing of Ig heavy chains is reduced in this technology by mutating selected amino acids forming the interface of the CH3 domains in IgG. At positions within the CH3 domain at which the two heavy chains interact directly, an amino acid with a small side chain (hole) is introduced into the sequence of one

heavy chain and an amino acid with a large side chain (knob) into the counterpart interacting residue location on the other heavy chain. In some embodiments, compositions of the invention have immunoglobulin chains in which the CH3 domains have been modified by mutating selected amino acids that interact at the interface between two polypeptides to form a bispecific antibody. The bispecific antibodies can be composed of immunoglobulin chains of the same subclass (*e.g.*,IgG1 or IgG3) or different subclasses (*e.g.*, IgG1 and IgG3, or IgG3 and IgG4)

[00315] In one embodiment, a bispecific antibody that binds to OX40 and/or GITR comprises a T366W mutation in the "knobs chain" and T366S, L368A, Y407V mutations in the "hole chain," and optionally an additional interchain disulfide bridge between the CH3 domains by, *e.g.*, introducing a Y349C mutation into the "knobs chain" and a E356C mutation or a S354C mutation into the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" a T366W mutation in the "knobs chain" and T366S, L368A, Y407V mutations in the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" Y349C, T366W mutations in one of the chains and E356C, T366S, L368A, Y407V mutations in the counterpart chain; Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain; Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain; and Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain, numbering according to the EU numbering system.

[00316] Bispecific antibodies that bind to OX40 and/or GITR can, in some instances contain, IgG4 and IgG1, IgG4 and IgG2, IgG4 and IgG2, IgG4 and IgG3, or IgG1 and IgG3 chain heterodimers. Such heterodimeric heavy chain antibodies, can routinely be engineered by, for example, modifying selected amino acids forming the interface of the CH3 domains in human IgG4 and the IgG1 or IgG3 so as to favor heterodimeric heavy chain formation.

In particular embodiments, a multispecific (*e.g.*, bispecific) antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a multispecific (*e.g.*, bispecific) antibody can be a $F(ab')_2$ fragment. A $F(ab')_2$ fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[00317] Multispecific (*e.g.*, bispecific) antibodies described herein can be generated by any technique known to those of skill in the art. For example, $F(ab')_2$ fragments described herein can

be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as pepsin.

5.3.1 Polynucleotides

[00318] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding an antibody described herein or a fragment thereof (*e.g.*, a light chain variable region and/or heavy chain variable region) that immunospecifically binds to an OX40 and/or GITR (*e.g.*, human OX40 and/or GITR) antigen, and vectors, *e.g.*, vectors comprising such polynucleotides for recombinant expression in host cells (*e.g.*, *E. coli* and mammalian cells). Provided herein are polynucleotides comprising nucleotide sequences encoding any of the antibodies provided herein, as well as vectors comprising such polynucleotide sequences, *e.g.*, expression vectors for their efficient expression in host cells, *e.g.*, mammalian cells.

[00319] As used herein, an "isolated" polynucleotide or nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source (*e.g.*, in a mouse or a human) of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. For example, the language "substantially free" includes preparations of polynucleotide or nucleic acid molecule having less than about 15%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (in particular less than about 10%) of other material, *e.g.*, cellular material, culture medium, other nucleic acid molecules, chemical precursors and/or other chemicals. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody described herein is isolated or purified.

[00320] In particular aspects, provided herein are polynucleotides comprising nucleotide sequences encoding antibodies, which immunospecifically bind to an OX40 and/or GITR polypeptide (*e.g.*, human OX40 and/or GITR) and comprises an amino acid sequence as described herein, as well as antibodies that compete with such antibodies for binding to an OX40 and/or GITR polypeptide (*e.g.*, in a dose-dependent manner), or which binds to the same epitope as that of such antibodies.

[00321] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding the light chain or heavy chain of an antibody described herein. The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VL

CDRs of antibodies described herein (*see*, *e.g.*, Tables 2, 4, 7, 9, and 12). The polynucleotides can comprise nucleotide sequences encoding a heavy chain comprising the VH CDRs of antibodies described herein (*see*, *e.g.*, Tables 2, 3, 7, 8, and 12). In specific embodiments, a polynucleotide described herein encodes a heavy chain variable region and/or a light chain variable region comprising an amino acid sequence set forth in Tables 2, 5, 7, 10, or 13.

[00322] In particular embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-OX40 and/or GITR antibody comprising three VL chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Tables 4, 9, and 12). In specific embodiments, provided herein are polynucleotides comprising three VH chain CDRs, *e.g.*, containing VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies described herein (*e.g.*, see Tables 3, 8, and 12). In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-OX40 and/or GITR antibody comprising three VH chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Tables 4, 9, and 12) and three VH chain CDRs, *e.g.*, containing VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies described herein (*e.g.*, see Tables 3, 8, and 12).

[00323] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding an antibody or antigen-binding fragment thereof provided herein comprising a light chain variable region comprising an amino acid sequence described herein (*e.g.*, see Tables 2, 5, 7, 10, and 13), wherein the antibody immunospecifically binds to OX40 and/or GITR (*e.g.*, human OX40 and/or GITR).

[00324] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding an antibody or antigen-binding fragment thereof provided herein comprising a heavy chain variable region comprising an amino acid sequence described herein (*e.g.*, see Tables 2, 5, 7, 10, and 13), wherein the antibody immunospecifically binds to OX40 and/or GITR (*e.g.*, human OX40 and/or GITR).

[00325] In specific aspects, provided herein is a polynucleotide comprising a nucleotide sequence encoding an antibody comprising a light chain and a heavy chain, *e.g.*, a separate light chain and heavy chain. With respect to the light chain, in a specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a kappa light chain. In another specific embodiment, a polynucleotide provided herein comprises a nucleotide

sequence encoding a lambda light chain. In yet another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein comprising a human kappa light chain or a human lambda light chain. In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody, which immunospecifically binds to OX40 and/or GITR (*e.g.*, human OX40 and/or GITR), wherein the antibody comprises a light chain, and wherein the amino acid sequence of the light chain variable region can comprise a light chain variable region amino acid sequence set forth in Tables 2, 5, 7, 10, or 13, and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region. In another particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody, which immunospecifically binds to OX40 and/or GITR (*e.g.*, human OX40 and/or GITR), and comprises a light chain, wherein the amino acid sequence of the light chain variable region can comprise a light chain variable region amino acid sequence set forth in Tables 2, 5, 7, 10, or 13, and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. For example, human constant region sequences can be those described in U.S. Patent No. 5,693,780.

[00326] In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein, which immunospecifically binds to OX40 (*e.g.*, human OX40), wherein the antibody comprises a heavy chain, wherein the amino acid sequence of the heavy chain variable region can comprise the VH amino acid sequence set forth in Tables 2, 5, 7, 10, or 13, and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region.

[00327] In a certain embodiment, a polynucleotide provided herein comprises a nucleotide sequence(s) encoding a heavy chain variable region and/or a light chain variable region of an antibody described herein (*e.g.*, see Tables 2, 5, 7, 10, and 13), which immunospecifically binds to OX40 and/or GITR (*e.g.*, human OX40 and/or GITR).

[00328] In yet another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein, which immunospecifically binds OX40 and/or GITR (*e.g.*, human OX40 and/or GITR), wherein the antibody comprises a light chain variable region and a heavy chain variable region comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the

constant regions of a human IgG_1 (*e.g.*, allotype 1, 17, or 3), human IgG_2, or human IgG_4.

[00329] In a specific embodiment, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-OX40 and/or GITR antibody or domain thereof, designated herein, *see*, *e.g.*, Tables 1-5, 7-10, 12, and 13.

[00330] Also provided herein are polynucleotides encoding an anti-OX40 and/or GITR antibody or a fragment thereof that are optimized, *e.g.*, by codon/RNA optimization, replacement with heterologous signal sequences, and elimination of mRNA instability elements. Methods to generate optimized nucleic acids encoding an anti-OX40 antibody or a fragment thereof (*e.g.*, light chain, heavy chain, heavy chain variable region, or light chain variable region) for recombinant expression by introducing codon changes and/or eliminating inhibitory regions in the mRNA can be carried out by adapting the optimization methods described in, *e.g.*, U.S. Patent Nos. 5,965,726; 6,174,666; 6,291,664; 6,414,132; and 6,794,498, accordingly. For example, potential splice sites and instability elements (*e.g.*, A/T or A/U rich elements) within the RNA can be mutated without altering the amino acids encoded by the nucleic acid sequences to increase stability of the RNA for recombinant expression. The alterations utilize the degeneracy of the genetic code, *e.g.*, using an alternative codon for an identical amino acid. In some embodiments, it can be desirable to alter one or more codons to encode a conservative mutation, *e.g.*, a similar amino acid with similar chemical structure and properties and/or function as the original amino acid.

[00331] In certain embodiments, an optimized polynucleotide sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment thereof (*e.g.*, heavy chain variable region or light chain variable region) can hybridize to an antisense (*e.g.*, complementary) polynucleotide of an unoptimized polynucleotide sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment thereof (*e.g.*, heavy chain variable region or light chain variable region). In specific embodiments, an optimized nucleotide sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment hybridizes under high stringency conditions to antisense polynucleotide of an unoptimized polynucleotide sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment thereof. In a specific embodiment, an optimized nucleotide sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment thereof hybridizes under high stringency, intermediate or lower stringency hybridization conditions to an antisense polynucleotide of an unoptimized nucleotide

sequence encoding an anti-OX40 and/or GITR antibody described herein or a fragment thereof. Information regarding hybridization conditions has been described, see, *e.g.*, U.S. Patent Application Publication No. US 2005/0048549 (*e.g.*, paragraphs 72-73), which is incorporated herein by reference.

[00332] The polynucleotides can be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Nucleotide sequences encoding antibodies described herein, *e.g.*, antibodies described in Tables 2-5, 7-10, and 12-14, and modified versions of these antibodies can be determined using methods well known in the art, *i.e.*, nucleotide codons known to encode particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody. Such a polynucleotide encoding the antibody can be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier G *et al.*, (1994), BioTechniques 17: 242-246), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[00333] Alternatively, a polynucleotide encoding an antibody or fragment thereof described herein can be generated from nucleic acid from a suitable source (*e.g.*, a hybridoma) using methods well known in the art (*e.g.*, PCR and other molecular cloning methods). For example, PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of a known sequence can be performed using genomic DNA obtained from hybridoma cells producing the antibody of interest. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the light chain and/or heavy chain of an antibody. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the variable light chain region and/or the variable heavy chain region of an antibody. The amplified nucleic acids can be cloned into vectors for expression in host cells and for further cloning, for example, to generate chimeric and humanized antibodies.

[00334] If a clone containing a nucleic acid encoding a particular antibody or fragment thereof is not available, but the sequence of the antibody molecule or fragment thereof is known, a nucleic acid encoding the immunoglobulin or fragment can be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library or a cDNA library generated from, or nucleic acid, for example poly A+ RNA, isolated from, any tissue or cells expressing the

antibody, such as hybridoma cells selected to express an antibody described herein) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR can then be cloned into replicable cloning vectors using any method well known in the art.

[00335] DNA encoding anti-OX40 and/or GITR antibodies described herein can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the anti-OX40 and/or GITR antibodies). Hybridoma cells can serve as a source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells (*e.g.*, CHO cells from the CHO GS System™ (Lonza)), or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of anti-OX40 antibodies in the recombinant host cells.

[00336] To generate antibodies, PCR primers including heavy or light chain variable region nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the heavy or light chain variable region sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified heavy chain variable regions can be cloned into vectors expressing a heavy chain constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified light chain variable regions can be cloned into vectors expressing a light chain constant region, *e.g.*, human kappa or lambda constant regions. In certain embodiments, the vectors for expressing the heavy or light chain variable regions comprise an EF-1α promoter, a secretion signal, a cloning site for the variable domain, constant domains, and a selection marker such as neomycin. The heavy and light chain variable regions can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00337] The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the murine sequences, or by

covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

[00338] Also provided are polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides that encode an antibody described herein. In specific embodiments, polynucleotides described herein hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides encoding a heavy chain variable region and/or light chain variable region (*e.g.*, see Tables 2, 5, 7, 10, and 13) provided herein.

[00339] Hybridization conditions have been described in the art and are known to one of skill in the art. For example, hybridization under stringent conditions can involve hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65°C; hybridization under highly stringent conditions can involve hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C. Hybridization under other stringent hybridization conditions are known to those of skill in the art and have been described, see, for example, Ausubel FM *et al.*, eds., (1989) Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3.

5.3.2 Cells and Vectors

[00340] In certain aspects, provided herein are cells (*e.g.*, host cells) expressing (*e.g.*, recombinantly) antibodies described herein which specifically bind to OX40 (including, *e.g.*, antibodies that bind to human OX40 and GITR) and related polynucleotides and expression vectors. Provided herein are vectors (*e.g.*, expression vectors) comprising polynucleotides comprising nucleotide sequences encoding anti-OX40 and/or GITR antibodies or a fragment for recombinant expression in host cells, for example in mammalian cells. Also provided herein are host cells comprising such vectors for recombinantly expressing anti-OX40 antibodies (including, *e.g.*, antibodies that bind to human OX40 and GITR described herein (*e.g.*, human or humanized antibody). In a particular aspect, provided herein are methods for producing an antibody described herein, comprising expressing such antibody in a host cell.

[00341] Recombinant expression of an antibody or fragment thereof described herein (*e.g.*, a heavy or light chain of an antibody described herein) that specifically binds to OX40 and/or

GITR (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) involves construction of an expression vector containing a polynucleotide that encodes the antibody or fragment. Once a polynucleotide encoding an antibody or fragment thereof (*e.g.*, heavy or light chain variable domains) described herein has been obtained, the vector for the production of the antibody molecule can be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody or antibody fragment (*e.g.*, light chain or heavy chain) encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody or antibody fragment (*e.g.*, light chain or heavy chain) coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Also provided are replicable vectors comprising a nucleotide sequence encoding an antibody molecule described herein, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a fragment thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors can, for example, include the nucleotide sequence encoding the constant region of the antibody molecule (see, *e.g.*, International Publication Nos. WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464) and variable domains of the antibody can be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[00342] An expression vector can be transferred to a cell (*e.g.*, host cell) by conventional techniques and the resulting cells can then be cultured by conventional techniques to produce an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12) or a fragment thereof. Thus, provided herein are host cells containing a polynucleotide encoding an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12) or fragments thereof (*e.g.*, a heavy or light chain thereof, or fragment thereof), operably linked to a promoter for expression of such sequences in the host cell. In certain embodiments, for the expression of double-chained antibodies, vectors encoding both the heavy and light chains, individually, can be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below. In certain embodiments, a host cell contains a vector comprising a polynucleotide

encoding both the heavy chain and light chain of an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12), or a fragment thereof. In specific embodiments, a host cell contains two different vectors, a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12), or a fragment thereof, and a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12), or a fragment thereof. In other embodiments, a first host cell comprises a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12), or a fragment thereof, and a second host cell comprises a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12). In specific embodiments, a heavy chain/heavy chain variable region expressed by a first cell associated with a light chain/light chain variable region of a second cell to form an anti-OX40 and/or GITR antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12). In certain embodiments, provided herein is a population of host cells comprising such first host cell and such second host cell.

[00343] In a particular embodiment, provided herein is a population of vectors comprising a first vector comprising a polynucleotide encoding a light chain/light chain variable region of an anti-OX40 and/or GITR antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12), and a second vector comprising a polynucleotide encoding a heavy chain/heavy chain variable region of an anti-OX40 antibody described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12).

[00344] A variety of host-expression vector systems can be utilized to express antibody molecules described herein (see, *e.g.*, U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also represent cells which can, when transformed or transfected with the appropriate

nucleotide coding sequences, express an antibody molecule described herein *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems (*e.g.*, green algae such as *Chlamydomonas reinhardtii*) infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS (*e.g.*, COS1 or COS), CHO, BHK, MDCK, HEK 293, NS0, PER.C6, VERO, CRL7O3O, HsS78Bst, HeLa, and NIH 3T3, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20 and BMT10 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). In a specific embodiment, cells for expressing antibodies described herein (*e.g.*, a monospecific or multispecific antibody comprising the CDRs in Tables 2, 3, 4, 7, 8, 9, and/or 12) are CHO cells, for example CHO cells from the CHO GS System™ (Lonza). In a particular embodiment, cells for expressing antibodies described herein are human cells, *e.g.*, human cell lines. In a specific embodiment, a mammalian expression vector is pOptiVEC™ or pcDNA3.3. In a particular embodiment, bacterial cells such as *Escherichia coli*, or eukaryotic cells (*e.g.*, mammalian cells), especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary (CHO) cells in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking MK & Hofstetter H (1986) Gene 45: 101-105; and Cockett MI *et al.*, (1990) Biotechnology 8: 662-667). In certain embodiments, antibodies described herein are produced by CHO cells or NS0 cells. In a specific embodiment, the expression of nucleotide sequences encoding antibodies described herein which immunospecifically bind OX40 and/or GITR (*e.g.*, human OX40 and/or GITR) is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

[00345] In bacterial systems, a number of expression vectors can be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such an antibody is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified can be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruether U & Mueller-Hill B (1983) EMBO J 2: 1791-1794), in which the antibody coding sequence can be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye S & Inouye M (1985) Nuc Acids Res 13: 3101-3109; Van Heeke G & Schuster SM (1989) J Biol Chem 24: 5503-5509); and the like. For example, pGEX vectors can also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[00346] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV), for example, can be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[00347] In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest can be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene can then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region El or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan J & Shenk T (1984) PNAS 81: 3655-3659). Specific initiation signals can also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These

exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (see, *e.g.*, Bitter G *et al.*, (1987) Methods Enzymol 153: 516-544).

[00348] In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products can be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product can be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, Hela, MDCK, HEK 293, NIH 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O, COS (*e.g.*, COS1 or COS), PER.C6, VERO, HsS78Bst, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20, BMT10 and HsS78Bst cells. In certain embodiments, anti-OX40 and/or GITR antibodies described herein are produced in mammalian cells, such as CHO cells.

[00349] In a specific embodiment, the antibodies described herein have reduced fucose content or no fucose content. Such antibodies can be produced using techniques known one skilled in the art. For example, the antibodies can be expressed in cells deficient or lacking the ability of to fucosylate. In a specific example, cell lines with a knockout of both alleles of α1,6-fucosyltransferase can be used to produce antibodies with reduced fucose content. The Potelligent® system (Lonza) is an example of such a system that can be used to produce antibodies with reduced fucose content.

[00350] For long-term, high-yield production of recombinant proteins, stable expression cells can be generated. For example, cell lines which stably express an anti-OX40 and/or GITR antibody described herein can be engineered.

[00351] In certain aspects, rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control

elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA/polynucleotide, engineered cells can be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express an anti-OX40 and/or GITR antibody described herein or a fragment thereof. Such engineered cell lines can be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[00352] A number of selection systems can be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler M *et al.*, (1977) Cell 11(1): 223-232), hypoxanthineguanine phosphoribosyltransferase (Szybalska EH & Szybalski W (1962) PNAS 48(12): 2026-2034) and adenine phosphoribosyltransferase (Lowy I *et al.*, (1980) Cell 22(3): 817-823) genes can be employed in tk-, hgprt- or aprt-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler M *et al.*, (1980) PNAS 77(6): 3567-3570; O'Hare K *et al.*, (1981) PNAS 78: 1527-1531); *gpt*, which confers resistance to mycophenolic acid (Mulligan RC & Berg P (1981) PNAS 78(4): 2072-2076); neo, which confers resistance to the aminoglycoside G-418 (Wu GY & Wu CH (1991) Biotherapy 3: 87-95; Tolstoshev P (1993) Ann Rev Pharmacol Toxicol 32: 573-596; Mulligan RC (1993) Science 260: 926-932; and Morgan RA & Anderson WF (1993) Ann Rev Biochem 62: 191-217; Nabel GJ & Felgner PL (1993) Trends Biotechnol 11(5): 211-215); and *hygro*, which confers resistance to hygromycin (Santerre RF *et al.*, (1984) Gene 30(1-3): 147-156). Methods commonly known in the art of recombinant DNA technology can be routinely applied to select the desired recombinant clone and such methods are described, for example, in Ausubel FM *et al.*, (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler M, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli NC *et al.*, (eds.), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colbère-Garapin F *et al.*, (1981) J Mol Biol 150: 1-14, which are incorporated by reference herein in their entireties.

[00353] The expression levels of an antibody molecule can be increased by vector

amplification (for a review, see Bebbington CR & Hentschel CCG, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3 (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse GF *et al.*, (1983) Mol Cell Biol 3: 257-66).

[00354] The host cell can be co-transfected with two or more expression vectors described herein, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors can contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. The host cells can be co-transfected with different amounts of the two or more expression vectors. For example, host cells can be transfected with any one of the following ratios of a first expression vector and a second expression vector: 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, or 1:50.

[00355] Alternatively, a single vector can be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot NJ (1986) Nature 322: 562-565; and Köhler G (1980) PNAS 77: 2197-2199). The coding sequences for the heavy and light chains can comprise cDNA or genomic DNA. The expression vector can be monocistronic or multicistronic. A multicistronic nucleic acid construct can encode 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, or in the range of 2-5, 5-10 or 10-20 genes/nucleotide sequences. For example, a bicistronic nucleic acid construct can comprise in the following order a promoter, a first gene (*e.g.*, heavy chain of an antibody described herein), and a second gene and (*e.g.*, light chain of an antibody described herein). In such an expression vector, the transcription of both genes can be driven by the promoter, whereas the translation of the mRNA from the first gene can be by a cap-dependent scanning mechanism and the translation of the mRNA from the second gene can be by a cap-independent mechanism, *e.g.*, by an IRES.

[00356] Once an antibody molecule described herein has been produced by recombinant expression, it can be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity,

particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies described herein can be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[00357] In specific embodiments, an antibody described herein is isolated or purified. Generally, an isolated antibody is one that is substantially free of other antibodies with different antigenic specificities than the isolated antibody. For example, in a particular embodiment, a preparation of an antibody described herein is substantially free of cellular material and/or chemical precursors. The language "substantially free of cellular material" includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein") and/or variants of an antibody, for example, different post-translational modified forms of an antibody. When the antibody or fragment is recombinantly produced, it is also generally substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, 2%, 1%, 0.5%, or 0.1% of the volume of the protein preparation. When the antibody or fragment is produced by chemical synthesis, it is generally substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody or fragment have less than about 30%, 20%, 10%, or 5% (by dry weight) of chemical precursors or compounds other than the antibody or fragment of interest. In a specific embodiment, antibodies described herein are isolated or purified.

5.4 Pharmaceutical Compositions

[00358] Provided herein are compositions comprising an antibody described herein having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed.

[00359] Pharmaceutical compositions described herein can be useful in enhancing, inducing, or activating an OX40 and/or GITR activity and treating a condition, such as cancer or an

infectious disease. In one embodiment, the present invention relates to a pharmaceutical composition of the present invention comprising an antibody (*e.g.*, a monospecific or multispecific antibody) of the present invention for use as a medicament. In another embodiment, the present invention relates to a pharmaceutical composition of the present invention for use in a method for the treatment of cancer or an infectious disease. Examples of cancer that can be treated in accordance with the methods described herein include, but are not limited to, B cell lymphomas (*e.g.*, B cell chronic lymphocytic leukemia, B cell non-Hodgkin lymphoma, cutaneous B cell lymphoma, diffuse large B cell lymphoma), basal cell carcinoma, bladder cancer, blastoma, brain metastasis, breast cancer, Burkitt lymphoma, carcinoma (*e.g.*, adenocarcinoma (*e.g.*, of the gastroesophageal junction)), cervical cancer, colon cancer, colorectal cancer (colon cancer and rectal cancer), endometrial carcinoma, esophageal cancer, Ewing sarcoma, follicular lymphoma, gastric cancer, gastroesophageal junction carcinoma, gastrointestinal cancer, glioblastoma (*e.g.*, glioblastoma multiforme, *e.g.*, newly diagnosed or recurrent), glioma, head and neck cancer (*e.g.*, head and neck squamous cell carcinoma), hepatic metastasis, Hodgkin's and non-Hodgkin's lymphoma, kidney cancer (*e.g.*, renal cell carcinoma and Wilms' tumors), laryngeal cancer, leukemia (*e.g.*, chronic myelocytic leukemia, hairy cell leukemia), liver cancer (*e.g.*, hepatic carcinoma and hepatoma), lung cancer (*e.g.*, non-small cell lung cancer and small-cell lung cancer), lymphblastic lymphoma, lymphoma, mantle cell lymphoma, metastatic brain tumor, metastatic cancer, myeloma (*e.g.*, multiple myeloma), neuroblastoma, ocular melanoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer (*e.g.*, pancreatis ductal adenocarcinoma), prostate cancer (*e.g.*, hormone refractory (*e.g.*, castration resistant), metastatic, metastatic hormone refractory (*e.g.*, castration resistant, androgen independent)), renal cell carcinoma (*e.g.*, metastatic), salivary gland carcinoma, sarcoma (*e.g.*, rhabdomyosarcoma), skin cancer (*e.g.*, melanoma (*e.g.*, metastatic melanoma)), soft tissue sarcoma, solid tumor, squamous cell carcinoma, synovia sarcoma, testicular cancer, thyroid cancer, transitional cell cancer (urothelial cell cancer), uveal melanoma (*e.g.*, metastatic), verrucous carcinoma, vulval cancer, and Waldenstrom macroglobulinemia.

[00360] Pharmaceutical compositions described herein that comprise an antagonistic antibody described herein can be useful in diminishing, reducing, inhibiting, or deactivating an OX40 and/or GITR activity and treating a condition, such as an inflammatory or autoimmune disease or disorder or an infectious disease.

[00361] Pharmaceutical compositions described herein that comprise an antagonistic antibody described herein can be useful in reducing, deactivating, or inhibiting an OX40 and/or GITR activity and treating a condition selected from the group consisting of infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), pelvic inflammatory disease, Alzheimer's Disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme disease, arthritis, meningoencephalitis, uveitis, autoimmune uveitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis, lupus (such as systemic lupus erythematosus) and Guillain-Barr syndrome, dermatitis, Atopic dermatitis, autoimmune hepatitis, fibrosing alveolitis, Grave's disease, IgA nephropathy, idiopathic thrombocytopenic purpura, Meniere's disease, pemphigus, primary biliary cirrhosis, sarcoidosis, scleroderma, Wegener's granulomatosis, pancreatitis, trauma (surgery), graft-versus-host disease, transplant rejection, heart disease (*i.e.*, cardiovascular disease) including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, osteoarthritis, periodontitis, hypochlorhydia, and neuromyelitis optica. In one embodiment, the present invention relates to a pharmaceutical composition of the present invention comprising an antibody (*e.g.*, a monospecific or multispecific antibody) of the present invention for use as a medicament. In another embodiment, the present invention relates to a pharmaceutical composition of the present invention for use in a method for the treatment of an autoimmune or inflammatory disease or disorder.

[00362] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.,* sterile filtration membranes.

5.5 Uses and Methods

5.5.1 Therapeutic Uses and Methods

[00363] In one aspect, presented herein are methods for modulating one or more immune functions or responses in a subject, comprising to a subject in need thereof administering an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein, or a composition thereof. In a specific aspect, presented herein are methods for activating, enhancing or inducing one or more immune

functions or responses in a subject, comprising to a subject in need thereof administering an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In a specific embodiment, presented herein are methods for preventing and/or treating diseases in which it is desirable to activate or enhance one or more immune functions or responses, comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein or a composition thereof. In a certain embodiment, presented herein are methods of treating an infectious disease comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In a certain embodiment, presented herein are methods of treating cancer comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. The cancer can be selected from a group consisting of melanoma, renal cancer, and prostate cancer. The cancer can be selected from a group consisting of melanoma, renal cancer, prostate cancer, colon cancer, and lung cancer. In a certain embodiment, presented herein are methods of treating melanoma comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In a certain embodiment, presented herein are methods of treating renal cancer comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In a certain embodiment, presented herein are methods of treating prostate cancer comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In certain embodiments, presented herein are methods of treating colon cancer comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In certain embodiments, presented herein are methods of treating lung cancer comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind

to human OX40 and/or GITR) or a composition thereof. In certain embodiments, presented herein are methods of treating non-small cell lung cancer (NSCLC) comprising administering to a subject in need thereof an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof.

[00364] In a certain embodiment, presented herein are methods of treating a cancer selected from the group consisting of: B cell lymphomas (*e.g.*, B cell chronic lymphocytic leukemia, B cell non-Hodgkin lymphoma, cutaneous B cell lymphoma, diffuse large B cell lymphoma), basal cell carcinoma, bladder cancer, blastoma, brain metastasis, breast cancer, Burkitt lymphoma, carcinoma (*e.g.*, adenocarcinoma (*e.g.*, of the gastroesophageal junction)), cervical cancer, colon cancer, colorectal cancer (colon cancer and rectal cancer), endometrial carcinoma, esophageal cancer, Ewing sarcoma, follicular lymphoma, gastric cancer, gastroesophageal junction carcinoma, gastrointestinal cancer, glioblastoma (*e.g.*, glioblastoma multiforme, *e.g.*, newly diagnosed or recurrent), glioma, head and neck cancer (*e.g.*, head and neck squamous cell carcinoma), hepatic metastasis, Hodgkin's and non-Hodgkin's lymphoma, kidney cancer (*e.g.*, renal cell carcinoma and Wilms' tumors), laryngeal cancer, leukemia (*e.g.*, chronic myelocytic leukemia, hairy cell leukemia), liver cancer (*e.g.*, hepatic carcinoma and hepatoma), lung cancer (*e.g.*, non-small cell lung cancer and small-cell lung cancer), lymphblastic lymphoma, lymphoma, mantle cell lymphoma, metastatic brain tumor, metastatic cancer, myeloma (*e.g.*, multiple myeloma), neuroblastoma, ocular melanoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer (*e.g.*, pancreatis ductal adenocarcinoma), prostate cancer (*e.g.*, hormone refractory (*e.g.*, castration resistant), metastatic, metastatic hormone refractory (*e.g.*, castration resistant, androgen independent)), renal cell carcinoma (*e.g.*, metastatic), salivary gland carcinoma, sarcoma (*e.g.*, rhabdomyosarcoma), skin cancer (*e.g.*, melanoma (*e.g.*, metastatic melanoma)), soft tissue sarcoma, solid tumor, squamous cell carcinoma, synovia sarcoma, testicular cancer, thyroid cancer, transitional cell cancer (urothelial cell cancer), uveal melanoma (*e.g.*, metastatic), verrucous carcinoma, vulval cancer, and Waldenstrom macroglobulinemia.

[00365] In another embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) is administered to a patient diagnosed with cancer to increase the proliferation and/or effector function of one or more immune cell populations (*e.g.*, T cell effector cells, such as $CD4^+$ and $CD8^+$ T cells) in the

patient.

[00366] In a specific embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein activates or enhances or induces one or more immune functions or responses in a subject by at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative to the immune function in a subject not administered the anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein using assays well known in the art, *e.g.*, ELISPOT, ELISA, and cell proliferation assays. In a specific embodiment, the immune function is cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13 production). In another embodiment, the immune function is T cell proliferation/expansion, which can be assayed, *e.g.*, by flow cytometry to detect the number of cells expressing markers of T cells (*e.g.*, CD3, CD4, or CD8). In another embodiment, the immune function is antibody production, which can be assayed, *e.g.*, by ELISA. In some embodiments, the immune function is effector function, which can be assayed, *e.g.*, by a cytotoxicity assay or other assays well known in the art. In another embodiment, the immune function is a Th1 response. In another embodiment, the immune function is a Th2 response. In another embodiment, the immune function is a memory response.

[00367] In specific embodiments, non-limiting examples of immune functions that can be enhanced or induced by an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) are proliferation/expansion of effector lymphocytes (*e.g.*, increase in the number of effector T lymphocytes), and inhibition of apoptosis of effector lymphocytes (*e.g.*, effector T lymphocytes). In particular embodiments, an immune function enhanced or induced by an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is proliferation/expansion in the number of or activation of $CD4^+$ T cells (*e.g.*, Th1 and Th2 helper T cells), $CD8^+$ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, $CD122^+$ T cells, natural killer (NK) cells), macrophages, monocytes, dendritic

cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes. In one embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein activates or enhances the proliferation/expansion or number of lymphocyte progenitors. In some embodiments, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein increases the number of $CD4^+$ T cells (*e.g.*, Th1 and Th2 helper T cells), $CD8^+$ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, $CD122^+$ T cells, natural killer cells (NK cells), macrophages, monocytes, dendritic cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes by approximately at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative a negative control (*e.g.*, number of the respective cells not treated, cultured, or contacted with an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein.

[00368] In some embodiments, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is administered to a subject in combination with a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent. In some embodiments, 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.

[00369] In some embodiments, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is administered to a subject in combination with a compound that targets an immunomodulatory enzyme(s) such as IDO (indoleamine-(2,3)-dioxygenase) and TDO (tryptophan 2,3-dioxygenase). In particular embodiments, such compound is selected from the group consisting of epacadostat (Incyte Corp), F001287 (Flexus Biosciences), indoximod

(NewLink Genetics), and NLG919 (NewLink Genetics). In one embodiment, the compound is epacadostat. In another embodiment, the compound is F001287. In another embodiment, the compound is indoximod. In another embodiment, the compound is NLG919.

[00370] In some embodiments, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is administered to a subject in combination with a vaccine.

[00371] In some embodiments, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is administered to a subject in combination with a heat shock protein based tumor vaccine or a heat shock protein based pathogen vaccine. In a specific embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) is administered to a subject in combination with a heat shock protein based tumor-vaccine. Heat shock proteins (HSPs) are a family of highly conserved proteins found ubiquitously across all species. Their expression can be powerfully induced to much higher levels as a result of heat shock or other forms of stress, including exposure to toxins, oxidative stress or glucose deprivation. Five families have been classified according to molecular weight: HSP-110, -90, -70, -60 and -28. HSPs deliver immunogenic peptides through the cross-presentation pathway in antigen presenting cells (APCs) such as macrophages and dendritic cells (DCs), leading to T cell activation. HSPs function as chaperone carriers of tumor-associated antigenic peptides forming complexes able to induce tumor-specific immunity. Upon release from dying tumor cells, the HSP-antigen complexes are taken up by antigen-presenting cells (APCs) wherein the antigens are processed into peptides that bind MHC class I and class II molecules leading to the activation of anti-tumor CD8+ and CD4+ T cells. The immunity elicited by HSP complexes derived from tumor preparations is specifically directed against the unique antigenic peptide repertoire expressed by the cancer of each subject.

[00372] A heat shock protein peptide complex (HSPPC) is a protein peptide complex consisting of a heat shock protein non-covalently complexed with antigenic peptides. HSPPCs elicit both innate and adaptive immune responses. In a specific embodiment, the antigenic peptide(s) displays antigenicity for the cancer being treated. HSPPCs are efficiently seized by APCs via membrane receptors (mainly CD91) or by binding to Toll-like receptors. HSPPC internalization results in functional maturation of the APCs with chemokine and cytokine

production leading to activation of natural killer cells (NK), monocytes and Th1 and Th-2-mediated immune responses. In some embodiments, HSPPCs used in methods disclosed herein comprise one or more heat shock proteins from the hsp60, hsp70, or hsp90 family of stress proteins complexed with antigenic peptides. In some embodiments, HSPPCs comprise hsc70, hsp70, hsp90, hsp110, grp170, gp96, calreticulin, or combinations of two or more thereof.

[00373] In a specific embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) is administered to a subject in combination with a heat shock protein peptide complex (HSPPC), *e.g.*, heat shock protein peptide complex-96 (HSPPC-96), to treat cancer. HSPPC-96 comprises a 96 kDa heat shock protein (Hsp), gp96, complexed to antigenic peptides. HSPPC-96 is a cancer immunotherapy manufactured from a subject's tumor and contains the cancer's antigenic "fingerprint." In some embodiments, this fingerprint contains unique antigens that are present only in that particular subject's specific cancer cells and injection of the vaccine is intended to stimulate the subject's immune system to recognize and attack any cells with the specific cancer fingerprint.

[00374] In some embodiments, the HSPPC, *e.g.*, HSPPC-96, is produced from the tumor tissue of a subject. In a specific embodiment, the HSPPC (*e.g.*, HSPPC-96) is produced from tumor of the type of cancer or metastasis thereof being treated. In another specific embodiment, the HSPPC (*e.g.*, HSPPC-96) is autologous to the subject being treated. In some embodiments, the tumor tissue is non-necrotic tumor tissue. In some embodiments, at least 1 gram (*e.g.*, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 grams) of non-necrotic tumor tissue is used to produce a vaccine regimen. In some embodiments, after surgical resection, non-necrotic tumor tissue is frozen prior to use in vaccine preparation. In some embodiments, the HSPPC, *e.g.*, HSPPC-96, is isolated from the tumor tissue by purification techniques, filtered and prepared for an injectable vaccine. In some embodiments, a subject is administered 6-12 doses of the HSPPC, *e.g.*, HSPCC-96. In such embodiments, the HSPPC, *e.g.*, HSPPC-96, doses may be administered weekly for the first 4 doses and then biweekly for the 2-8 additional doses.

[00375] Further examples of HSPPCs that may be used in accordance with the methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes, U.S. Patent Nos. 6,391,306,

6,383,492, 6,403,095, 6,410,026, 6,436,404, 6,447,780, 6,447,781 and 6,610,659.

[00376] In one aspect, the methods for modulating one or more immune functions or responses in a subject as presented herein are methods for deactivating, reducing, or inhibiting one or more immune functions or responses in a subject, comprising to a subject in need thereof administering an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) or a composition thereof. In a specific embodiment, presented herein are methods for preventing and/or treating diseases in which it is desirable to deactivate, reduce, or inhibit one or more immune functions or responses, comprising administering to a subject in need thereof an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein or a composition thereof. In a certain embodiment, presented herein are methods of treating an autoimmune or inflammatory disease or disorder comprising administering to a subject in need thereof an effective amount of an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein or a composition thereof. In certain embodiments, the subject is a human. In certain embodiments, the disease or disorder is selected from the group consisting of: infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), pelvic inflammatory disease, Alzheimer's Disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme disease, arthritis, meningoencephalitis, uveitis, autoimmune uveitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis, lupus (such as systemic lupus erythematosus) and Guillain-Barr syndrome, dermatitis, Atopic dermatitis, autoimmune hepatitis, fibrosing alveolitis, Grave's disease, IgA nephropathy, idiopathic thrombocytopenic purpura, Meniere's disease, pemphigus, primary biliary cirrhosis, sarcoidosis, scleroderma, Wegener's granulomatosis, pancreatitis, trauma (surgery), graft-versus-host disease, transplant rejection, heart disease (*i.e.*, cardiovascular disease) including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, osteoarthritis, periodontitis, hypochlorhydia, and neuromyelitis optica. In certain embodiments, the 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.

[00377] In another embodiment, an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is administered to a patient diagnosed with an autoimmune or inflammatory disease or disorder to decrease the proliferation and/or effector function of one or more immune cell populations (*e.g.*, T cell effector cells, such as $CD4^+$ and $CD8^+$ T cells) in the patient.

[00378] In a specific embodiment, an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein deactivates or reduces or inhibits one or more immune functions or responses in a subject by at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative to the immune function in a subject not administered the anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein using assays well known in the art, *e.g.*, ELISPOT, ELISA, and cell proliferation assays. In a specific embodiment, the immune function is cytokine production (*e.g.*, IL-2, TNF-α, IFN-γ, IL-4, IL-10, and/or IL-13 production). In another embodiment, the immune function is T cell proliferation/expansion, which can be assayed, *e.g.*, by flow cytometry to detect the number of cells expressing markers of T cells (*e.g.*, CD3, CD4, or CD8). In another embodiment, the immune function is antibody production, which can be assayed, *e.g.*, by ELISA. In some embodiments, the immune function is effector function, which can be assayed, *e.g.*, by a cytotoxicity assay or other assays well known in the art. In another embodiment, the immune function is a Th1 response. In another embodiment, the immune function is a Th2 response. In another embodiment, the immune function is a memory response.

[00379] In specific embodiments, non-limiting examples of immune functions that can be reduced or inhibited by an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) are proliferation/expansion of effector lymphocytes (*e.g.*, decrease in the number of effector T

lymphocytes), and stimulation of apoptosis of effector lymphocytes (*e.g.*, effector T lymphocytes). In particular embodiments, an immune function reduced or inhibited by an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein is proliferation/expansion in the number of or activation of $CD4^+$ T cells (*e.g.*, Th1 and Th2 helper T cells), $CD8^+$ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, $CD122^+$ T cells, natural killer (NK) cells), macrophages, monocytes, dendritic cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes. In one embodiment, an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein deactivates or reduces or inhibits the proliferation/expansion or number of lymphocyte progenitors. In some embodiments, an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein decreases the number of $CD4^+$ T cells (*e.g.*, Th1 and Th2 helper T cells), $CD8^+$ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, $CD122^+$ T cells, natural killer cells (NK cells), macrophages, monocytes, dendritic cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes by approximately at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative a negative control (*e.g.*, number of the respective cells not treated, cultured, or contacted with an anti-OX40 and/or GITR antagonistic antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein.

[00380] In one embodiment, the present invention relates to an antibody (*e.g.*, a monospecific or multispecific antibody) and/or pharmaceutical composition of the present invention for use in a method of the present invention, wherein the method further comprises administering an additional therapeutic agent to the subject. In one embodiment, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody) and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent for use as a

medicament. In one embodiment, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody) and/or pharmaceutical composition of the present invention, and (b) an additional therapeutic agent for use in a method for the treatment of cancer or an infectious disease. In one embodiment, the present invention relates to (a) an antibody (*e.g.*, a monospecific or multispecific antibody) and/or pharmaceutical composition of the present invention, and (b) an additional therapeutic agent for use in a method for the treatment of an autoimmune or inflammatory disease or disorder. In one embodiment, the present invention relates to a pharmaceutical composition, kit or kit-of-parts comprising (a) an antibody (*e.g.*, a monospecific or multispecific antibody) and/or pharmaceutical composition of the present invention and (b) an additional therapeutic agent.

5.5.1.1 Routes of Administration & Dosage

[00381] An antibody or composition described herein can be delivered to a subject by a variety of routes.

[00382] The amount of an antibody or composition which will be effective in the treatment and/or prevention of a condition will depend on the nature of the disease, and can be determined by standard clinical techniques.

[00383] The precise dose to be employed in a composition will also depend on the route of administration, and the seriousness of the disease, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the patient (including age, body weight and health), whether the patient is human or an animal, other medications administered, or whether treatment is prophylactic or therapeutic. Usually, the patient is a human but non-human mammals including transgenic mammals can also be treated. Treatment dosages are optimally titrated to optimize safety and efficacy.

[00384] In certain embodiments, an *in vitro* assay is employed to help identify optimal dosage ranges. Effective doses may be extrapolated from dose response curves derived from *in vitro* or animal model test systems.

[00385] Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible.

5.5.2 Detection & Diagnostic Uses

[00386] An anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein (see, *e.g.*, Section 5.2) can be used to assay OX40 and/or GITR protein levels in a biological sample using classical immunohistological methods known to those of skill in the art, including immunoassays, such as the enzyme linked immunosorbent assay (ELISA), immunoprecipitation, or Western blotting. Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{121}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. Such labels can be used to label an antibody described herein. Alternatively, a second antibody that recognizes an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein can be labeled and used in combination with an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) to detect OX40 protein levels.

[00387] Assaying for the expression level of OX40 protein and/or GITR protein is intended to include qualitatively or quantitatively measuring or estimating the level of an OX40 and/or GITR protein in a first biological sample either directly (*e.g.*, by determining or estimating absolute protein level) or relatively (*e.g.*, by comparing to the disease associated protein level in a second biological sample). OX40 and/or GITR polypeptide expression level in the first biological sample can be measured or estimated and compared to a standard OX40 and/or GITR protein level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once the "standard" OX40 and/or GITR polypeptide level is known, it can be used repeatedly as a standard for comparison.

[00388] As used herein, the term "biological sample" refers to any biological sample obtained from a subject, cell line, tissue, or other source of cells potentially expressing OX40 and/or GITR. Methods for obtaining tissue biopsies and body fluids from animals (*e.g.*, humans) are well known in the art. Biological samples include peripheral mononuclear blood cells.

[00389] An anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein can be used for prognostic, diagnostic, monitoring and screening applications, including *in vitro* and *in vivo* applications well known and standard to the skilled artisan and based on the present description. Prognostic, diagnostic, monitoring and screening assays and kits for *in vitro* assessment and evaluation of immune system status and/or immune response may be utilized to predict, diagnose and monitor to evaluate patient samples including those known to have or suspected of having an immune system-dysfunction or with regard to an anticipated or desired immune system response, antigen response or vaccine response. The assessment and evaluation of immune system status and/or immune response is also useful in determining the suitability of a patient for a clinical trial of a drug or for the administration of a particular chemotherapeutic agent or an antibody, including combinations thereof, versus a different agent or antibody. This type of prognostic and diagnostic monitoring and assessment is already in practice utilizing antibodies against the HER2 protein in breast cancer (HercepTest™, Dako) where the assay is also used to evaluate patients for antibody therapy using Herceptin®. *In vivo* applications include directed cell therapy and immune system modulation and radio imaging of immune responses.

[00390] In one embodiment, the present invention relates to an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) and/or pharmaceutical composition of the present invention for use as a diagnostic.

[00391] In one embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) can be used in immunohistochemistry of biopsy samples.

[00392] In another embodiment, an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) can be used to detect levels of OX40 and/or GITR, or levels of cells which contain OX40 and/or GITR on their membrane surface, which levels can then be linked to certain disease symptoms. Anti-OX40 and/or GITR antibodies (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein can carry a detectable or functional label. When fluorescence labels are used, currently available microscopy and fluorescence-activated cell sorter analysis (FACS) or combination of both methods procedures known in the art can be utilized to identify and to quantitate the specific binding members. Anti-OX40 and/or GITR

antibodies (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein can carry a fluorescence label. Exemplary fluorescence labels include, for example, reactive and conjugated probes, *e.g.*, Aminocoumarin, Fluorescein and Texas red, Alexa Fluor dyes, Cy dyes and DyLight dyes. An anti-OX40 antibody can carry a radioactive label, such as the isotopes ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{67}Cu, ^{90}Y, ^{99}Tc, ^{111}In, ^{117}Lu, ^{121}I, ^{124}I, ^{125}I, ^{131}I, ^{198}Au, ^{211}At, ^{213}Bi, ^{225}Ac and ^{186}Re. When radioactive labels are used, currently available counting procedures known in the art may be utilized to identify and quantitate the specific binding of an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR). In the instance where the label is an enzyme, detection may be accomplished by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques as known in the art. This can be achieved by contacting a sample or a control sample with an anti-OX40 and/or GITR antibody (including, *e.g.*, monospecific or multispecific antibodies that bind to human OX40 and/or GITR) described herein under conditions that allow for the formation of a complex between the antibody and OX40 and/or GITR. Any complexes formed between the antibody and OX40 and/or GITR are detected and compared in the sample and the control. In light of the specific binding of the antibodies described herein for OX40 and/or GITR, the antibodies thereof can be used to specifically detect OX40 and/or GITR expression on the surface of cells. The antibodies described herein can also be used to purify OX40 and/or GITR via immunoaffinity purification.

[00393] Also included herein is an assay system which can be prepared in the form of a test kit for the quantitative analysis of the extent of the presence of, for instance, OX40, OX40/OX40L, GITR, and/or GITR/GITRL complexes. The system or test kit can comprise a labeled component, *e.g.*, a labeled antibody, and one or more additional immunochemical reagents. *See*, *e.g.*, Section 5.6 below for more on kits.

5.6 Kits

[00394] Provided herein are kits comprising one or more antibodies described herein or conjugates thereof. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies provided herein. In some embodiments, the kits contain a pharmaceutical composition described herein and any

prophylactic or therapeutic agent, such as those described herein. In certain embodiments, the kits may contain a T cell mitogen, such as, *e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00395] Also provided herein are kits that can be used in the above methods. In one embodiment, a kit comprises an antibody described herein, for example a purified antibody, in one or more containers. In a specific embodiment, kits described herein contain a substantially isolated anti-OX40 and/or GITR antigen (*e.g.*, human OX40 and/or GITR) that can be used as a control. In another specific embodiment, the kits described herein further comprise a control antibody which does not react with an OX40 and/or GITR antigen. In another specific embodiment, kits described herein contain one or more elements for detecting the binding of an antibody to an OX40 and/or GITR antigen (*e.g.*, the antibody can be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody can be conjugated to a detectable substrate). In specific embodiments, a kit provided herein can include a recombinantly produced or chemically synthesized OX40 and/or GITR antigen. The OX40 and/or GITR antigen provided in the kit can also be attached to a solid support. In a more specific embodiment, the detecting means of the above described kit includes a solid support to which an OX40 and/or GITR antigen is attached. Such a kit can also include a non-attached reporter-labeled anti-human antibody or anti-mouse/rat antibody. In this embodiment, binding of the antibody to the OX40 and/or GITR antigen can be detected by binding of the said reporter-labeled antibody.

[00396] The following examples are offered by way of illustration and not by way of limitation.

6. EXAMPLES

[00397] The examples in this Section (*i.e.*, Section 6) are offered by way of illustration, and not by way of limitation.

6.1 Example 1: Characterization of antibodies against human OX40

[00398] This example describes the characterization of antibodies that bind to human OX40. The sequence information of the variable regions of these anti-OX40 antibodies is listed in Table 5.

6.1.1 Antibody binding to OX40-expressing cells

[00399] The binding characteristics of the anti-OX40 antibodies to cells expressing human OX40 were analyzed by flow cytometry. Briefly, Jurkat cells were transduced to recombinantly express human OX40. Stable clones were generated via single-cell sorting (FACS ARIA Fusion). OX40 expression was verified by flow cytometry using positive control antibodies. For binding analysis, OX40-expressing Jurkat cells were incubated with anti-OX40 antibodies (12-point dose titration, 10 μg/ml to 0.00005 μg/ml) for 30 minutes at 4°C. The samples were washed twice and then incubated with FITC-conjugated mouse anti-human kappa detection antibody (Life Technologies, Catalog number: HP6062) for 30 minutes at 4°C. The samples were then washed twice and analyzed using the LSRFortessa flow cytometer (BD Biosciences). The flow cytometry plots were analyzed using a combination of FACS DIVA and WEHI Weasel software.

[00400] As shown in Figures 1A-1J, all the anti-OX40 antibodies tested bound to OX40-expressing cells in a dose-dependent manner.

6.1.2 Effect of anti-OX40 antibodies in blocking OX40L induced NF-κB signaling

[00401] An OX40 reporter assay was developed to test the activity of the anti-OX40 antibodies. This reporter assay was built using Jurkat cells which expressed minimum amount, if any, of FcR, diminishing the possibility of FcR-mediated clustering of OX40 molecules.

[00402] Cells ectopically expressing OX40 as well as NF-κB-luciferase (Nano luciferase, NanoLuc®) reporter were generated by transduction of lentiviral vectors (EF1a promoter) into Jurkat cells. Stable clones were generated via single-cell sorting (FACS ARIA Fusion). Expression of OX40 was verified by flow cytometry. To evaluate the ability of anti-OX40 antibodies to neutralize OX40L-induced NF-κB signaling, Jurkat-huOX40-NF-κB-luciferase cells were incubated with increasing concentrations of anti-OX40 antibodies or an isotype control antibody (8-point dose titration, 20 μg/ml to 0.01 μg/ml) for 30 minutes in RPMI media, supplemented with 10% heat-inactivated FBS at 37°C and 5% CO_2. The samples were then washed twice, resuspended in 1 μg/ml of multimeric OX40L, and incubated for two additional hours at 37°C. For detection of luciferase activities, the samples were incubated with prepared

Nano-Glo® Luciferase Assay Substrate (Promega, 1:1 v/v) in passive lysis buffer for 5 minutes at room temperature. Data were collected using the EnVision® Multilabel Plate Reader (Perkin-Elmer). To determine % OX40L activity, the RLU value for OX40L (1 μg/ml) without addition of antibody was established as 100% activity. Relative values for anti-OX40 antibodies and the isotype control were calculated accordingly.

[00403] As shown in Figures 2A-2I, pre-incubation of Jurkat-huOX40-NF-κB-luciferase reporter cells with increasing concentrations of anti-OX40 antibodies tested here significantly reduced OX40L-induced NF-κB-luciferase activity in a dose-dependent manner.

6.2 Example 2: Characterization of antibodies against human GITR

[00404] This example describes the characterization of antibodies that bind to human GITR. The sequence information of the variable regions of these anti-GITR antibodies is listed in Table 10.

6.2.1 Antibody binding to GITR-expressing cells

[00405] In this example, anti-GITR antibodies were tested for their binding to GITR-expressing cells by flow cytometry. Cells ectopically expressing human GITR were generated by transduction of lentiviral vectors (EF1a promoter) into the Jurkat cell line. Stable clones were generated via single-cell sorting (FACS ARIA Fusion). GITR expression was verified by flow cytometry using positive control antibodies. For binding analysis, GITR-expressing Jurkat cells were incubated with anti-GITR antibodies or an isotype control antibody for 30 minutes at 4°C. The samples were washed twice and then incubated with FITC-conjugated mouse anti-human kappa detection antibody (Life Technologies, Catalog number: HP6062) for 30 minutes at 4°C. The samples were then washed twice and analyzed using the LSRFortessa flow cytometer (BD Biosciences). The flow cytometry plots were analyzed using a combination of FACS DIVA and WEHI Weasel software.

[00406] All the anti-GITR antibodies tested exhibited dose-dependent binding to GITR-expressing cells (Figures 3A-3G).

* * *

[00407] The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures.

Such modifications are intended to fall within the scope of the appended claims.

[00408] All references (*e.g.*, publications or patents or patent applications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual reference (*e.g.*, publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00409] Other embodiments are within the following claims.

WHAT IS CLAIMED:

1. An isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G;

(b) CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L;

(c) CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A;

(d) CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32);

(e) CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and

(f) CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W,

and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38.

2. The isolated antibody of claim 1, wherein CDRH2 comprises the amino acid sequence of RIRSKAXSYATAYAASVKG (SEQ ID NO: 44), wherein: X is N or Y.
3. The isolated antibody of claim 1 or 2, wherein CDRH3 comprises the amino acid sequence of $GIX_1X_2SSGX_3X_4Y$ (SEQ ID NO: 45), wherein: X_1 is Y or A; X_2 is D or A; X_3 is Y or A; and X_4 is D or A.
4. The isolated antibody of any one of the preceding claims, wherein CDRH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-20.
5. The isolated antibody of any one of the preceding claims, wherein CDRH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 21-24.
6. The isolated antibody of any one of the preceding claims, wherein CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-31.
7. The isolated antibody of any one of the preceding claims, wherein CDRL3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 34-38.
8. The isolated antibody of any one of the preceding claims, wherein CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively.
9. The isolated antibody of any one of the preceding claims, wherein CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively.
10. The isolated antibody of any one of the preceding claims, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16,

21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively.

11. An isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34, respectively.
12. An isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 37, respectively.
13. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 47 or 48.
14. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.
15. The isolated antibody of claim 14, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.
16. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 49.
17. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15.
18. The isolated antibody of claim 17, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15.

19. An isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-10.
20. An isolated antibody that specifically binds to human OX40, the antibody comprising a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-14.
21. An isolated antibody that specifically binds to human OX40, the antibody comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.
22. The isolated antibody of claim 21, wherein the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11, respectively.
23. The isolated antibody of claim 21, wherein the heavy chain variable region and the light chain variable region comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively.
24. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-73 germline sequence.
25. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a light chain variable region having an amino acid sequence derived from a human IGKV2-28 germline sequence.
26. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2.
27. The isolated antibody of any one of claims 1-25, wherein the heavy chain constant region is IgG_1.
28. The isolated antibody of claim 27, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 88, 89, 90, or 91.
29. The isolated antibody of claim 27, wherein the amino acid sequence of IgG_1 comprises

S239D and I332E mutations, numbered according to the EU numbering system.

30. The isolated antibody of claim 29, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 107.
31. The isolated antibody of claim 27, wherein the amino acid sequence of IgG_1 comprises S239D, A330L, and I332E mutations, numbered according to the EU numbering system.
32. The isolated antibody of claim 31, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 108.
33. The isolated antibody of claim 27, wherein the amino acid sequence of IgG_1 comprises L235V, F243L, R292P, Y300L, and P396L mutations, numbered according to the EU numbering system.
34. The isolated antibody of claim 33, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 109.
35. The isolated antibody of claim 27, wherein the IgG_1 is non-fucosylated IgG_1.
36. The isolated antibody of claim 27, wherein the amino acid sequence of IgG_1 comprises a N297A or N297Q mutation, numbered according to the EU numbering system.
37. The isolated antibody of claim 36, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 92.
38. The isolated antibody of any one of claims 1-25, wherein the heavy chain constant region is IgG_4.
39. The isolated antibody of claim 38, wherein the amino acid sequence of IgG_4 comprises a S228P mutation, numbered according to the EU numbering system.
40. The isolated antibody of claim 39, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 93.
41. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a light chain constant region selected from the group consisting of human IgGκ and IgGλ.
42. The isolated antibody of claim 41, wherein the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 94.
43. An isolated antibody that comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences

of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody cross-competes for binding to human OX40 with the antibody of any one of the preceding claims.

44. An isolated antibody that comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 sequences of the antibody are not respectively either SEQ ID NOs: 16, 21, 25, 32, 33, and 34 or SEQ ID NOs: 16, 21, 25, 32, 33, and 38, and wherein the antibody binds to the same epitope of human OX40 as the antibody of any one of the preceding claims.
45. The isolated antibody of any one of the preceding claims, wherein the antibody is human.
46. The isolated antibody of any one of the preceding claims conjugated to a cytotoxic agent, cytostatic agent, toxin, radionuclide, or detectable label.
47. An isolated multispecific antibody comprising a first antigen-binding domain of the antibody of any one of the preceding claims, wherein the first antigen-binding domain specifically binds to human OX40 and comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein the isolated multispecific antibody further comprises a second antigen-binding domain.
48. The isolated multispecific antibody of claim 47, wherein CDRH1, CDRH2, and CDRH3 of the first antigen-binding domain that specifically binds to human OX40 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 16, 21, and 25; 16, 22, and 25; 16, 21, and 26; 16, 21, and 27; 16, 21, and 28; 16, 21, and 29; 17, 21, and 30; 18, 23, and 25; 19, 24, and 25; or 20, 21, and 31, respectively.
49. The isolated multispecific antibody of claim 47 or 48, wherein CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically binds to human OX40 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 32, 33, and 34; 32, 33, and 35; 32, 33, and 36; 32, 33, and 37; or 32, 33, and 38, respectively.
50. The isolated multispecific antibody of any one of claims 47-49, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically

binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 22, 25, 32, 33, and 34; 16, 21, 26, 32, 33, and 34; 16, 21, 27, 32, 33, and 34; 16, 21, 28, 32, 33, and 34; 16, 21, 29, 32, 33, and 34; 17, 21, 30, 32, 33, and 38; 18, 23, 25, 32, 33, and 38; 19, 24, 25, 32, 33, and 38; 20, 21, 31, 32, 33, and 38; 16, 21, 25, 32, 33, and 35; 16, 21, 25, 32, 33, and 36; or 16, 21, 25, 32, 33, and 37, respectively.

51. The isolated multispecific antibody of any one of claims 47-50, wherein the heavy chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-10.

52. The isolated multispecific antibody of any one of claims 47-51, wherein the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 11-15.

53. The isolated multispecific antibody of any one of claims 47-52, wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 2 and 11; 3 and 11; 4 and 11; 5 and 11; 6 and 11; 7 and 15; 8 and 15; 9 and 15; 10 and 15; 1 and 12; 1 and 13; or 1 and 14, respectively.

54. The isolated multispecific antibody of any one of claims 47-53, wherein the second antigen-binding domain specifically binds to human GITR.

55. The isolated multispecific antibody of claim 54, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 76), wherein

X_1 is D, E or G,

X_2 is A or V, and

X_3 is Y or H;

(b) CDRH2 comprises the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO: 77), 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;

(c) CDRH3 comprises the amino acid sequence of SGTVXGFAY (SEQ ID NO: 99), wherein;

X is R or A;

(d) CDRL1 comprises the amino acid sequence of KSSQSLLNSX$_1$NQKNYLX$_2$ (SEQ ID NO: 80), wherein

X_1 is G or S, and

X_2 is T or S;

(e) CDRL2 comprises the amino acid sequence of WASTRES (SEQ ID NO: 71); and

(f) CDRL3 comprises the amino acid sequence of QNX$_1$YSX$_2$PYT (SEQ ID NO: 81), wherein

X_1 is D, E, or A; and

X_2 is Y, F, or S.

56. The isolated multispecific antibody of claim 55, wherein CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of X$_1$YAMX$_2$ (SEQ ID NO: 78), wherein: X_1 is D, G, or E; and X_2 is Y or H.

57. The isolated multispecific antibody of claim 55 or 56, wherein CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of X$_1$IRTYSGX$_2$VX$_3$YNQKFX$_4$X$_5$ (SEQ ID NO: 79), 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.

58. The isolated multispecific antibody of any one of claims 55-57, wherein CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises the amino acid sequence of KSSQSLLNSXNQKNYLT (SEQ ID NO: 82), wherein: X is G or S.

59. The isolated multispecific antibody of any one of claims 55-58, wherein CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises the amino

acid sequence of QNX_1YSX_2PYT (SEQ ID NO: 83), wherein: X_1 is D, E, or A; and X_2 is Y or F.

60. The isolated multispecific antibody of any one of claims 55-59, wherein CDRH1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-62.

61. The isolated multispecific antibody of any one of claims 55-60, wherein CDRH2 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-67.

62. The isolated multispecific antibody of any one of claims 55-61, wherein CDRH3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 68 and 97.

63. The isolated multispecific antibody of any one of claims 55-62, wherein CDRL1 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 69 and 70.

64. The isolated multispecific antibody of any one of claims 55-63, wherein CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 73, and 98.

65. The isolated multispecific antibody of any one of claims 55-64, wherein CDRH1, CDRH2, and CDRH3 of the second antigen-binding domain that specifically binds to human GITR comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 60, 63, and 68; 60, 64, and 68; 60, 63, and 97; 61, 65, and 68; 62, 66, and 68; or 62, 67, and 68, respectively.

66. The isolated multispecific antibody of any one of claims 55-65, wherein CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 69, 71, and 72; 69, 71, and 98; 70, 71, and 73; or 69, 71, and 72, respectively.

67. The isolated multispecific antibody of any one of claims 55-66, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 60, 63, 68, 69, 71, and 72; 60, 64, 68, 69, 71, and 72; 60, 63, 97, 69, 71, and 72; 60, 63, 68, 69, 71, and 98; 61, 65, 68, 70, 71, and 73; 62, 66, 68, 69, 71, and 72; or 62, 67, 68, 69, 71,

and 72, respectively.

68. The isolated multispecific antibody of any one of claims 55-67, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 84.
69. The isolated multispecific antibody of any one of claims 55-68, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-56, and 95.
70. The isolated multispecific antibody of claim 69, wherein the heavy chain variable region of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-56, and 95.
71. The isolated multispecific antibody of any one of claims 55-70, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 85.
72. The isolated multispecific antibody of any one of claims 55-71, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-59, and 96.
73. The isolated multispecific antibody of claim 72, wherein the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 57-59, and 96.
74. The isolated multispecific antibody of any one of claims 55-73, wherein the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 52 and 57; 53 and 57; 95 and 57; 52 and 96; 54 and 58; 55 and 59; or 56 and 59, respectively.
75. The isolated multispecific antibody of any one of claims 55-74, 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.

76. The isolated multispecific antibody of any one of claims 55-75, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain variable region having an amino acid sequence derived from a human IGKV4-1 germline sequence.
77. The isolated multispecific antibody of any one of claims 55-76, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2.
78. The isolated multispecific antibody of any one of claims 55-76, wherein the heavy chain constant region of the second antigen-binding domain that specifically binds to human GITR is IgG_1.
79. The isolated multispecific antibody of claim 78, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 88, 89, 90, or 91.
80. The isolated multispecific antibody of claim 78, wherein the amino acid sequence of IgG_1 comprises S239D and I332E mutations, numbered according to the EU numbering system.
81. The isolated multispecific antibody of claim 80, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 107.
82. The isolated multispecific antibody of claim 78, wherein the amino acid sequence of IgG_1 comprises S239D, A330L, and I332E mutations, numbered according to the EU numbering system.
83. The isolated multispecific antibody of claim 82, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 108.
84. The isolated multispecific antibody of claim 78, wherein the amino acid sequence of IgG_1 comprises L235V, F243L, R292P, Y300L, and P396L mutations, numbered according to the EU numbering system.
85. The isolated multispecific antibody of claim 84, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 109.
86. The isolated multispecific antibody of claim 78, wherein the IgG_1 is non-fucosylated IgG_1.
87. The isolated multispecific antibody of claim 78, wherein the amino acid sequence of IgG_1 of

the second antigen-binding domain that specifically binds to human GITR comprises a N297A or N297Q mutation, numbered according to the EU numbering system.

88. The isolated multispecific antibody of claim 87, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 92.

89. The isolated multispecific antibody of any one of claims 55-76, wherein the heavy chain constant region of the second antigen-binding domain that specifically binds to human GITR is IgG_4.

90. The isolated multispecific antibody of claim 89, wherein the amino acid sequence of IgG_4 of the second antigen-binding domain that specifically binds to human GITR comprises a S228P mutation, numbered according to the EU numbering system.

91. The isolated multispecific antibody of claim 90, wherein the second antigen-binding domain that specifically binds to human GITR comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 93.

92. The isolated multispecific antibody of any one of claims 55-91, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain constant region selected from the group consisting of human IgGκ and IgGλ.

93. The isolated multispecific antibody of claim 92, wherein the second antigen-binding domain that specifically binds to human GITR comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 94.

94. The isolated multispecific antibody of any one of claims 55-93, wherein the second antigen-binding domain that specifically binds to human GITR is humanized.

95. The isolated multispecific antibody of claim 55, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain that specifically binds to human OX40 and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences listed in a single row of Table 12.

96. An isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain that specifically binds to human GITR, wherein the first antigen-binding domain comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 and a light chain variable region

comprising CDRL1, CDRL2, and CDRL3, and wherein the second antigen-binding domain comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising CDRL1, CDRL2, and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding domain and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 12.

97. The isolated multispecific antibody of claim 55, wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain that specifically binds to human OX40 and the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences listed in a single row of Table 13.

98. An isolated multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain that specifically binds to human GITR, wherein the first antigen-binding domain comprises a heavy chain variable region and a light chain variable region, and wherein the second antigen-binding domain comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region and the light chain variable region of the first antigen-binding domain and the heavy chain variable region and the light chain variable region of the second antigen-binding domain comprise the amino acid sequences listed in a single row of Table 13.

99. An isolated antibody that specifically binds to human GITR, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 60, 64, 68, 69, 71, and 72, respectively.

100. The isolated antibody of claim 99, wherein the heavy chain variable region and the light chain variable region of the antibody comprise the amino acid sequences set forth in SEQ ID NOs: 53 and 57, respectively.

101. An isolated antibody that specifically binds to human GITR, the antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53.

102. An isolated multispecific antibody comprising a first antigen-binding domain and a second antigen-binding domain, wherein the second antigen-binding domain specifically binds to human GITR and comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 60, 64, 68, 69, 71, and 72, respectively.

103. The isolated multispecific antibody of claim 102, wherein the heavy chain variable region and the light chain variable region of the second antigen-binding domain that specifically binds to human GITR comprise the amino acid sequences set forth in SEQ ID NOs: 53 and 57, respectively.

104. An isolated multispecific antibody comprising a first antigen-binding domain and a second antigen-binding domain, wherein the second antigen-binding domain specifically binds to human GITR and comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53.

105. The isolated multispecific antibody of any one of claims 102-104, wherein the first antigen-binding domain specifically binds to human OX40.

106. The isolated multispecific antibody of claim 105, wherein the first antigen-binding domain that specifically binds to human OX40 comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of $X_1X_2X_3MH$ (SEQ ID NO: 41), wherein

X_1 is G, Q, H, or E,

X_2 is S, E, or Y, and

X_3 is A, S, or G;

(b) CDRH2 comprises the amino acid sequence of $RIRSKX_1X_2X_3X_4X_5TAYAASVKG$ (SEQ ID NO: 42), wherein

X_1 is A, S, or Y,

X_2 is N, E, or Y,

X_3 is S, Q, or G,

X_4 is Y, E, or Q, and

X_5 is A, E, or L;

(c) CDRH3 comprises the amino acid sequence of $GIX_1X_2X_3X_4X_5X_6X_7Y$ (SEQ ID NO: 43), wherein

X_1 is Y or A,

X_2 is D or A,

X_3 is S, T, or W,

X_4 is S, E, or L,

X_5 is G or A,

X_6 is Y or A, and

X_7 is D or A;

(d) CDRL1 comprises the amino acid sequence of RSSQSLLHSNGYNYLD (SEQ ID NO: 32);

(e) CDRL2 comprises the amino acid sequence of LGSNRAS (SEQ ID NO: 33); and

(f) CDRL3 comprises the amino acid sequence of $MQX_1X_2X_3X_4PLT$ (SEQ ID NO: 46), wherein

X_1 is A or G,

X_2 is L or S,

X_3 is Q or K, and

X_4 is T or W.

107. The isolated multispecific antibody of claim 106, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 34, respectively.

108. The isolated multispecific antibody of claim 106, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions of the first antigen-binding domain that specifically binds to human OX40 comprise the amino acid sequences set forth in SEQ ID NOs: 16, 21, 25, 32, 33, and 38, respectively.

109. A pharmaceutical composition comprising the antibody of any one of claims 1-46 or 99-101, or the multispecific antibody of any one of claims 47-98 or 102-108, and a

pharmaceutically acceptable carrier or excipient.

110. An isolated polynucleotide encoding the antibody of any one of claims 1-46 or 99-101 or the multispecific antibody of any one of claims 47-98 or 102-108.

111. A vector comprising the polynucleotide of claim 110.

112. A recombinant host cell comprising the polynucleotide of claim 110 or the vector of claim 111.

113. A method of producing an antibody that specifically binds to human OX40, a multispecific antibody comprising a first antigen-binding domain that specifically binds to human OX40 and a second antigen-binding domain, an antibody that specifically binds to human GITR, or a multispecific antibody comprising a first antigen-binding domain and a second antigen-binding domain that specifically binds to human GITR, the method comprising culturing the host cell of claim 112 so that the polynucleotide is expressed and the antibody or the multispecific antibody is produced.

114. 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 1-46 or 99-101, the multispecific antibody of any one of claims 47-98 or 102-108, or the pharmaceutical composition of claim 109.

115. A method of 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 1-35, 41-46, or 99-101, the multispecific antibody of any one of claims 47-86, 92-98, or 102-108, or the pharmaceutical composition of claim 109.

116. 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 1-35, 41-46, or 99-101, the multispecific antibody of any one of claims 47-86, 92-98, or 102-108, or the pharmaceutical composition of claim 109.

117. The method of claim 116, wherein the cancer is selected from the group consisting of melanoma, renal cancer, prostate cancer, colon cancer, and lung cancer.

118. The method of any one of claims 115-117, further comprising administering an additional therapeutic agent to the subject.

119. The method of claim 118, wherein the additional therapeutic agent is a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent.

120. The method of claim 119, 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.

121. The method of claim 118, wherein the additional therapeutic agent is an inhibitor of indoleamine-2,3-dioxygenase (IDO).

122. The method of claim 121, wherein the inhibitor is selected from the group consisting of epacadostat, F001287, indoximod, and NLG919.

123. The method of claim 118, wherein the additional therapeutic agent is a vaccine.

124. The method of claim 123, wherein the vaccine comprises a heat shock protein peptide complex (HSPPC) comprising a heat shock protein complexed with an antigenic peptide.

125. The method of claim 124, wherein the heat shock protein is hsc70 and is complexed with a tumor-associated antigenic peptide.

126. The method of claim 124, 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 a subject.

127. 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 1-27, 36-46, or 99-101, the multispecific antibody of any one of claims 47-78, 87-98, or 102-108, or the pharmaceutical composition of claim 109.

128. 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 1-27, 36-46, or 99-101, the multispecific antibody of any one of claims 47-78, 87-98, or 102-108, or the pharmaceutical composition of claim 109.

129. The method of claim 128, 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.

Figure 1A

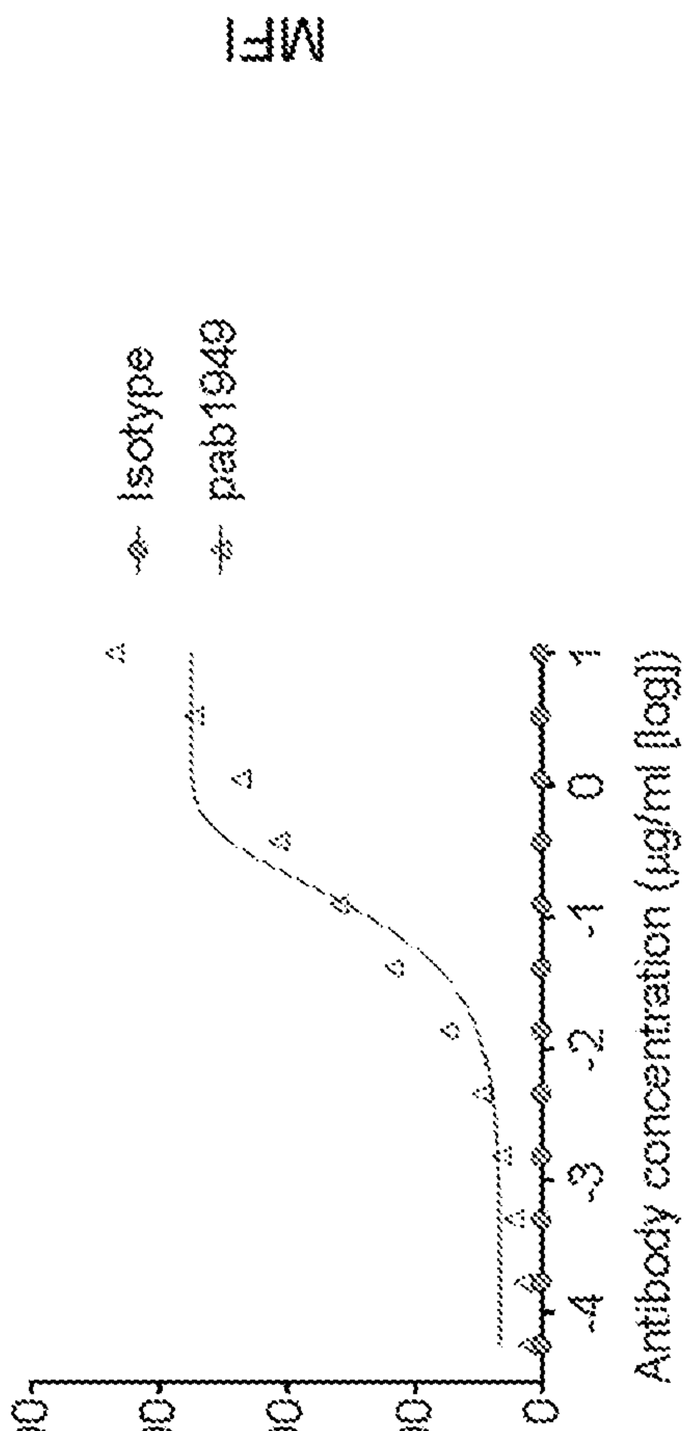

Figure 1B

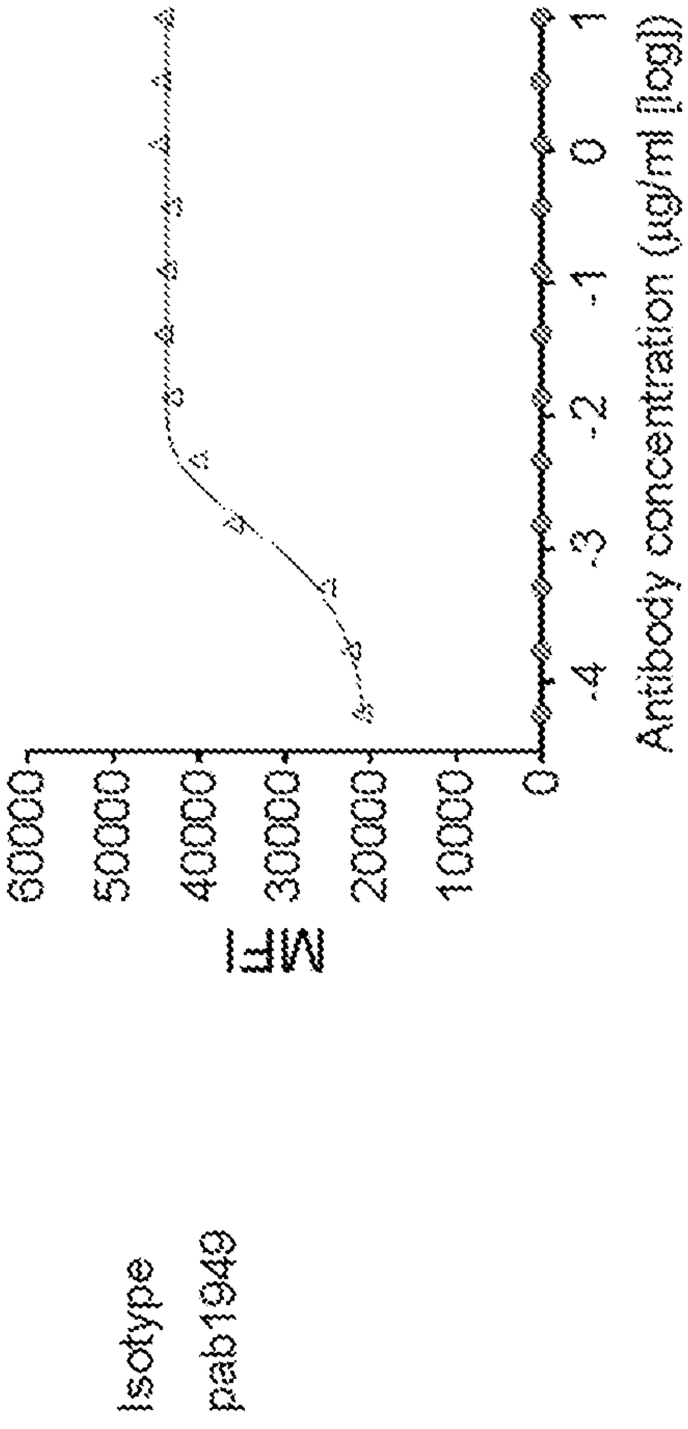

Figure 1C

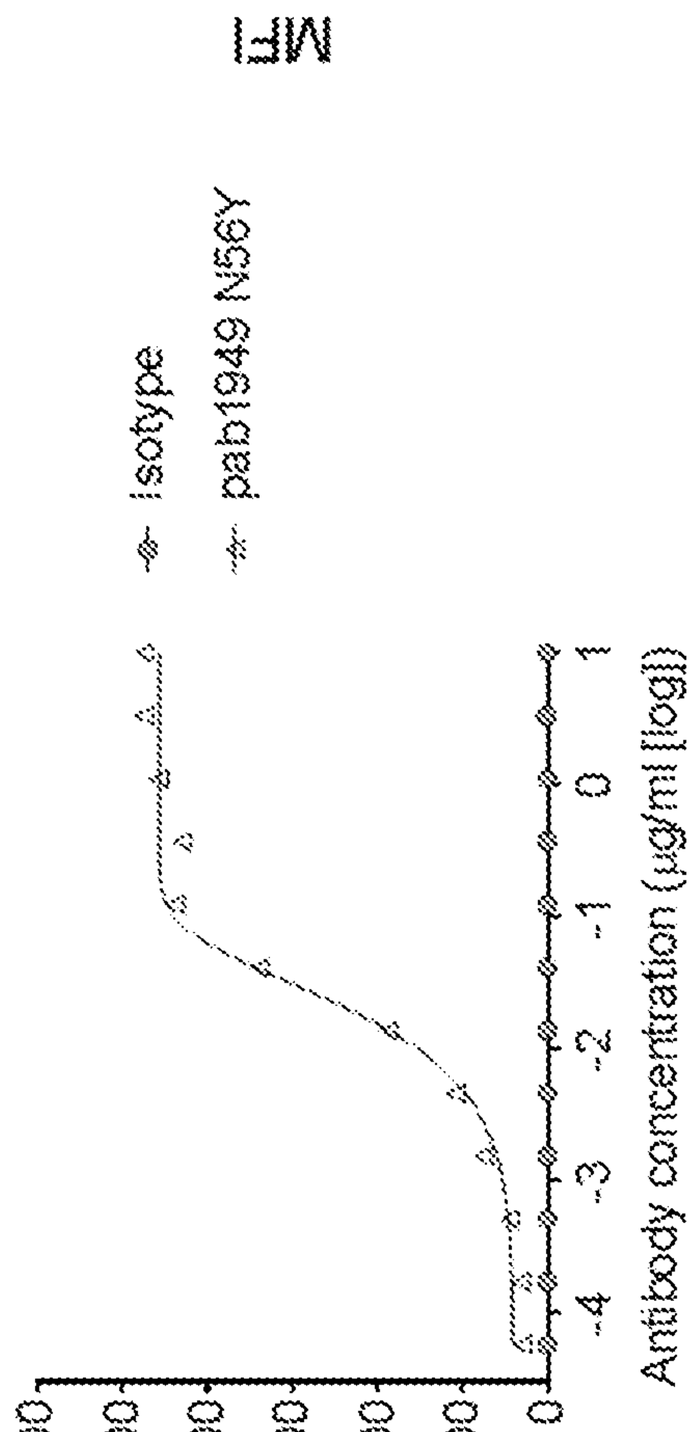

Figure 1D

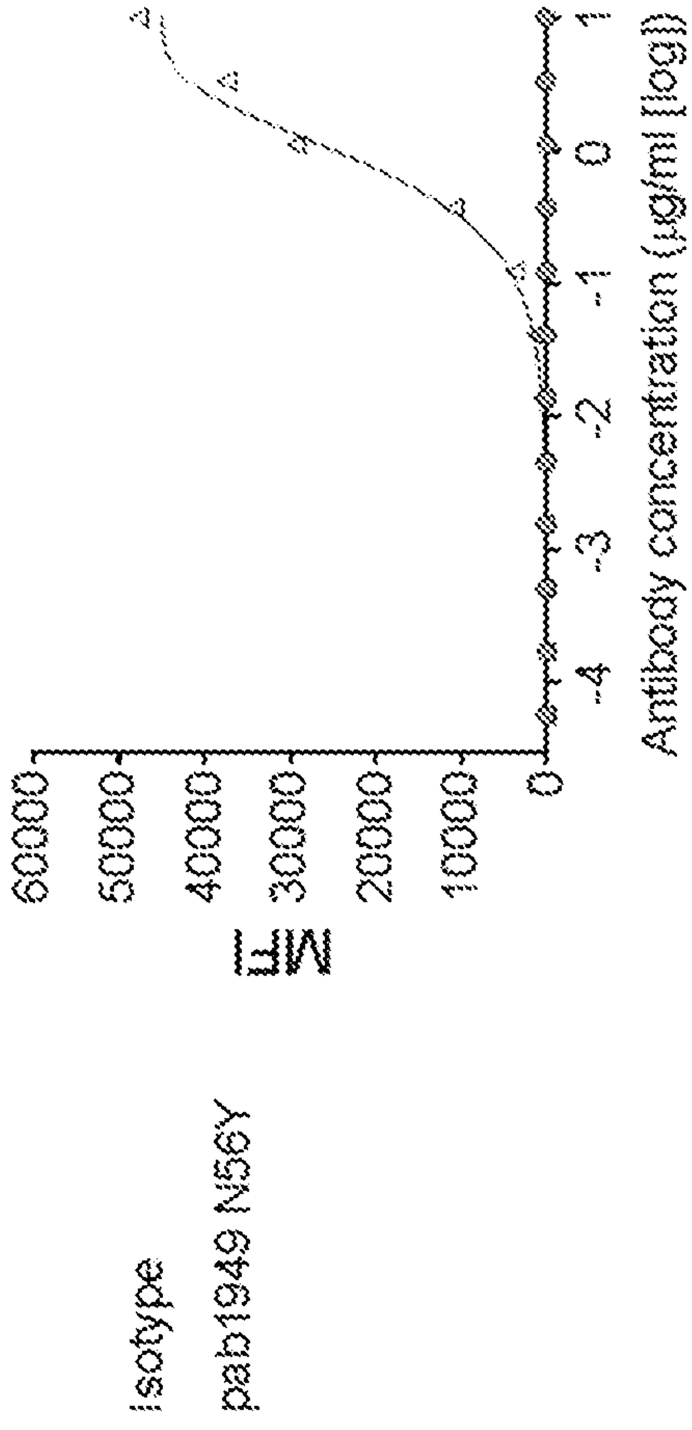

Figure 1F

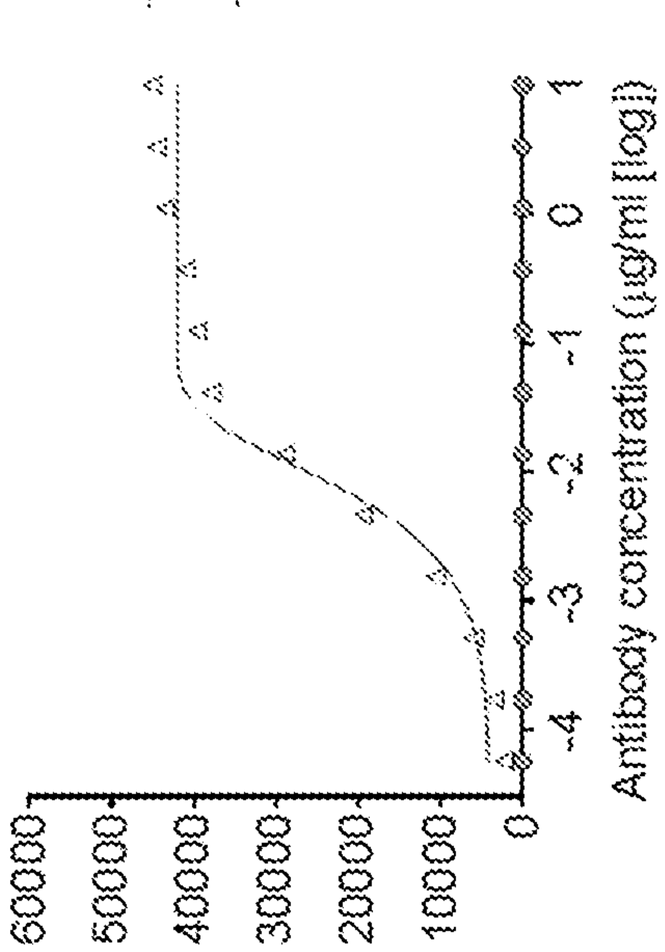

Figure 1H

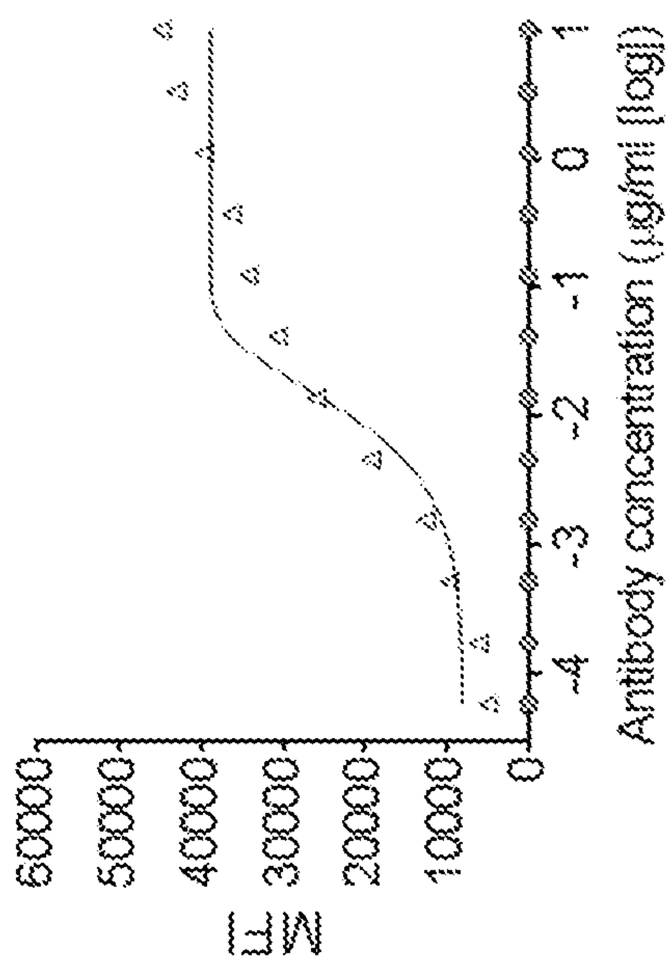

Figure 1E

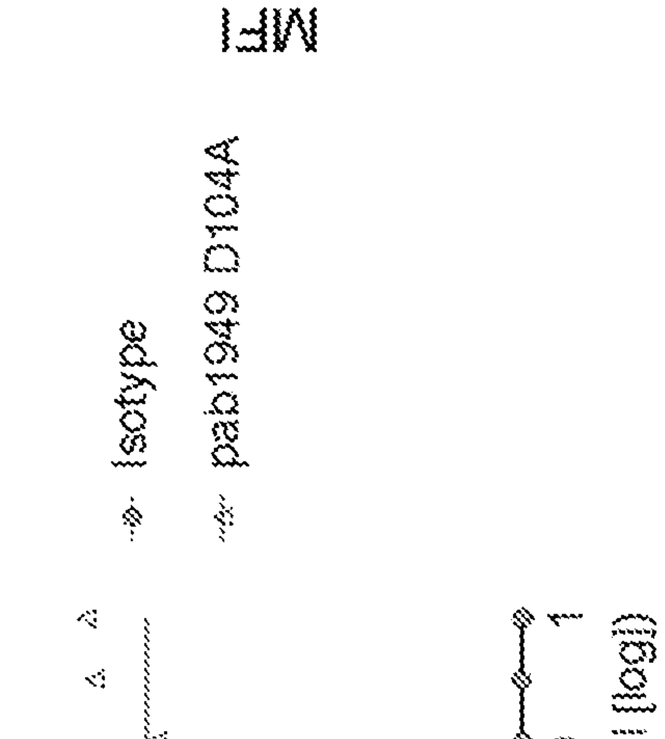

Figure 1G

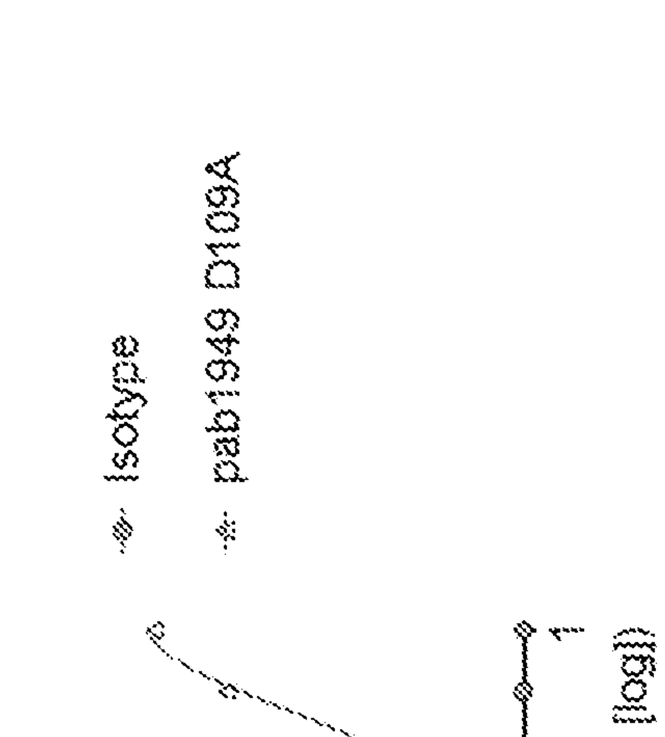

Figure 1J

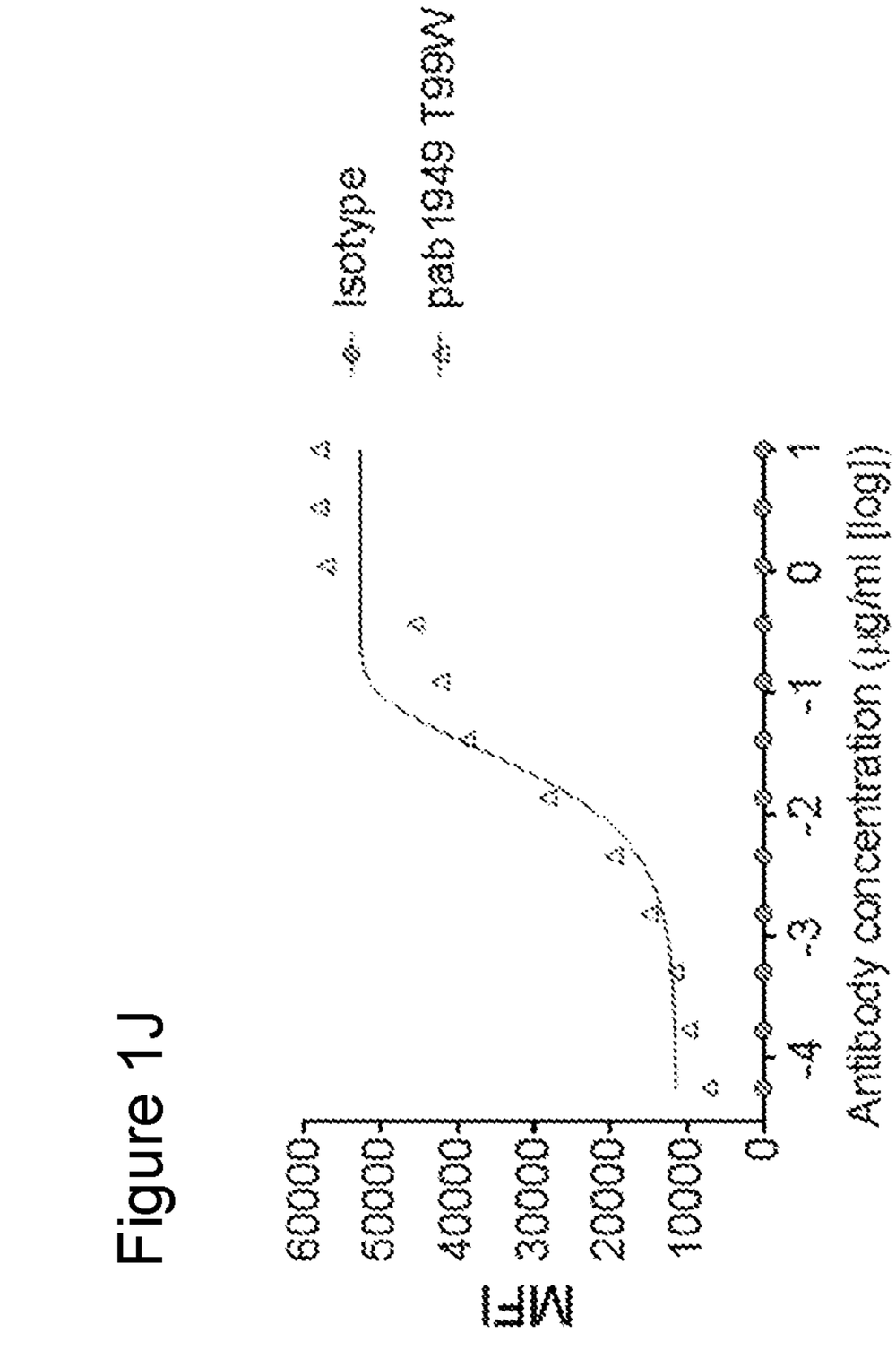

Figure 1I

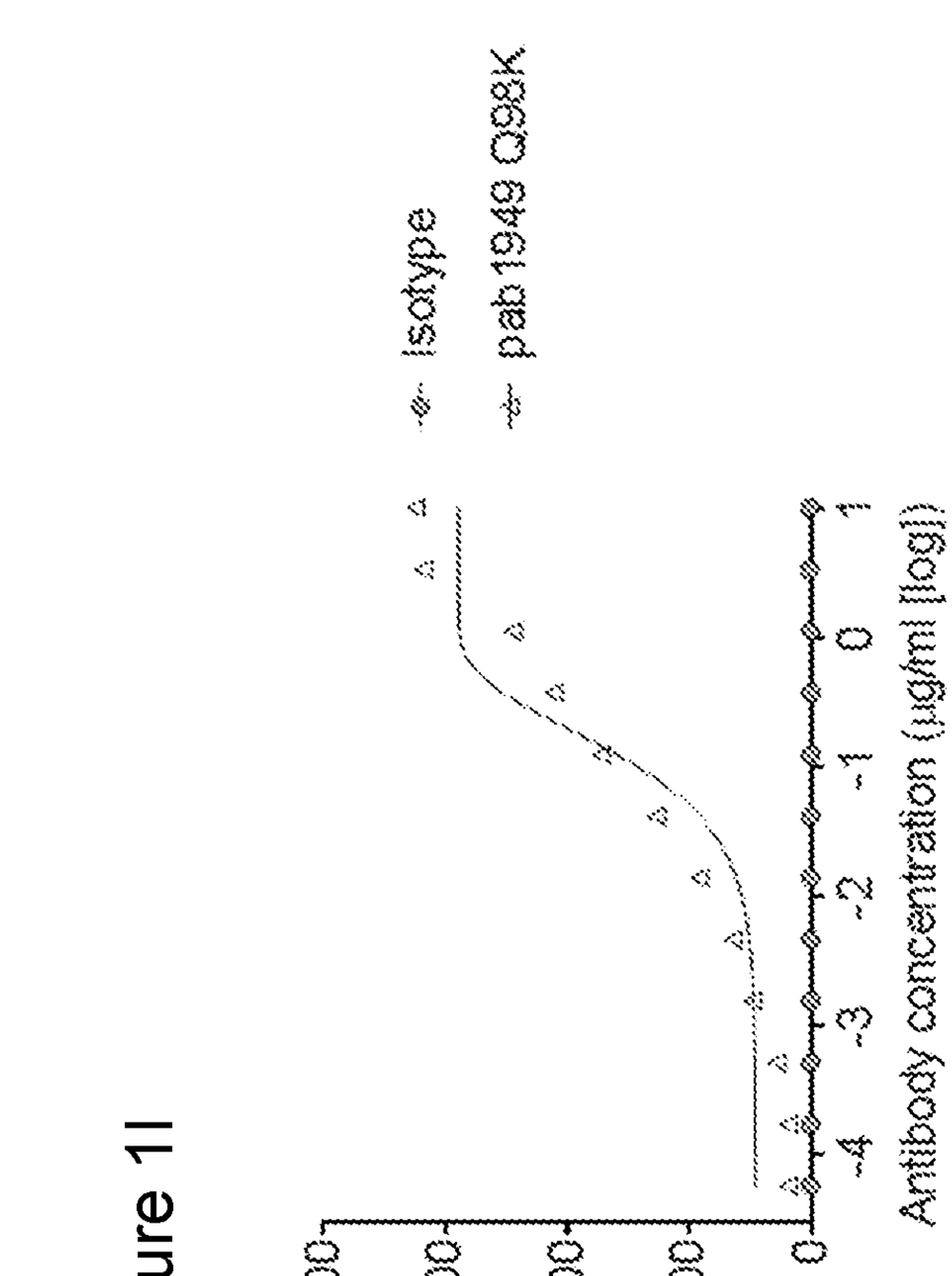

Figure 2A

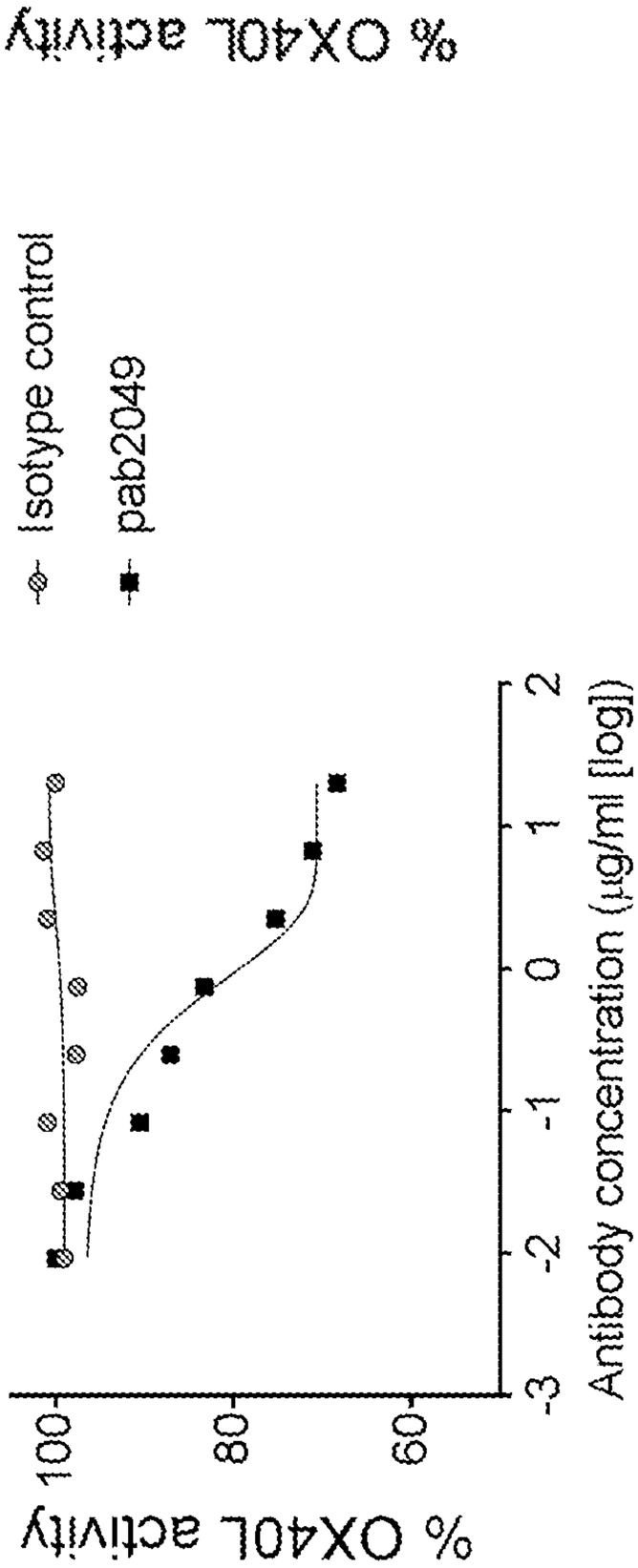

Figure 2B

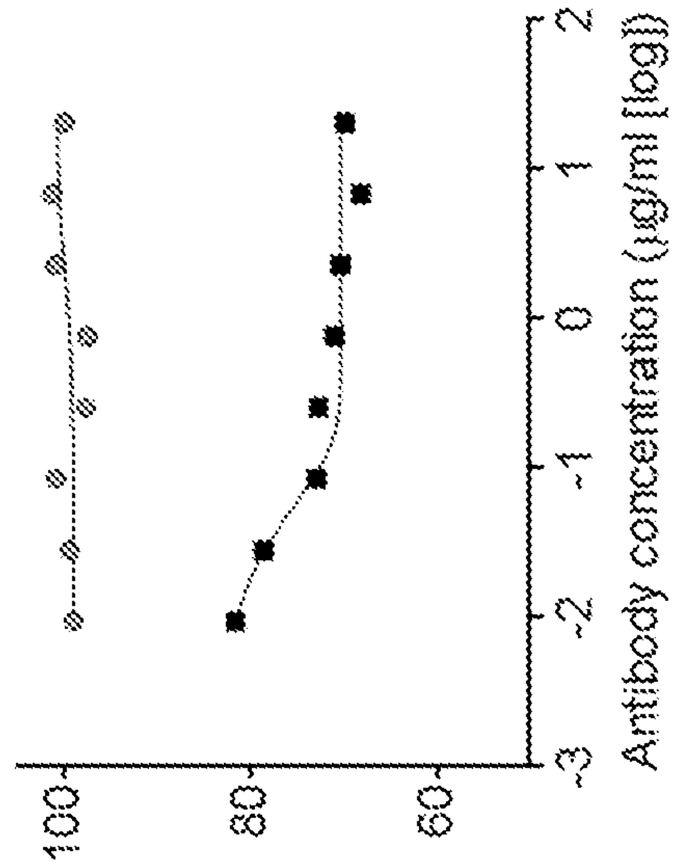

Figure 2C

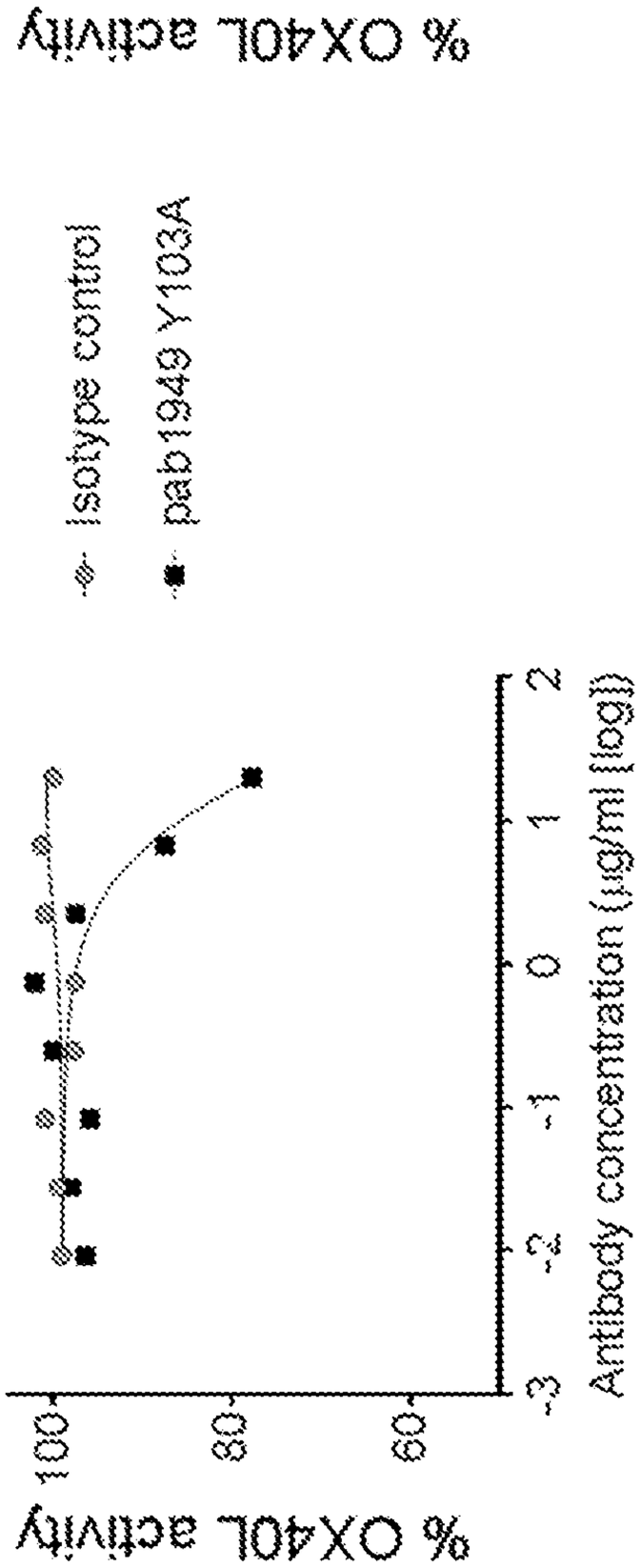

Figure 2D

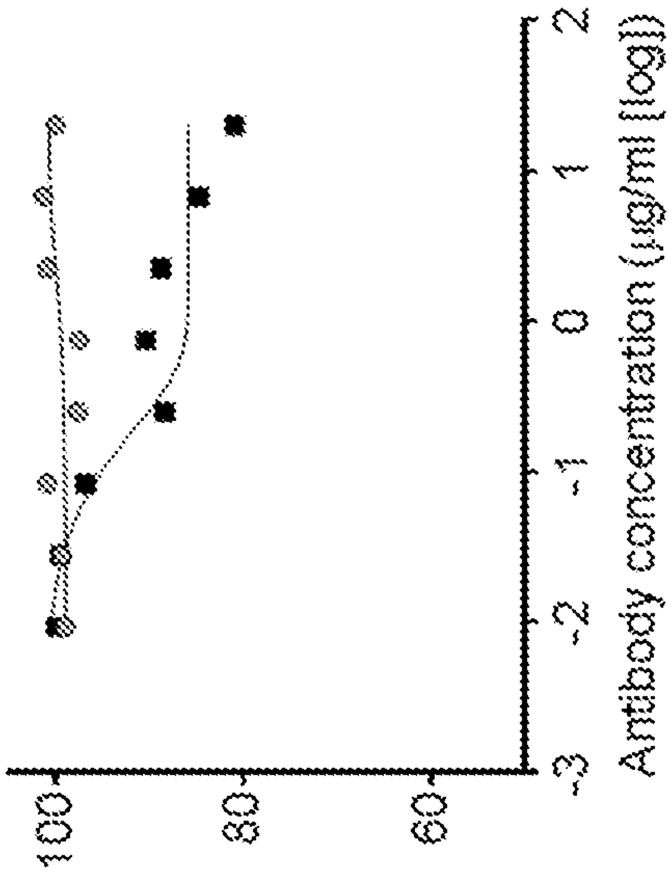

Figure 2E

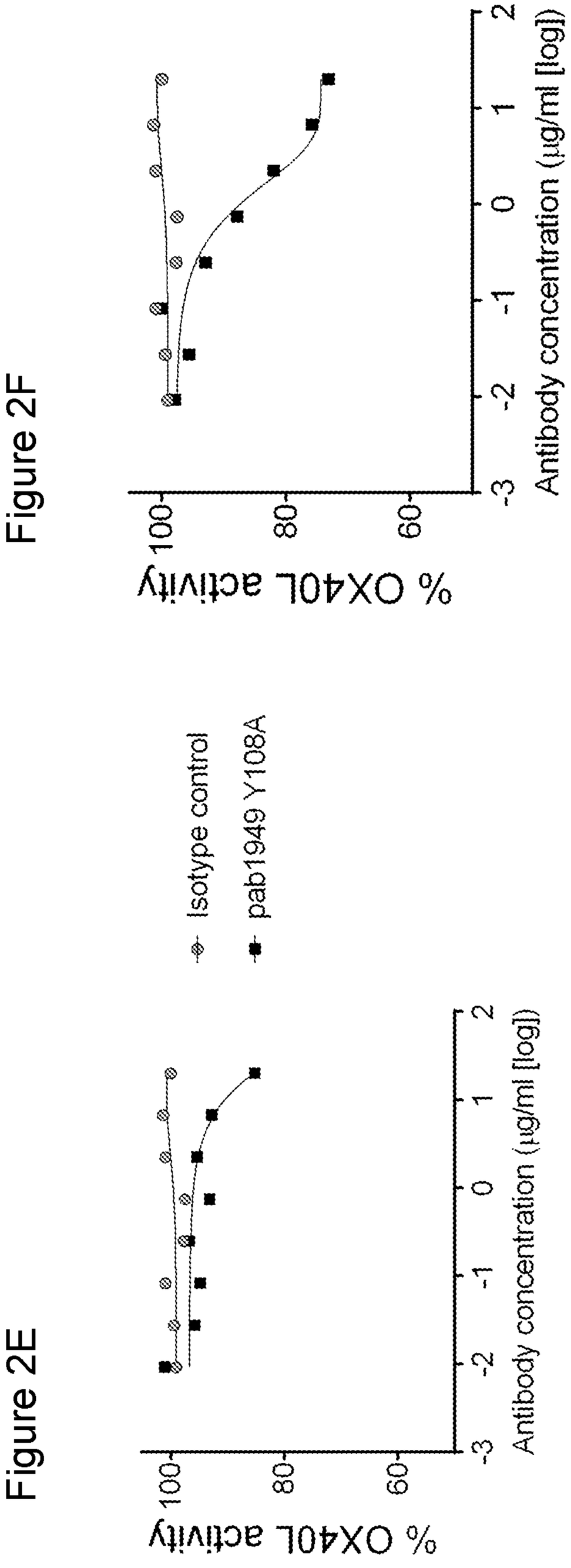

Figure 2F

Figure 2G

Figure 2H

Figure 2I

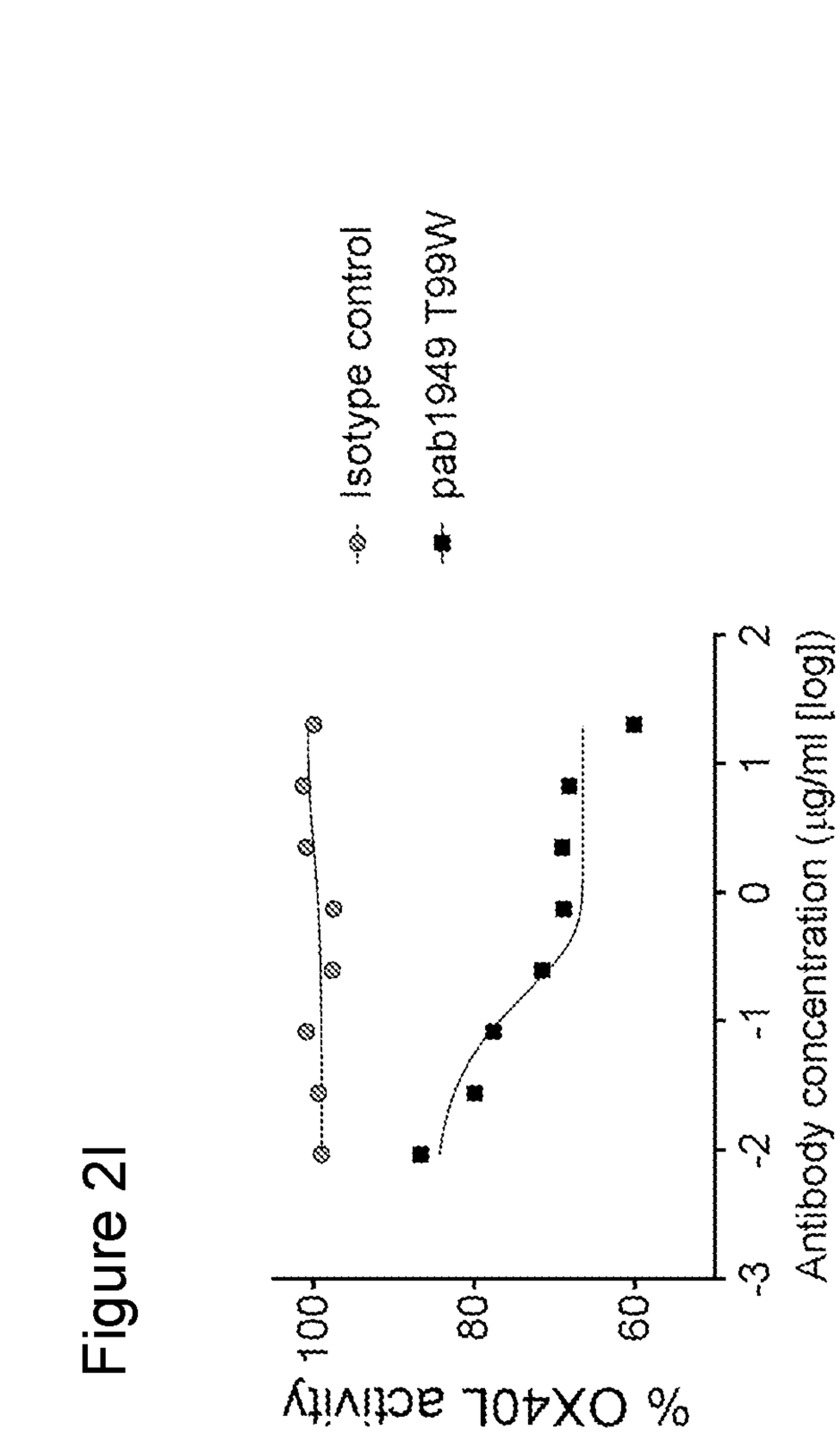
Isotype control
pab1949 T99W
% OX40L activity
100
80
60
-3
-2
-1
0
1
2
Antibody concentration (µg/ml [log])

Figure 3A

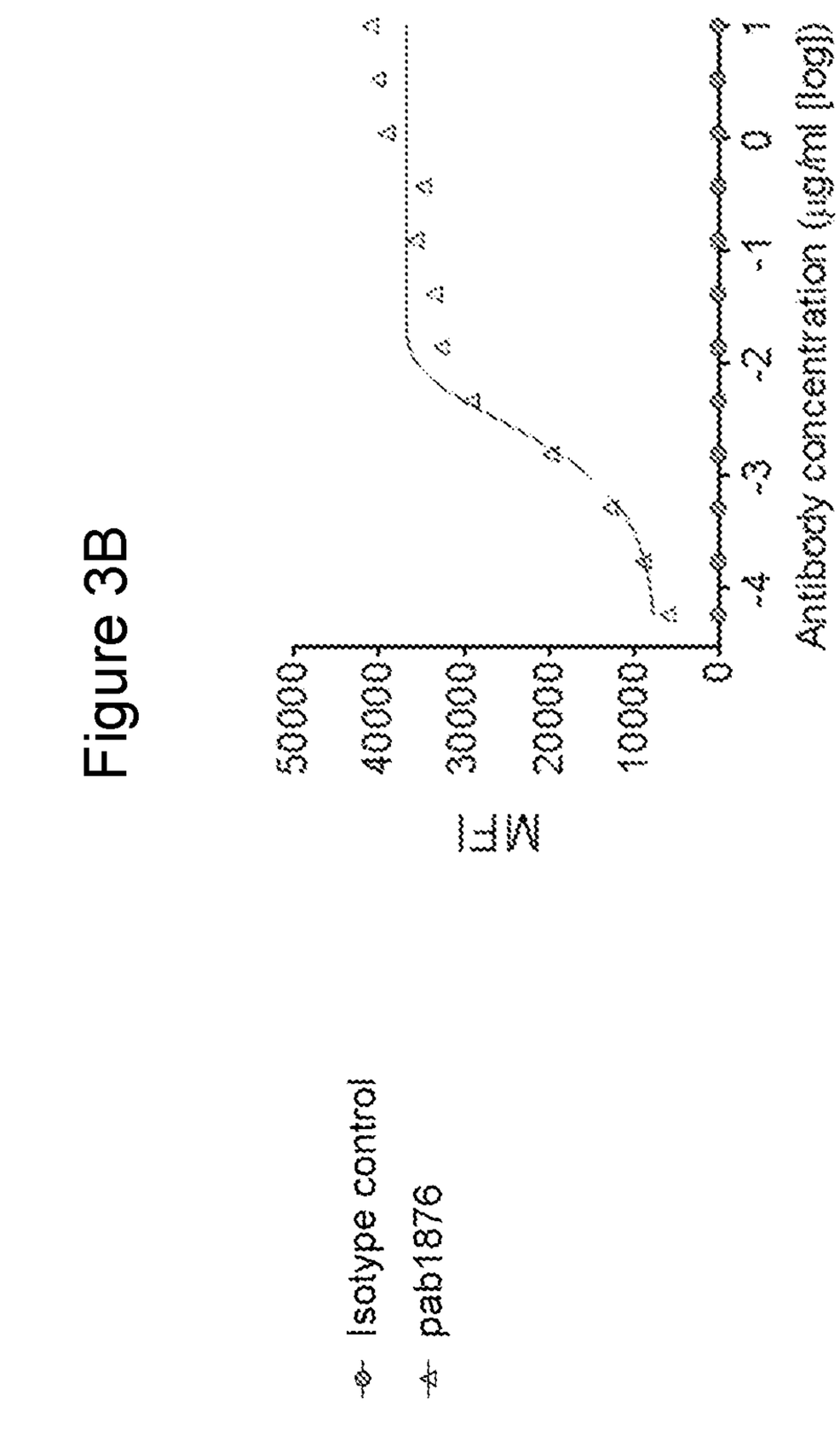

Figure 3B

Figure 3C

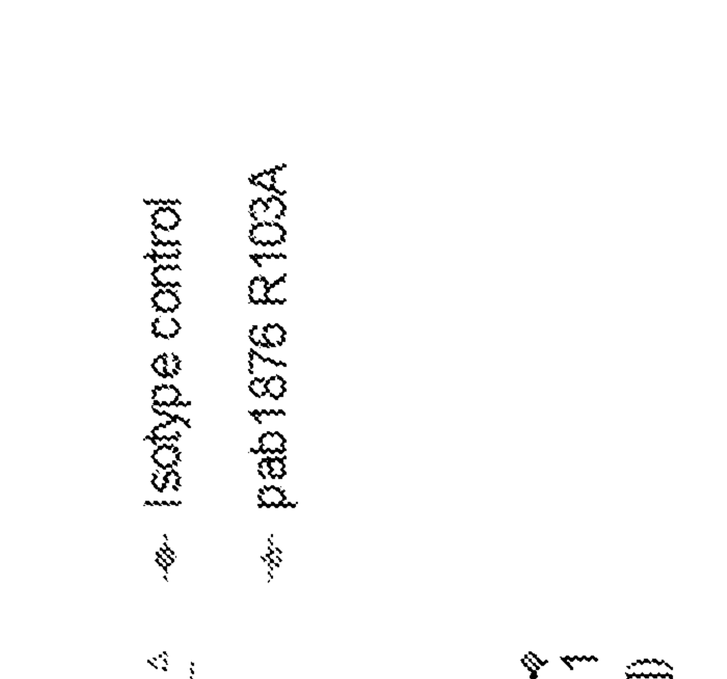

Figure 3D

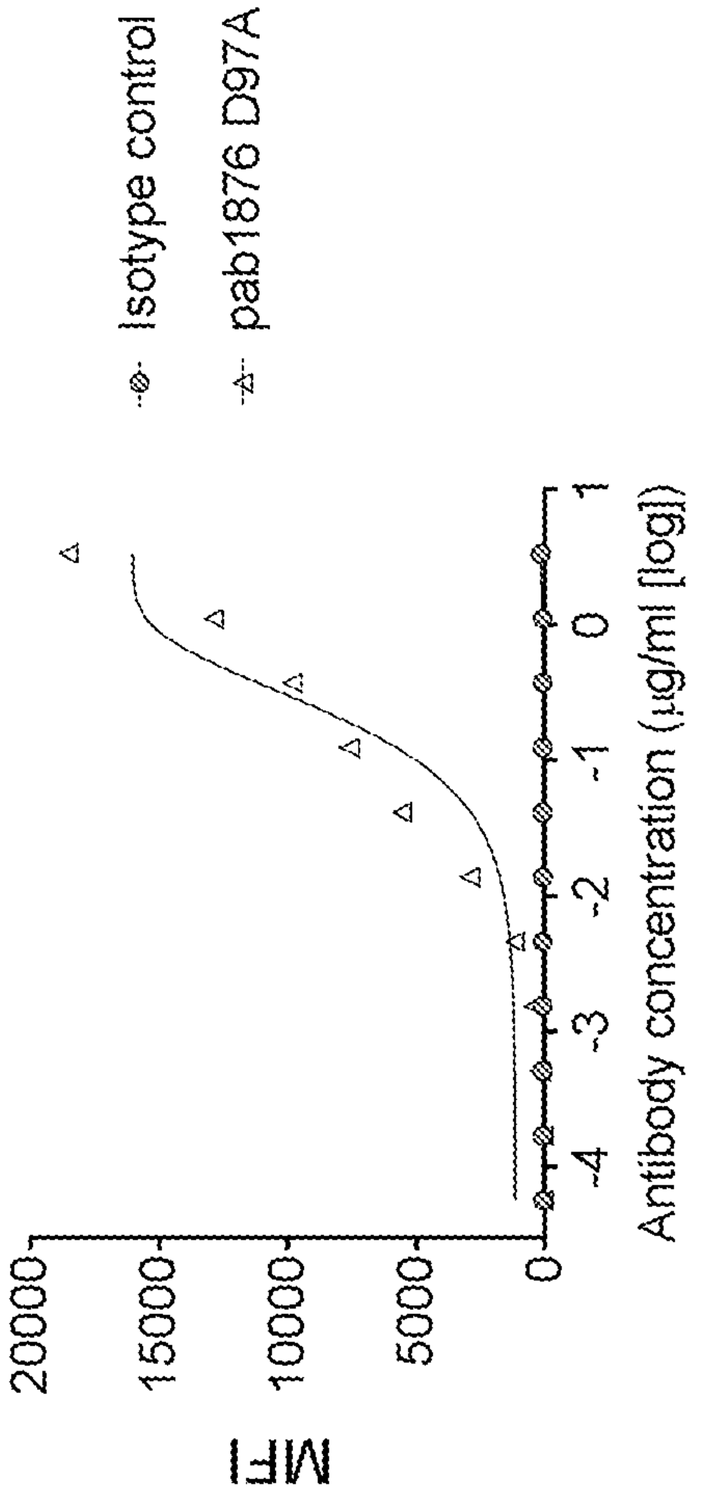

Figure 3F

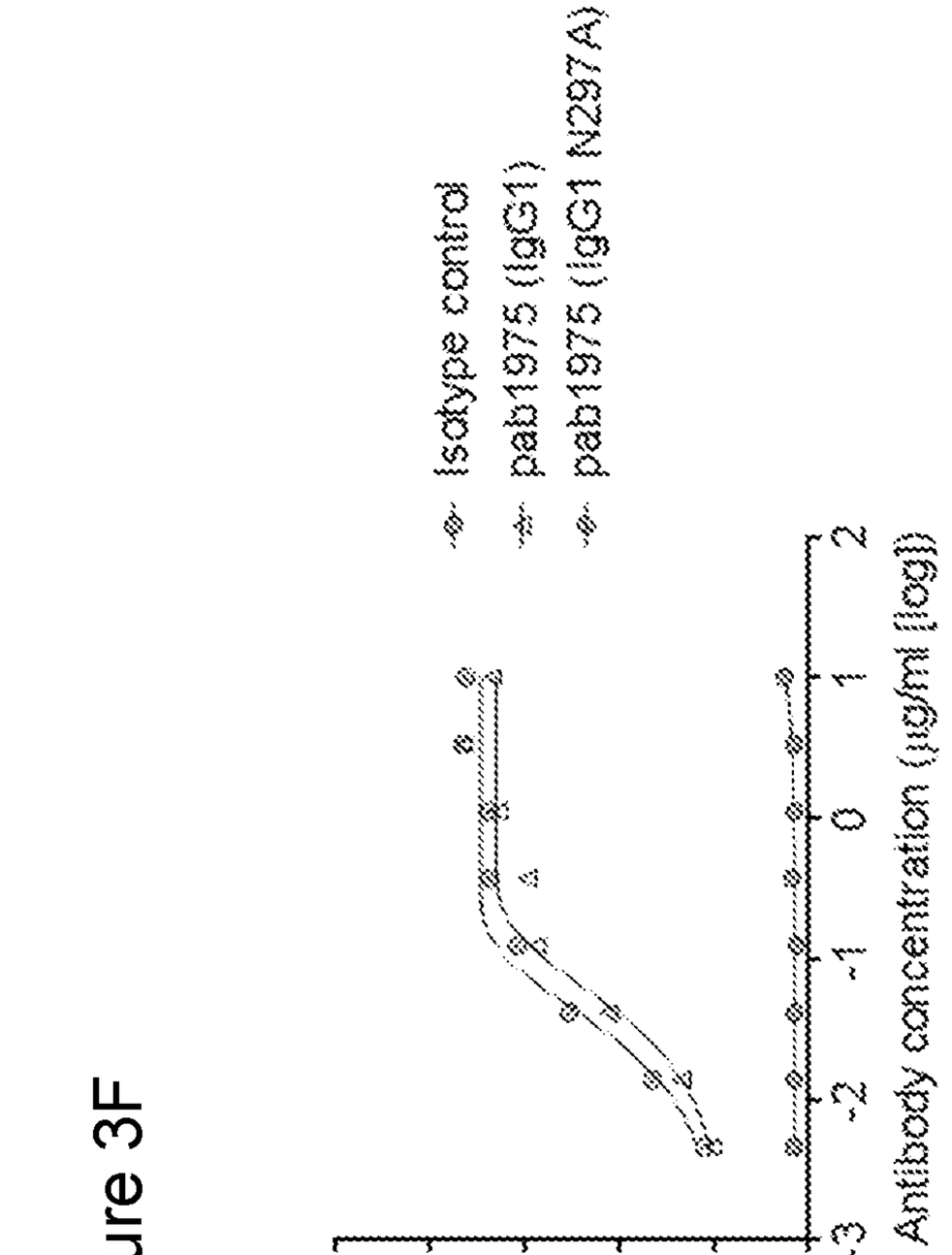

Figure 3E

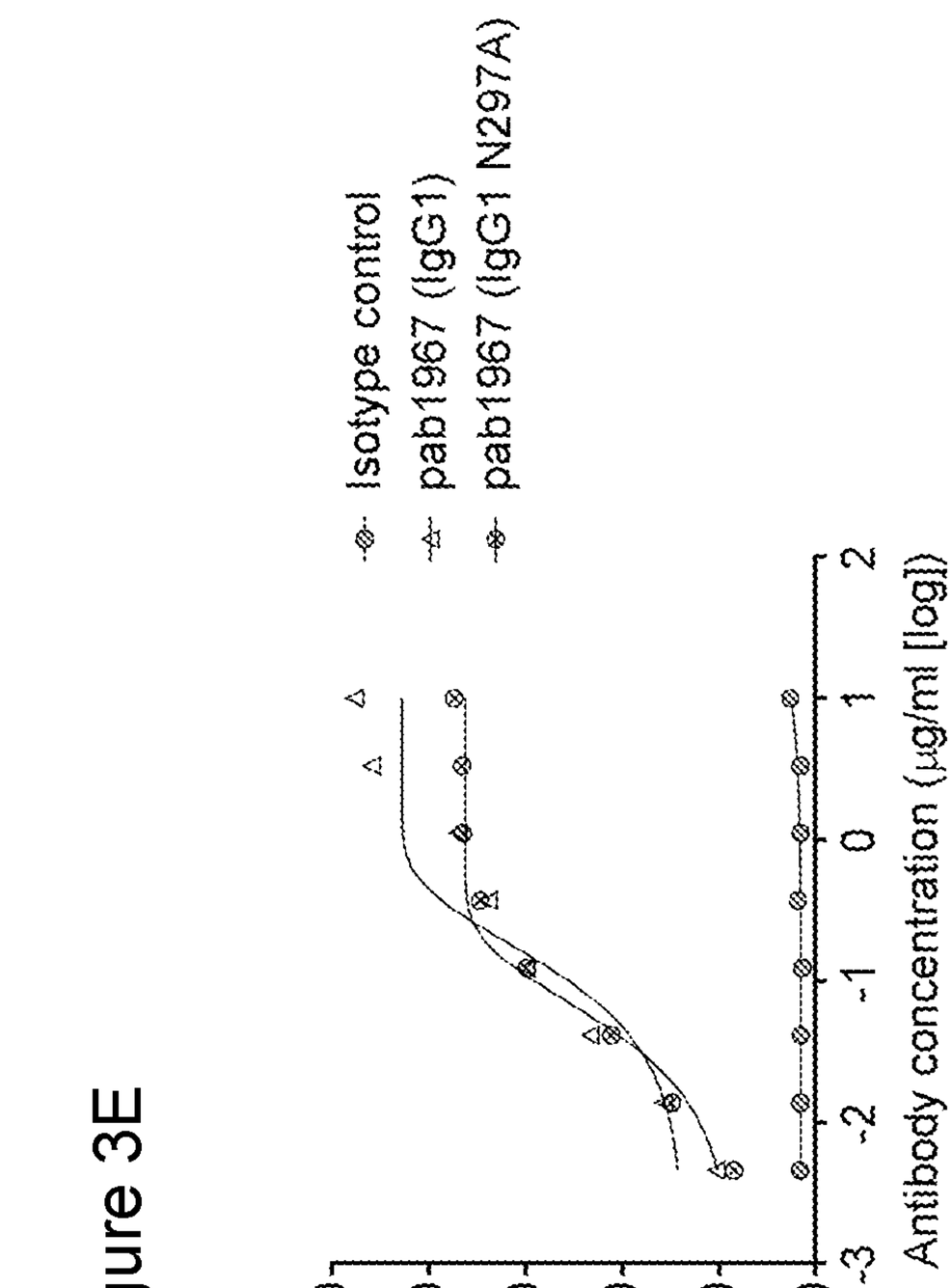

Figure 3G