(19) DANMARK

(10) **DK/EP 3265123 T5**

Patent- og Varemærkestyrelsen

(12) Rettet oversættelse af europæisk patentskrift

(51) Int.Cl.: ***A 61 K 39/395 (2006.01)*** ***A 61 K 39/00 (2006.01)*** ***C 07 K 16/00 (2006.01)*** ***C 07 K 16/28 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2024-09-16**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-10-26**

(86) Europæisk ansøgning nr.: **16715337.8**

(86) Europæisk indleveringsdag: **2016-03-03**

(87) Den europæiske ansøgnings publiceringsdag: **2018-01-10**

(86) International ansøgning nr.: **GB2016050565**

(87) Internationalt publikationsnr.: **WO2016139482**

(30) Prioritet:
2015-03-03 WO PCT/GB2015/050614
2015-04-30 US 201514700896
2015-07-28 US 201514811163
2015-09-09 GB 201516008
2015-11-09 US 201514935937
2015-12-01 US 201514955843

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Kymab Limited, The Bennet Building (B930) , Babraham Research Campus, Cambridge CB22 3AT, Storbritannien**

(72) Opfinder: **BLAND-WARD, Philip, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien**
KOSMAC, Miha, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien
HOLMES, Steve, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien
KIRBY, Ian, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien
CAMPBELL, Jamie, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien
TKACHEV, Victor, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien
KEAN, Leslie Susan, Kymab Limited, The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT, Storbritannien

(74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**

(54) Benævnelse: **ANTISTOFFER, ANVENDELSER OG FREMGANGSMÅDER**

(56) Fremdragne publikationer:
WO-A1-2009/141239

Fortsættes ...

WO-A1-2011/073180
WO-A1-2013/008171
WO-A2-2006/029879
WO-A2-2007/133290
US-A1- 2004 110 226
US-B1- 7 291 331
MICHAEL CROFT: "Control of Immunity by the TNFR-Related Molecule OX40 (CD134)", ANNUAL REVIEW OF IMMUNOLOGY, vol. 28, no. 1, 1 March 2010 (2010-03-01), pages 57-78, XP055039398, ISSN: 0732-0582, DOI: 10.1146/annurev-immunol-030409-101243
RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS), US, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436, ISSN: 0027-8424, DOI: 10.1073/PNAS.79.6.1979
COLMAN ET AL: "Effects of amino acid sequence changes on antibody-antigen interactions", RESEARCH IN IMMUNOLOGY, EDITIONS SCIENTIFIQUES ET MEDICALES ELSEVIER, FR, vol. 145, no. 1, 1 January 1994 (1994-01-01), pages 33-36, XP023944838, ISSN: 0923-2494, DOI: 10.1016/S0923-2494(94)80039-1 [retrieved on 1994-01-01]
Ph Kussie ET AL: "A single engineered amino acid substitution changes antibody fine specificity", The Journal of Immunology, 1 January 1994 (1994-01-01), page 146, XP055530279, United States Retrieved from the Internet: URL:http://www.jimmunol.org/content/jimmun ol/152/1/146.full.pdf [retrieved on 2018-12-05]
C. Chen ET AL: "Enhancement and destruction of antibody function by somatic mutation: unequal occurrence is controlled by V gene combinatorial associations.", The EMBO Journal, vol. 14, no. 12, 1 June 1995 (1995-06-01), pages 2784-2794, XP055530299, ISSN: 0261-4189, DOI: 10.1002/j.1460-2075.1995.tb07278.x

DESCRIPTION

[0001] The present invention is as defined by the claims and relates to anti-human OX40L antibodies, new medical uses and methods. The invention is defined by the claims and any other aspects, configurations or embodiments set forth herein not falling within the scope of the claims are for information.

[0002] Any references in the description to methods of treatment refer to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy (or for diagnosis).

BACKGROUND

[0003] OX40 ligand (OX40L) is a TNF family member; a 34 kDa type II transmembrane protein. The crystallized complex of human OX40 and OX40L is a trimeric configuration of one OX40L (trimer) and three OX40 monomers. The human extracellular domain is 42% homologous to mouse OX40L.

[0004] OX40L is not constitutively expressed but can be induced on professional APCs such as B-cells, dendritic cells (DCs) and macrophages. Other cell types such as Langerhans cells, endothelial cells, smooth muscle cells, mast cells and natural killer (NK) cells can be induced to express OX40L. T-cells can also express OX40L. The OX40L receptor, OX40, is expressed on activated T-cells (CD4 and CD8 T-cells, Th2, Th1 and Th17 cells) and CD4+Foxp3+ cells, even in the absence of activation.

[0005] The interaction between OX40 and OX40L occurs during the T-cell-DC interaction 2 or 3 days after antigen recognition. After leaving DCs, the OX40-expressing T-cell may interact with an OX40L-expressing cell other than a DC and receive an OX40 signal from this cell, which may provide essential signals for the generation of memory T-cells, the enhancement of Th2 response and the prolongation of the inflammatory responses. OX40 signals into responder T-cells render them resistant to Treg mediated suppression.

[0006] Graft versus host disease is a major cause of mortality following allogeneic bone marrow treatment. In the acute version of the disease, mature T-cells present in the bone marrow graft recognise the donor tissue as foreign in an environment of damaged tissue, which, via host APC's cause the activation and proliferation of the donor T-cells, with subsequent T-cell migration into the liver, spleen, gut, skin and lungs, causing tissue damage by the CTL effector response and inflammatory cytokine/chemokine release. Onset for acute disease is usually within the first 100 days post transplantation (Hill-Ferrara, Blood May 1, 2000 vol. 95 no. 9 2754-275, Reddy-Ferrara Blood, Volume 17, Issue 4, December 2003).

[0007] Chronic GvHD usually appears 100 days post transplantation and several factors are thought to be involved, including thymic damage caused by prior acute GvHD which results in a reduced clearance of pathogenic T-cells (Zhang *et al*, September 1, 2007 vol. 179 no. 5 3305-3314), up-regulation of TGF-β, which causes fibrosis (McCormick et al J Immuno, November 15, 1999 vol. 163 no. 10 5693-5699), and a B-cell component driven by elevated B-Cell activating factor (BAFF) (Sarantopoulos et al, Clin Cancer Res October 15, 2007 13; 6107) as well as auto-antibodies against platelet derived growth factor receptor (Svegliati et al, Blood July 1, 2007 vol. 110 no. 1 237-241).

[0008] Clinical studies have shown that OX40 is up-regulated in both acute (Morante et al, Clinical and Experimental Immunology,145:36-43) and chronic (Kotani et al, Blood November 15, 2001 vol. 98 no. 10 3162-3164) GvHD. Administration of an antagonistic anti-OX40L enhanced survival in a lethal acute mouse model of GvHD, with a 70% survival in the treated group compared to the untreated who all died by day 43 (Tsukada et al, Blood, 1 April 2000, Volume 95, Number 7) whereas treatment with an agonistic anti-OX40 Ab accelerated the disease and mortality (Blazar et al Blood May 1, 2003 vol. 101 no. 9 3741-3748). Blockade of the OX40-OX40L interaction has been shown to be efficacious in several other inflammatory disease, with anti-OX40L Ab being used to treat a mouse model of colitis (Totsuka et al., AJP - GI April 1, 2003 vol. 284 no. 4 G595-G603), and that an anti-OX40L Ab could block the development of diabetes in NOD mice (Pakala et al European Journal of Immunology Volume 34, Issue 11, pages 3039-3046, November 2004).

References

[0009]

Lamb, L.S., Abhyankar, S.A., Hazlett, L., O'Neal, W., Folk, R.S., Vogt, S., Parrish, R.S., Bridges, K., Henslee-Downey, P.J. and Gee, A. P. (1999), Expression of CD134 (OX-40) on T-cells during the first 100 days following allogeneic bone marrow transplantation as a marker for lymphocyte activation and therapy-resistant graft-versus-host disease. Cytometry, 38: 238-243.

Xupeng Ge, Julia Brown, Megan Sykes, Vassiliki A. Boussiotis, CD134-Alldepletion Allows Selective Elimination of Alloreactive Human T-cells without Loss of Virus-Specific and Leukemia-Specific Effectors, Biology of Blood and Marrow Transplantation, Volume 14, Issue 5, May 2008, Pages 518-530.

Naoto Ishii, Takeshi Takahashi, Pejman Soroosh, Kazuo Sugamura, Chapter 3 - OX40-OX40 Ligand Interaction in T-Cell-Mediated Immunity and Immunopathology, In: Frederick W. Alt, Editor(s), Advances in Immunology, Academic Press, 2010, Volume 105, Pages 63-98.

Croft, M., So, T., Duan, W. and Soroosh, P. (2009), The significance of OX40 and OX40L to T-cell biology and immune disease. Immunological Reviews, 229: 173-191.

WO 2006/029879 (F. Hoffman-La Roche) describes anti-OX40L antibodies and, in particular, to anti-OX40L antibodies and variants thereof that contain a Fc part derived from human origin and do not bind complement factor C1q.

SUMMARY OF THE INVENTION

[0010] The invention is defined by the claims and any other aspects, configurations or embodiments set forth herein not falling within the scope of the claims are for information. The invention provides anti-human OX40L (hOX40L) antibodies and fragments and novel medical applications for treating or preventing hOX40L-mediated diseases or conditions in humans. To this end, the invention provides:-

In a first configuration

[0011] An antibody or a fragment thereof that specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition in a human in a method wherein the antibody or fragment is administered to said human, wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing one, more or all of

1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
2. b. the proliferation of leukocytes of the human; and
3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

In a second configuration

[0012] An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

In a third configuration

[0013] Use of an antibody or a fragment thereof, that specifically binds to hOX40L in the manufacture of a medicament for administration to a human, for treating or preventing a hOX40L-mediated disease or condition in the human by decreasing one, more or all of

1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
2. b. the proliferation of leukocytes of the human; and
3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

In a fourth configuration

[0014] A method of treating or preventing a hOX40L-mediated disease or condition in a human by decreasing one, more or all of

1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
2. b. the proliferation of leukocytes of the human; and
3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L;

wherein the method comprises administering to said human a therapeutically effective amount of an antibody or fragment that specifically binds to hOX40L.

In a fifth configuration

[0015] An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

In a sixth configuration

[0016] An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises the HCDR3 sequence of SEQ ID NO:40 or 46 or the HCDR3 sequence of SEQ ID NO:40 or 46 comprising less than 5 amino acid substitutions.

In a seventh configuration

[0017] A human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L for treating or preventing an autoimmune disease selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

In an eighth configuration

[0018] Use of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

In a ninth configuration

[0019] A method of treating or preventing a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection, comprising administering to said human a therapeutically effective amount of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6, which specifically binds to hOX40L, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

[0020] The invention also provides pharmaceutical compositions, kits, nucleic acids, vectors and hosts.

BRIEF DESCRIPTION OF THE FIGURES

[0021]

Figure 1: Profiling of fully human recombinant anti-OX40L antibodies in HTRF Ligand/Receptor Neutralisation assay. Data shown is representative of three repeat experiments.

Figure 2: Determining effect of anti-OX40L antibodies in allogeneic PBMC/T Mixed Lymphocyte Reaction. Data shown is from three independent donor pairings where it is assumed each donor is a different individual.

Figure 3: Expansion of Tscm cells following allogeneic HCT. Plots are gated on CD4+CD45RA+CCR7+ T-cells.

Figure 4: OX40L blockade controls expansion of CD4+ Tscm cells while preserving CD4+ T naïve cells following allogeneic HCT. Absolute numbers of peripheral blood CD4+ Tscm (left) and Tnaive (right) following allogeneic HCT in control animal and 2D10 IgG4PE treated animals.

Figure 5: OX40 expression on naïve CD4+ T and memory stem T-cells in a representative animal following allogeneic HCT. Left and middle FACS plots were gated on CD3+CD4+CD45RA+CCR7+. The histogram on the right shows OX40 expression in different T-cell subsets of CD4+ T-cells: Naïve (CD45RA+CCR7+CD95-), memory stem (SCM: CD45RA+CCR7+CD95+), central memory (CM: CD45RA-CCR7+), effector memory (EM: CD45RA-CCR7-) and terminally differentiated effector-memory cells re-expressing CD45RA (TEMRA: CD45RA+CCR7-).

Figure 6a: Effects of OX40L blockade on SCM CD4+ T-cells. Datapoints for 02D10 IgG4PE are shown by circles, rapamycin by filled squares and tacrolimus plus methotrexate (Tac/MTX) by open squares.

Figure 6a: Effects of OX40L blockade on SCM CD8+ T-cells. Datapoints for 02D10 IgG4PE are shown by circles, rapamycin by filled squares and Tac/MTX by unfilled squares.

Figure 7: Kaplan-Meier survival curve for rhesus monkey recipients of hematopoietic stem cell transplants derived from the peripheral blood of haploidentical half-sibling donors. Results are shown for animals that did not receive post-transplant prophylactic therapy (No-treatment control; median survival time, MST= 8 days; n=4), and those receiving rapamycin monotherapy (MST= 17 days; n=4), 2D10 monotherapy (MST= 19 days; n=4), or rapamycin plus 2D10 (MST > 82 days; n=3). Note that animals 2 and 3 indicated on the figure were on-study at the time of drafting; neither showed signs of GVHD at Day 82 or Day

41 post-transplant, respectively. Asterix * for the no treatment control and rapamycin monotherapy groups is data taken from Furlan et al., 2015, Science Translational Medicine, vol 7 (315), 315ra191.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The description provides the following aspects 1 to 113.

[0023] The invention is useful, for example, for treating or preventing transplant rejection, e.g., graft versus host disease (GvHD) or allogeneic transplant rejection. The invention is also useful, for example, for treating or preventing an inflammatory bowel disease, e.g., UC or CD, or for treating or preventing an airway inflammatory disease or condition. In an example this aspect is useful for treating or preventing asthma. The invention is also useful, for example, for treating or preventing fibrosis. The invention is also useful, for example, for treating or preventing diabetes. The invention is also useful, for example, for treating or preventing uveitis. The invention is also useful, for example, for treating or preventing pyoderma gangrenosum. The invention is also useful, for example, for treating or preventing giant cell arteritis. The invention is also useful, for example, for treating or preventing Schnitzler syndrome. The invention is also useful, for example, for treating or preventing non-infectious scleritis.

1. 1. An antibody or a fragment thereof that specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition in a human in a method wherein the antibody or fragment is administered to said human, wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing one, more or all of
    1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
    2. b. the proliferation of leukocytes of the human; and
    3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

[0024] The inventors, thus identified for the first time decreases of (a), (b) and (c) as ways of treating and/or preventing OX40L-mediated disease and conditions in humans and they provide antibodies and antibody fragments for this purpose.

[0025] In an example, the secretion is leukocyte secretion. In an example, (a) is indicated by a significantly elevated level of the cytokine(s) in human blood, plasma or serum.

[0026] In an example, the cytokine is selected from (i) TNF alpha, (ii) IL-2 and (iii) interferon gamma. In example, the cytokine TNF alpha. In example, the cytokine is IL-2. In an example, the cytokine is interferon gamma. In an example, the cytokines are (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii).

[0027] In an example, the decrease of (a), (b) or (c) or any other decrease disclosed herein is a decrease of at least 10 or 20% compared to the level in a human at risk of or suffering from the hOX40L-mediated disease or condition. In an example, the latter is the human recited in aspect 1 prior to administration of the antibody or fragment; in another example the latter human is a different human. In an example, said decrease is at least 10, 20, 30, 40, 50 or 60%.

1. (i) In an example, the antibody or fragment is capable of effecting a decrease of secretion of the relevant cytokine from leukocytes (eg, human T-cells) in an *in vitro* assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (a).
2. (ii) In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (eg, human PBMCs and/or human T-cells) in an *in vitro* assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (b).
3. (iii) In an example, the antibody or fragment is capable of effecting a decrease of the binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L in an *in vitro* assay (as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of (c).

[0028] In an example, (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii) apply.

[0029] Additionally or alternatively, assessment of said decreases can be performed using samples from the treated human. For example, reference is made to J. Clin. Immunol., 2004 Jan, 24(1):74-85; "Increased expression of CCL20 in human inflammatory bowel disease"; Kaser A *et al.* This publication provides an example of a generally-applicable technique of using tissue biopsies and reading out decreased cytokine levels indicative of decreased cytokine secretion after treatment with an antibody *in vivo*. Similar methods can be used to determine decrease of the secretion of one or more cytokines in a human having received an antibody of the invention. The skilled person will be familiar with techniques for assessing cytokine levels in patients and patient samples, for example, by use of one or more of tissue biopsy, immunohistochemistry, immunofluorescence, tissue staining, cytokine mRNA quantification (e.g., using PCR, such as Taqman™ PCR), cytokine protein detection and quantification (e.g., using cytokine-specific tool antibody and quantification, such as by ELISA or another standard protein quantification technique). For example, where the disease or condition is one of the GI tract (e.g., IBD), one can perform biopsy of relevant gut tissue from a patient that has received an antibody of the invention, followed by quantification of cytokine mRNA and/or cytokine protein (e.g., using quantitative PCR). The result can be compared with a cytokine quantification in biopsied relevant tissue from the same patient prior to antibody administration or compared to another human patient suffering from the same disease or condition but receiving no anti-OX40L treatment or no treatment for the disease or condition. In this way, the skilled person can determine that the antibody of the invention decreases secretion of the cytokine in the human recipient. Instead of assessing gut tissue levels, one can instead use a different tissue or sample from the human patient dependent upon the nature and location of the disease or condition. For example, where the disease or condition is one of the airways (e.g., lung), it is possible to take a lung or other airway tissue sample for cytokine assessment. Alternatively, one can use a Bronchoalveolar lavage (BAL) sample, as will be apparent to the skilled person. In another example, for some disease or conditions one can assess the decrease in cytokine in a blood, serum or plasma sample taken from a human that has received an antibody of the invention, and then comparing to the level before receiving the antibody or comparing to the level in an untreated human, as discussed above.

[0030] As is known in the art, the term "leukocytes" includes, for example, one or more of lymphocytes, polymorphonuclear leukocyte and monocytes. As is also readily apparent to the skilled person the term "monocytes" includes, for example, peripheral blood mononuclear cells (PBMCs) or monocyte derived cells, e.g., dendritic cells (DCs). See, for example, Immunobiology, 2013 Nov,218(11):1392-401. doi: 10.1016/j.imbio.2013.07.005. Epub 2013 Jul 25; "Leukoreduction system chambers are an efficient, valid, and economic source of functional monocyte-derived dendritic cells and lymphocytes", Pfeiffer IA *et al.*

[0031] The proliferation of leukocytes, e.g., lamina propria lymphocytes (LPLs), can be assessed using tissue biopsy, staining and histology, as will be apparent to the skilled person. Hematoxylin and eosin stain (H&E stain or HE stain) is, for example, commonly used in histology to look for infiltrating lymphocytes a whole range of human tissue and is one of the principal stains in histology. It is the most widely used stain in medical diagnosis and is often the gold standard, and as such can be used to assess proliferation of leukocytes as per the invention. For example, GI tract tissue (e.g., gut tissue) from a human that is suffering from or at risk of a hOX40L-mediated disease or condition can be obtained, stained and assessed for the extent of infiltration of LPLs. Comparison can be made between such tissue from a human that has received an antibody of the invention compared to the extent of infiltration in tissue obtained from the same human prior to administration of antibody or from another human that has not received treatment and is at risk of or suffering from the disease or condition. For example, the comparison is between human gut tissues taken from the same (or different) humans suffering from IBD.

[0032] One can, for example, determine if the antibody or fragment is capable of decreasing binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L using standard binding assays are familiar to the skilled person, e.g., using ELISA or SPR.

[0033] Inflammatory bowel disease (IBD) is a chronic inflammatory disorder affecting the gastrointestinal tract with an apparently ever-increasing incidence and tendency to more severe clinical phenotypes. The disease is characterised by an exaggerated immune response to the luminal flora, suggesting that deficiencies in barrier function of intestinal flora may be involved, and studies support this notion (Cucchiara et al., 2012; Jostins et al., 2012; Manichanh et al., 2012; Salzman et al., 2007, all cited in Deuring et al., "The cell biology of the intestinal epithelium and its relation to inflammatory bowel disease", The International Journal of Biochemistry & Cell Biology 45 (2013) 798-806). IBD includes two main groups: Crohn's disease (CD) and ulcerative colitis (UC). CD patients can have inflammatory lesions in their entire gastrointestinal tract, whereas the inflammation in UC patients is restricted to the colon. Reference is also made to Hisamatsu et al. ("Immune aspects of the pathogenesis of inflammatory bowel disease", Pharmacology & Therapeutics 137 (2013) 283-297) and the documents cited therein.

[0034] Granuloma formation is the one of the most important pathological characteristics of human Crohn's disease. Mizoguchi *et al* demonstrated that F4/80-positive immature CD11c* dendritic cells (DCs) produce IL-23 and contribute to granuloma formation in a murine colitis model (Mizoguchi et al., 2007). A Th1 immune response is predominant in Crohn's disease. Indeed, CD4* T-cells in the LP of Crohn's disease expressed T-bet and produced large amounts of interferon (IFN)-γ (Matsuoka et al., 2004). Sakuraba *et al* demonstrated that DCs in the mesentric lymph nodes of patients with Crohn's disease strongly promoted a Th1 and Th17 immune response (Sakuraba *et al.*, 2009). Mesentric lymph node DCs contribute to IBD pathogenesis, particularly that of Crohn's disease.

Role of Cytokines in Disease and Conditions

[0035] Reference is made to Muzes et al, World J Gastroenterol 2012 November 7; 18(41): 5849-5861 ISSN 1007-9327 (print) ISSN 2219-2840 (online), "Changes of the cytokine profile in inflammatory bowel Diseased".

[0036] Cytokines are indispensable signals of the mucosa-associated immune system for maintaining normal gut homeostasis. An imbalance of their profile in favour of inflammation initiation may lead to disease states, such as that is observed in inflammatory bowel diseases (IBD), e.g., Crohn's disease (CD) and ulcerative colitis (UC). The role of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2,-6, -8, -12, -17, -23, IFN-gamma, or TNF alpha in IBD is associated with the initiation and progression of UC and CD. CD is often described as a prototype of T-helper (Th) 1-mediated diseases because the primary inflammatory mediators are the Th1 cytokines such as interleukin (IL)-12, interferon (IFN)-γ, and tumour necrosis factor (TNF)-α.

[0037] Binding of TNF-like ligands to their receptors triggers intracellular pathways that are directly involved in cell proliferation, differentiation, and survival. Most members of the TNF/TNF-receptor protein superfamilies are expressed on immune cells and play a critical role in multiple components of the immune response. TNF-α is a master cytokine in the pathogenesis of IBD. It exerts its pleiotropic effects through the expression of adhesion molecules, fibroblast proliferation, procoagulant factors, as well as the initiation of cytotoxic, apoptotic and acute-phase responses. The source of TNF-α in IBD is partly the innate immune cells, such as macrophages or monocytes, and also differentiated Th1 cells. The serum levels of TNF-α correlate with the clinical activity of UC and CD[31]. It plays an orchestrating role in colonic inflammation in IBD. The role of TNF-α in CD has been widely investigated. Binding TNF-α to serum soluble TNF receptor 1 and 2 (sTNFR1 and 2) initiates pro-inflammatory signalling. The levels of sTNFR1 and 2 are elevated in CD.

[0038] Tumour necrosis factor-like factor (TL1A), another member of the TNF family, stimulates IFN-γ secretion by binding to death receptor 3 (DR3). DR3 is expressed by a high percentage of cells from mucosal biopsies of UC and CD, and an increase of IFN-γ level has been observed with disease activity in IBD patients. The TL1A/DR3 system is involved in the pathogenesis of CD. The macrophages of the lamina propria are a major producer of TL1A, which expression is markedly enhanced in CD. It has been found that TL1A and IL-23 synergistically promotes the production of IFN-γ by mucosal T-cells. FN-Y. is produced by TH1 T-cells. Once inflammation is initiated, IFN-γ is produced and subsequently acts through various molecules and pathways of the immune system to intensify the inflammatory process. There is an overwhelming body of literature extensively documenting the proinflammatory nature of IFN-γ which has led to the mainstream opinion that IFN-γ is a prime proinflammatory cytokine in inflammation and autoimmune disease. Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice (Ito et al, Clinical and Experimental Immunology (2006), 146:330-338). The study clearly demonstrated that IFN-γ$^{-/-}$ mice manifested attenuated colitis after stimulation with DSS, in terms of the degree of body weight loss, DAI, histological score and MPO activity. IFN-γ was increasingly produced in the colon of DSS-treated WT mice that showed severe IBD-like symptoms.

[0039] Interleukin-2 (IL-2) is produced by T-cells and is mostly important for T-cells to differentiate into effector T-cells. IL-2 is also important for T-cell proliferation. This is important for IBD because effector T-cells are thought to be a major cell type to cause damage in IBD.

[0040] IL-8 (interleukin-8; aka CXCL8) primarily mediates the activation and migration of neutrophils into tissue from peripheral blood and to sites of inflammation. The tissue level of IL-8 has been found to be higher in active UC compared to normal colonic tissue, and its serum concentration has been related to endoscopic and histological severity of UC. IL-8 is important for inflammatory settings and cancer (see, e.g., "The Chemokine CXCL8 in Carcinogenesis and Drug Response", ISRN Oncol. 2013 Oct 9;2013:659154; Gales D *et al.*, and Future Oncol., 2010 Jan;6(1):111-6. doi: 10.2217/fon.09.128; "CXCL8 and its cognate receptors in melanoma progression and metastasis", Singh S *et al.*). In cancer particularly, IL-8 is thought to contribute also by supporting angiogenesis.

[0041] In any configuration, aspect, concept or example herein the antibody or fragment antagonises the binding of hOX40L to an OX40 receptor.

[0042] In any configuration, aspect, concept or example herein, the antibody or fragment antagonises the binding of hOX40L to OX40.

[0043] In any configuration, aspect, concept or example herein, the OX40L receptor can be human OX40.

[0044] In any configuration, aspect, concept or example herein the human is suffering from or at risk of asthma and the antibody or fragment decreases IgE in a human.

[0045] In any configuration, aspect, concept or example herein the human is suffering from or at risk of asthma and the antibody or fragment is for decreasing IgE in a human.

[0046] 2. The antibody or fragment of aspect 1, wherein the antibody or fragment decreases the binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L and decreases the proliferation of human T-cells; wherein the antibody or fragment is for treating or preventing said hOX40L-mediated disease or condition by decreasing the secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9 JL-10, IL-13, IL-17, RANTES and interferon gamma.

[0047] In an example, the cytokine is selected from (i) TNF alpha, (ii) IL-2 and (iii) interferon gamma. In an example, the cytokine is TNF alpha. In an example, the cytokine is IL-2. In an example, the cytokine is interferon gamma. In an example, the cytokines are (i) and (ii); or (i) and (iii); or (ii) and (iii); or (i)-(iii).

[0048] 3. The antibody or fragment of aspect 1, wherein the leukocytes are selected from the group consisting of polymorphonuclear leukocytes, monocytes, peripheral blood mononuclear cells (PBMCs), lymphocytes, T-cells, antigen presenting cells (APCs), dendritic cells (DC cells) and natural killer cells (NK cells).

[0049] In one embodiment, the leukocytes are peripheral blood mononuclear cells (PBMCs) and T-cells (e.g. PBMCs).

[0050] 4. The antibody or fragment of aspect 3, wherein the leukocytes comprise lamina propria lymphocytes (LPLs) and the disease or condition is a disease or condition of the gastrointestinal tract (GI tract).

[0051] 5. The antibody or fragment of any preceding aspect, wherein the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and airway (e.g., lung) epithelial cells.

[0052] In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

[0053] 6. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the proliferation of T-cells in said human.

[0054] In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of T-cells in an *in vitro* assay (e.g., in a human DC cell/T-cell *in vitro* assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of T-cells in said human.

[0055] 7. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by antagonising the interaction between hOX40L and leukocytes of the human, wherein the proliferation of leukocytes is decreased.

[0056] In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (e.g., monocuclear cells) in an *in vitro* assay (e.g., in a MLR *in vitro* assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of leukocytes in said human.

[0057] 8. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the proliferation of leukocytes of the human by antagonising the OX40L/OX40L receptor interaction mediated by T-cells in said human.

[0058] In an example, the antibody or fragment is capable of effecting a decrease of the proliferation of leukocytes (e.g., monocuclear cells) in an *in vitro* assay wherein the antibody or fragment antagonises OX40L/OX40L receptor interaction mediated by T-cells in said assay, and thus administration of such antibody or fragment to the human leads to decrease of the proliferation of leukocytes in said human.

[0059] 9. The antibody or fragment of any preceding aspect, for treating or preventing said hOX40L-mediated disease or condition in said human by decreasing the secretion of a cytokine selected from TNF alpha, IL-2 and interferon gamma in the human.

[0060] In an example, the antibody or fragment is for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the secretion of (i) IL-2 and interferon gamma, (ii) IL-2 and TNF alpha or (iii) interferon gamma and TNF alpha in the human.

[0061] In an example, the antibody or fragment is capable of effecting a decrease of the secretion of a cytokine selected from IL-2, TNF alpha and interferon gamma in an *in vitro* assay (e.g., in a MLR *in vitro* assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of said selected cytokine(s) in said human.

[0062] In an example, the antibody or fragment is capable of effecting a decrease of the secretion of IL-8 in an *in vitro* assay (e.g., in a MLR *in vitro* assay, for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of IL-8 in said human.

[0063] 10. The antibody or fragment of aspect 9, for treating or preventing said disease or condition by decreasing the secretion of said cytokine mediated by the interaction of dendritic cells (DC cells) with T-cells in the human.

[0064] In an example, the antibody or fragment is capable of effecting a decrease of said cytokine(s) secretion in a DC cell/T-cell *in* vitro assay (for example as explained further below), and thus administration of such antibody or fragment to the human leads to decrease of the secretion of said cytokine(s) in said human.

[0065] 11. The antibody or fragment of any preceding aspect, wherein gastrointestinal cell, colon cell, intestinal cell or airway (e.g., lung) cell damage is a symptom or cause of said disease or condition in humans.

[0066] In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

[0067] 12. The antibody or fragment of any preceding aspect, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, diabetes or airway inflammation in the human.

[0068] 12a. The antibody or fragment of any preceding aspect, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious sclentis, diabetes or airway inflammation in the human.

[0069] In an example of any preceding aspect the human is suffering from or at risk of an inflammatory or autoimmune disease or condition or has been diagnosed as such.

[0070] In an example, the autoimmune disease or condition is selected from the following:-

Acute disseminated encephalomyelitis (ADEM)

Addison's disease

Allergic granulomatosis and angiitis or Churg-Strauss syndrome (CSS)

Alopecia or Alopecia Areata (AA)

Anklosing spondylitis

Autoimmune chronic active hepatitis (CAH)

Autoimmune hemolytic anemia

Autoimmune pancreatitis (AIP)

Autoimmune retinopathy (AR) see Retinopathy

Autoimmune thrombocytopenic purpura

Autoimmune neutropenia

Autoimmune Inner Ear Disease (AIED)

Antiphospholipid Syndrome (APS)

Autoimmune Lymphoproliferative Syndrome (ALPS)

Behcet's syndrome

Bullus pemphigoid

Celiac disease

Churg-Strauss Syndrome (CSS) or Allergic Granulomatosis Angiitis

Chronic bullous disease of childhood

Chronic inflammatory demyelinating Polyradiculoneuropathy (CIDP)

Cictricial pemphigoid (CP)

Central Nervous System Vasculitis

Crohn's Disease

Cryoglobulinemia

Dermatitis herpetiformis (DH)

Discoid lupus erythematosus (DLE)

Encephalomyelitis

Epidermolysis bullosa acquisita (EBA)

Giant Cell Arteritis see Temporal arteritis

Graft-versus-host disease

Graves' Disease

Gullain-Barre syndrome

Hanot Syndrome see Primary biliary Cirrhosis

Hashimoto's thyroiditis also called autoimmune thyroiditis and chronic lymphocytic thyroiditis Hypersensitivity Vasculitis (HV) or small vessel vasculitis

Immune-mediated infertility

Inflammatory bowel disease

Insulin-dependent diabetes mellitus

Isolated vasculitis of the Central nervous system or CNS Vasculitis

Isaacs' Syndrome: Neuromyotonia

Kawasaki disease (KD)

Lambert-Eaton myasthenic syndrome (LEMS)

Linear IgA disease

Lupus - see Systemic lupus erythematosus

Meniere's Disease

Microscopic Polyangiitis (MPA)

Mixed connective tissue disease or MCTD

Monoclonal Gammopathy

Myasthenia Gravis

Multiple Sclerosis

Multifocal motor neuropathy

Neuromyotonia or Isaac's syndrome

Neutropenia see Autoimmune Neutropenia

Oophoritis

Opsoclonus-myoclonus syndrome

orchitis

Paraneoplastic neurologic disorders

Pemphigus vulgaris

Pemphigus follaceus PF)

Pemphigoid gestationis (PG)

Pernicious anemia

Paraneoplastic pemphigus (PNP)

Polyangiitis - see Microscopic polyangiitis

Polyarteritis nodosa (PAN)

Polymyositis/Dermatomyositis

Polymyalgia Rheumatica

Primary biliary Cirrhosis (PBC) also called Hanot Syndrome

Primary sclerosing cholangitis (PSC)

Raynaud's phenomenon

Recoverin-associated retinopathy(RAR) see Retinopathy

Reactive Arthritis formerly known as Reiter's syndrome,

Retinopathy

Rheumatoid arthritis (RA)

Sarcoidosis

Sclerosing cholangitis see Primary Sclerosing Cholangitis

Sjogren's syndrome

Systemic necrotizing vascolitides

Stiff man syndrome or Moersch-Woltmann syndrome

Systemic lupus erythematosus

Systemic sclerosis (scleroderma)

Temporal arteritis or giant cell arteritis (GCV)

Takayasu's arteritis

Thromboangiitis obliterans or Buerger's disease

Thyroiditis with hypothyroidism

Thyroiditis with hyperthyroidism

Type I autoimmune polyglandular syndrome (PAS)

Type II autoimmune polyglandular syndrome

Vasculitis

Wegener's granulomatosis

[0071] In an example of any aspect, configuration, concept or embodiment, the human is suffering from uveitis. For example, the uveitis is non-infectious and/or autoimmune in nature, i.e. is non-infectious uveitis or is autoimmune uveitis. For example, the non-infectious/autoimmune uveitis is caused by and/or is associated with Behçet disease, Fuchs heterochromic iridocyclitis, granulomatosis with polyangiitis, HLA-B27 related uveitis, juvenile idiopathic arthritis, sarcoidosis, spondyloarthritis, sympathetic ophthalmia, tubulointerstitial nephritis or uveitis syndrome. In an example, the uveitis is systemic in nature, i.e. is systemic uveitis. For example, the systemic uveitis is caused by and/or is associated with ankylosing spondylitis, Behçet's disease, chronic granulomatous disease, enthesitis, inflammatory bowel disease, juvenile rheumatoid arthritis, Kawasaki's disease, multiple sclerosis, polyarteritis nodosa, psoriatic arthritis, reactive arthritis, sarcoidosis, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome or Whipple's disease.

[0072] In an example of any aspect, configuration, concept or embodiment, the human is suffering from pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome or non-infectious scleritis. In an example, the human is suffering from pyoderma gangrenosum. In an example, the human is suffering from giant cell arteritis. In an example, the human is suffering from Schnitzler syndrome. In an example, the human is suffering from non-infectious scleritis.

[0073] In an example of any aspect, configuration, concept or embodiment, the human is suffering from a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD. In another embodiment, the human is suffering from or is at risk from multivisceral organ transplant rejection.
13. An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

[0074] In an example of any aspect, configuration, concept or embodiment, competition is determined by surface plasmon resonance (SPR), such techniques being readily apparent to the skilled person. SPR can be carried out using Biacore™, Proteon™ or another standard SPR technique. Such competition may be due, for example, to the antibodies/fragments binding to identical or overlapping epitopes of hOX40L. In an example of any aspect, configuration, concept or embodiment, competition is determined by ELISA, such techniques being readily apparent to the skilled person. In an example of any aspect, configuration, concept or embodiment, competition is determined by homogenous time resolved fluorescence (HTRF), such techniques being readily apparent to the skilled person. In an example of any aspect, configuration, concept or embodiment, competition is determined by fluorescence activated cell sorting (FACS), such techniques being readily apparent to the skilled person. In one aspect, the HTRF, ELISA and/or FACS methods are carried out as described in the Examples hereinbelow.

[0075] 14. The antibody or fragment of aspect 13, wherein the antibody or fragment is according to any one of aspects 1 to 12.

[0076] 15. The antibody or fragment of any preceding aspect, comprising lambda light chain variable domains (optionally which are human).

[0077] In an example of any aspect, configuration, concept or embodiment of the present invention, the variable domains of the antibody or fragment are human or humanised. Additionally, optionally the antibody or fragment further comprises human or humanised constant regions (e.g., human Fc and/or human CL). In an example of any aspect of the present invention, the variable domains of the antibody or fragment are produced by a transgenic animal (e.g., a rodent, mouse, rat, rabbit, chicken, sheep, Camelid or shark). In an example of any aspect of the present invention, the variable domains of the antibody or fragment are produced or identified by phage display, ribosome display or yeast display.

[0078] In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is recombinant.

[0079] In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is produced by a recombinant mammalian, bacterial, insect, plant or yeast cell. In an example, the mammalian cell is a CHO or HEK293 cell and the antibody or fragment comprises CHO or HEK293 cell glycosylation.

[0080] In an example of any aspect, configuration, concept or embodiment of the present invention, the antibody or fragment is isolated.

[0081] 16. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR1 sequence selected from the group consisting of the HCDR1 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0082] 17. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR2 sequence selected from the group consisting of the HCDR2 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0083] 18. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises a HCDR3 sequence selected from the group consisting of the HCDR3 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0084] 19. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises (i) the CDR1 and 2, (ii) CDR1 and 3, (iii) CDR2 and 3 or (iv) CDR1, 2 and 3 sequences:

1. a. recited in (a) of aspects 16-18, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. recited in (b) of aspects 16-18, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
3. c. recited in (c) of aspects 16-18, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; or
4. d. recited in (d) of aspects 16-18, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

[0085] 20. The antibody or fragment of any preceding aspect, comprising a VH domain which comprises an amino acid sequence selected from the group consisting of the VH amino acid sequences in the sequence listing.

[0086] In an aspect, the invention provides an anti-hOX40L antibody or fragment (optionally according to any other aspect recited herein) comprising a VH domain which comprises an amino acid sequence selected from the group consisting of the VH amino acid sequences in the sequence listing. In an aspect, the VH domain comprises an amino acid sequence selected from Seq ID No:2, Seq ID No:34, Seq ID No:66, Seq ID No:94, Seq ID No:122, Seq ID No:124, Seq ID NO:126, Seq ID No:128, Seq ID No:132 or Seq ID No:134.

[0087] In another example of the invention, the antibody or fragment comprises a VH domain amino acid sequence set out in the sequence listing below. Additionally or alternatively, the antibody or fragment comprises a HCDR1 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42). Additionally or alternatively, the antibody or fragment comprises a HCDR2 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44). Additionally or alternatively, the antibody or fragment comprises a HCDR3 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46).

[0088] In an example of the invention, the antibody or fragment comprises a VL domain amino acid sequence set out in the sequence listing below. Additionally or alternatively, the antibody or fragment comprises a LCDR1 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56). Additionally or alternatively, the antibody or fragment comprises a LCDR2 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58). Additionally or alternatively, the antibody or fragment comprises a LCDR3 domain amino acid sequence set out in the sequence listing below (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60).

[0089] In an example of any aspect herein, the antibody or fragment comprises a heavy chain comprising a constant region selected from the group consisting of the heavy chain constant region SEQ ID NOs in the sequence listing (i.e. any of Seq ID Nos: 126, 128, 132, or 134, in particular the constant region of Seq ID No: 128); and optionally a VH domain as recited in aspect 19 or 20. In an example, the antibody or fragment comprises two copies of such a heavy chain. In another example, the heavy chain comprise a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region (e.g., Fc), in particular a mouse constant region.

[0090] In an example of any aspect herein, the antibody or fragment comprises a heavy chain comprising a gamma (e.g., human gamma) constant region, e.g., a human gamma1 constant region. In another example of any aspect herein, the antibody of fragment comprises a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation (i.e. where the wild type leucine residue is mutated to a glutamic acid residue). In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4 comprising both the Leu235Glu mutation and the Ser228Pro mutation. This heavy chain constant region is referred to as "IgG4-PE" herein.

[0091] In an example of any aspect herein, the antibody or fragment is chimaeric, e.g., it comprises human variable domains and non-human (e.g., rodent, mouse or rat, such as mouse) constant regions.

[0092] 21. The antibody or fragment of any one of aspects 16 to 20, comprising first and second copies of said VH domain.

[0093] 22. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR1 sequence selected from the group consisting of the LCDR1 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0094] 23. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR2 sequence selected from the group consisting of the LCDR2 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0095] 24. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises a LCDR3 sequence selected from the group consisting of the LCDR3 of:

1. a. 02D10, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. 10A07, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
3. c. 09H04, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; and
4. d. 19H01, and wherein the antibody or fragment competes with 19H01for binding to said hOX40L.

[0096] 25. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises (i) the CDR1 and 2, (ii) CDR1 and 3, (iii) CDR2 and 3 or (iv) CDR1, 2 and 3 sequences:

1. a. recited in (a) of aspects 22-24, and wherein the antibody or fragment competes with 02D10 for binding to said hOX40L;
2. b. recited in (b) of aspects 22-24, and wherein the antibody or fragment competes with 10A07 for binding to said hOX40L;
3. c. recited in (c) of aspects 22-24, and wherein the antibody or fragment competes with 09H04 for binding to said hOX40L; or

4. d. recited in (d) of aspects 22-24, and wherein the antibody or fragment competes with 19H01 for binding to said hOX40L.

[0097] 26. The antibody or fragment of any preceding aspect, comprising a VL domain which comprises an amino acid sequence selected from the group consisting of the VL amino acid sequences in the sequence listing.

[0098] In an aspect of the invention, there is provided an anti-hOX40L antibody or fragment (optionally according to any other aspect herein), comprising a VL domain which comprises an amino acid sequence selected from the group consisting of the VL amino acid sequences in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80 or Seq ID No: 108, in particular Seq ID No:48).

[0099] In an example of any aspect herein, the antibody or fragment comprises a light chain (e.g., lambda light chain) comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No: 136, Seq ID No: 138, Seq ID No: 140, Seq ID No: 142, Seq ID No: 144, Seq ID No:146, Seq ID No: 148, Seq ID No: 152, Seq ID No: 154, Seq ID No: 156, Seq ID No: 158, Seq ID No: 160, Seq ID No: 162, Seq ID No: 164 or Seq ID No: 166); and optionally a VL domain (e.g., lambda VL) as recited in aspect 25 or 26. In an example, the antibody or fragment comprises two copies of such a light chain (optionally also two copies of the heavy chain described above). In another example, the light chain comprise a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region.

[0100] In an example of any aspect herein, the antibody or fragment comprises a light chain (e.g., kappa light chain) comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No: 136, Seq ID No:138, Seq ID No:140, Seq ID No:142, Seq ID No:144, Seq ID No:146, Seq ID No:148, Seq ID No: 152, Seq ID No: 154, Seq ID No: 156, Seq ID No: 158, Seq ID No: 160, Seq ID No: 162, Seq ID No: 164 or Seq ID No: 166); and optionally a VL domain (e.g., kappa VL) as recited in aspect 25 or 26. In an example, the antibody or fragment comprises two copies of such a light chain (optionally also two copies of the heavy chain described above). In another example, the light chain comprise a rodent, rat, mouse, human, rabbit, chicken, Camelid, sheep, bovine, non-human primate or shark constant region.

[0101] In an example, the antibody or fragment comprises a lambda light chain comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. Seq ID No:146, Seq ID No:148, Seq ID No:152, Seq ID No: 154, Seq ID No: 156, Seq ID No: 158, Seq ID No: 160, Seq ID No:162, Seq ID No:164 or Seq ID No: 166); and optionally a lambda VL domain.

[0102] In an example, the antibody or fragment comprises a kappa light chain comprising a constant region selected from the group consisting of the light chain constant region sequences in the sequence listing (i.e. i.e. Seq ID No:136, Seq ID No:138, Seq ID No: 140, Seq ID No:142 or Seq ID No:144); and optionally a kappa VL domain.

[0103] In an example, the VL domains of the antibody or fragment are lambda Light chain variable domains. In an example, the VL domains of the antibody or fragment are kappa Light chain variable domains.

[0104] 27. The antibody or fragment of any one of aspects 22 to 26, comprising first and second copies of said VL domain.

[0105] 28. The antibody or fragment of any preceding aspect, wherein the hOX40L is human cell surface-expressed hOX40L, e.g., on endothelial cells (e.g., an airway or GI tract endothelial cell).

[0106] In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

[0107] 29. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases the proliferation of human PBMCs or T-cells in the presence of hOX40L in an *in vitro* mixed lymphocyte reaction (MLR) assay by at least 20, 30, 40, 50 or 60% compared to the proliferation of human PBMCs or T-cells in the presence of hOX40L in an *in vitro* control MLR assay in the absence of an antibody that is specific for hOX40L. An illustration of a suitable assay is provided in the examples below.

[0108] 30. The antibody or fragment of aspect 29, wherein the hOX40L in the assay is surface-expressed on human dendritic cells (DC cells).

[0109] An illustration of a suitable assay is provided in the examples below.

[0110] 31. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases NF-κB activity in human HT-1080 cells expressing hOX40 receptor *in vitro* in the presence of hOX40L.

[0111] In an example, the antibody or fragment the decrease in NF-κB activity is determined by detecting a decrease in IL-8 secretion by HT-1080 cells (ATCC® CCL-121) (optionally transfected with hOX40 Receptor, in the presence of hOX40) *in vitro*.

[0112] 32. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-8 secretion from human HT-1080 cells expressing hOX40 receptor *in vitro* in the presence of hOX40L.

[0113] 33. The antibody or fragment of aspect 32, wherein the antibody or fragment decreases IL-8 secretion by at least 20, 30, 40, 50 or 60% compared to the IL-8 production by HT-1080 cells expressing hOX40 receptor *in vitro* in the presence of hOX40L in the absence of an antibody that is specific for hOX40L.

[0114] 34. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases hOX40L-stimulated human T-cell proliferation *in vitro*.

[0115] 35. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases hOX40L-stimulated IL-2 secretion from human T-cells *in vitro*.

[0116] 36. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases cytokine secretion mediated by the interaction of human dendritic cells (DC cells) with human T-cells, wherein the cytokine is selected from one, two, more or all of TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,IL-10, IL-13, IL-17, RANTES and interferon gamma.

[0117] This can be assessed, for example, using a MLR *in vitro* assay (e.g., a DC/T-cell MLR *in vitro* assay). An illustration of a suitable assay is provided in the examples below.

[0118] In an example, the DC cells are mismatched to the T-cells, e.g., MHC mis-matched, as is possible for example when the DC cells are from a human that is different from the T-cell human source. In an example, the DC cells are produced by *in vitro* induction of human monocytes with GMCSF and IL-4.

[0119] 37. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases interferon gamma secretion by at least 20, 30, 40, 50 or 60% compared to the production of interferon gamma mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

[0120] 38. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases TNF alpha secretion by at least 20, 30, 40, 50 or 60% compared to the production of TNF alpha mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

[0121] 39. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-2 secretion by at least 10, 20, 30, 40, 50 or 60% compared to the production of IL-2 mediated by the interaction of human dendritic cells (DC cells) with human T-cells in the absence of an antibody that is specific for hOX40L.

[0122] 40. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases cytokine secretion (e.g., leukocyte cytokine secretion) in a human peripheral blood mononuclear cell (PBMC) mixed lymphocyte (MLR) assay, wherein the cytokine is selected from one, two, more or all of TNF alpha, IL-2, IL-4, IL-3, IL-6, IL-8, IL-10, IL-17, RANTES and interferon gamma.

[0123] 41. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases interferon gamma secretion by at least 20, 30, 40, 50 or 60% compared to the production of interferon gamma in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

[0124] In one embodiment, the comparison is to the production of interferon gamma in a human PBMC MLR assay in the absence of antibody.

[0125] 42. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases TNF alpha secretion by at least 20, 30, 40, 50 or 60% compared to the production of TNF alpha in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

[0126] 43. The antibody or fragment of any preceding aspect, wherein the antibody or fragment decreases IL-2 secretion by at least 10, 20, 30, 40, 50 or 60% compared to the production of IL-2 in a human PBMC MLR assay in the absence of an antibody that is specific for hOX40L.

[0127] 44. The antibody or fragment of any one of aspects 36 to 43, wherein the cells are primary cells.

[0128] A "primary cell" refers to a cell in a human or such a cell that has been taken from the patient for binding to the antibody or fragment of the invention *in vitro* (as may be useful, for example, in a method of diagnosis of OX40L status or disease/condition status in the human). Primary cells as used herein are not cells of human cell lines, which typically have undergone many cultures *in vitro*. The ability of the antibody or fragment of the invention to specifically inhibit hOX40L binding to receptor in this embodiment is advantageous since it provides a direct indication of the utility for addressing cells in human patients suffering or at risk of a hOX40L-mediated disease or condition.

[0129] 45. The antibody or fragment of any preceding aspect, wherein the antibody or fragment inhibits binding of hOX40L to a hOX40L receptor (e.g., hOX40) with an IC_{50} of 1×10^{-8} or less in a HTRF (homogenous time resolved fluorescence) assay.

[0130] In an example, the IC_{50} is in the range from 1×10^{-8} to 1×10^{-11} or in the range from 1×10^{-9} to 1×10^{-10}.

[0131] 46. A pharmaceutical composition for treating and/or preventing a OX40L-mediated condition or disease, the composition comprising an antibody or fragment of any preceding aspect and a diluent, excipient or carrier; and optionally further comprising an anti-inflammatory drug.

[0132] In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies.

[0133] 47. A pharmaceutical composition or kit for treating and/or preventing a OX40L-mediated condition or disease, the composition or kit comprising an antibody or fragment of the invention (and optionally an anti-inflammatory drug) optionally in combination with a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

[0134] 48. A nucleic acid that encodes the HCDR3 of an antibody recited in any one of aspects 1 to 45.

[0135] In one embodiment, the HCDRs herein are according to Kabat nomenclature. In another embodiment, the HCDRs herein are according to the IMGT nomenclature.

[0136] 49. The nucleic acid of aspect 48 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR3 sequence in the sequence listing.

[0137] In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR3 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR3 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

[0138] In another embodiment, there is provided the nucleic acid of aspect 48 comprising a nucleotide sequence that is 100% identical to a HCDR3 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

[0139] Amino acid substitutions include alterations in which an amino acid is replaced with a different naturally-occurring amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally occurring amino acid of similar character either in relation to polarity, side chain functionality or size. Such conservative substitutions are well known in the art. Substitutions encompassed by the present invention may also be "non-conservative", in which an amino acid residue which is present in a peptide is substituted with an amino acid having different properties, such as naturally-occurring amino acid from a different group (e.g., substituting a charged or hydrophobic amino; acid with alanine), or alternatively, in which a naturally-occurring amino acid is substituted with a non- conventional amino acid.

[0140] Additionally or alternatively, there is provided the nucleic acid of aspect 49 comprising a nucleotide sequence that is 100% identical to a HCDR3 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

[0141] 50. A nucleic acid that encodes the HCDR2 of an antibody recited in any one of aspects 1 to 45; optionally wherein the nucleic acid is according to aspect 48 or 49.

[0142] 51. The nucleic acid of aspect 50 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR2 sequence in the sequence listing.

[0143] In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR2 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR2 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

[0144] In another embodiment, there is provided the nucleic acid of aspect 51 comprising a nucleotide sequence that is 100% identical to a HCDR2 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

[0145] Additionally or alternatively, there is provided the nucleic acid of aspect 50 comprising a nucleotide sequence that is 100% identical to a HCDR2 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

[0146] 52. A nucleic acid that encodes the HCDR1 of an antibody recited in any one of aspects 1 to 45; optionally wherein the nucleic acid is according to any one of aspects 48 to 51.

[0147] 53. The nucleic acid of aspect 52 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a HCDR1 sequence in the sequence listing.

[0148] In an aspect, the invention provides a nucleic acid comprising a nucleotide sequence that encodes a VH domain of an anti-hOX40L antibody, wherein the nucleotide sequence comprises a HCDR1 sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical or is 100% identical to a HCDR1 sequence in the sequence listing. Optionally, the antibody is according to any other aspect herein.

[0149] In another embodiment, there is provided the nucleic acid of aspect 52 comprising a nucleotide sequence that is 100% identical to a HCDR1 sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

[0150] Additionally or alternatively, there is provided the nucleic acid of aspect 52 comprising a nucleotide sequence that is 100% identical to a HCDR1 sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

[0151] 54. A nucleic acid that encodes a VH domain and/or a VL domain of an antibody recited in any one of aspects 1 to 45.

[0152] 55. The nucleic acid of aspect 54 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a VH domain nucleotide sequence in the sequence listing.

[0153] In another embodiment, there is provided the nucleic acid of aspect 54 comprising a nucleotide sequence that is 100% identical to a VH domain nucleotide sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

[0154] Additionally or alternatively, there is provided the nucleic acid of aspect 54 comprising a nucleotide sequence that is 100% identical to a VH domain nucleotide sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

[0155] 56. The nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is at least 80, 85, 90, 95, 96, 97, 98 or 99% identical to or is 100% identical to a VL domain nucleotide sequence in the sequence listing.

[0156] In another embodiment, there is provided the nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is 100% identical to a VL domain nucleotide sequence in the sequence listing, except for 1, 2 or 3 nucleotide substitutions, wherein each substitution produces no amino acid change or produces a conservative amino acid change (i.e., the nucleotide substitution is a synonymous substitution) in the corresponding protein sequence. The skilled person will be familiar with conservative amino acid changes.

[0157] Additionally or alternatively, there is provided the nucleic acid of aspect 54 or 55 comprising a nucleotide sequence that is 100% identical to a VL domain nucleotide sequence in the sequence listing, except for 1, 2, 3, 4, 5, 6 or 7 synonymous nucleotide substitutions and no, 1, 2 or 3 nucleotide substitutions that produce conservative amino acid changes in the corresponding protein sequence.

[0158] 57. A nucleic acid that encodes a heavy chain or a light chain of an antibody recited in any one of aspects 1 to 45.

[0159] 58. The nucleic acid of aspect 57, comprising a nucleotide sequence as recited in any one of aspects 48 to 56.

[0160] 59. A vector (e.g., a mammalian expression vector) comprising the nucleic acid of any one of aspects 48 to 58; optionally wherein the vector is a CHO or HEK293 vector. In an example, the vector is a yeast vector, e.g., a *Saccharomyces* or *Pichia* vector.

[0161] 60. A host comprising the nucleic acid of any one of aspects 48 to 58 or the vector of aspect 59. In an example, the host is a mammalian (e.g., human, e.g., CHO or HEK293) cell line or a yeast or bacterial cell line.

[0162] 61. Use of an antibody or a fragment thereof, that specifically binds to hOX40L in the manufacture of a medicament for administration to a human, for treating or preventing a hOX40L-mediated disease or condition in the human by decreasing one, more or all of

1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
2. b. the proliferation of leukocytes of the human; and
3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L.

[0163] The features of any of the previous aspects, configurations, concepts, examples or embodiments optionally apply *mutatis mutandis* to this use.

[0164] In an example, the human is suffering from or at risk of asthma and the antibody or fragment is for decreasing IgE in the human, thereby treating, preventing or reducing asthma in the human.

[0165] 62. A method of treating or preventing a hOX40L-mediated disease or condition in a human by decreasing one, more or all of

1. a. secretion of a cytokine selected from TNF alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, RANTES and interferon gamma in the human;
2. b. the proliferation of leukocytes of the human; and
3. c. binding of hOX40 receptor expressed by human T-cells with endothelial cell expressed hOX40L;

wherein the method comprises administering to said human a therapeutically effective amount of an antibody or fragment that specifically binds to hOX40L.

[0166] The features of any of the previous aspects, examples or embodiments optionally apply *mutatis mutandis* to this method.

[0167] The method of the invention treats or prevents said disease or condition in the human. A "therapeutically effective amount" of the antibody or fragment is that amount (administered in one or several doses, which may be spaced in time, e.g., substantially monthly administration) that is effective to bring about said treatment or prevention. This will be readily apparent to the skilled person and may vary according to the particular human patient and disease or condition being addressed.

[0168] In an example, the human is suffering from or at risk of asthma and the antibody or fragment decreases IgE in the human, thereby treating, preventing or reducing asthma in the human.

[0169] 63. The method or use of aspect 61 or 62, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the proliferation of T-cells in said human.

[0170] 64. The method or use of any one of aspects 61 to 63, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by antagonising the interaction between hOX40L and leukocytes of the human, wherein the proliferation of leukocytes is decreased.

[0171] 65. The method or use of any one of aspects 61 to 64, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the proliferation of leukocytes of the human by antagonising the OX40L/OX40L receptor interaction mediated by T-cells in said human.

[0172] 66. The method or use of any one of aspects 61 to 65, for treating or preventing said hOX40L-mediated disease, condition or epithelial cell damage in said human by decreasing the secretion of IL-8 cytokine in the human.

[0173] 67. The method of aspect 66, for treating or preventing said disease, condition or epithelial cell damage by decreasing the secretion of said IL-8 mediated by the interaction of dendritic cells (DC cells) with T-cells in the human.

[0174] 68. The method or use of any one of aspects 61 to 67, wherein gastrointestinal cell, colon cell, intestinal cell or airway (e.g., lung) cell damage is a symptom or cause of said disease or condition in humans.

[0175] In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells, ocular cells and airway (e.g., lung) epithelial cells. In another embodiment, the epithelial cells comprise cells selected from the group consisting of gastrointestinal cells, colon cells, intestinal cells and ocular cells. In a further embodiment, the epithelial cells comprise ocular cells.

[0176] 69. The method or use of any one of aspects 61 to 68, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, diabetes or airway inflammation in the human.

[0177] 69a. The method or use of any one of aspects 61 to 68, wherein the human is suffering from or at risk of an inflammatory bowel disease (IBD), allogeneic transplant rejection, graft-versus-host disease (GvHD), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation and said method treats or prevents IBD, allogeneic transplant rejection, GvHD, uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes or airway inflammation in the human.

[0178] In any aspect, configuration, concept or embodiment, the human is suffering from or at risk of a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

[0179] 70. The method or use of any one of aspects 61 to 69a, wherein the antibody or fragment is according to any one of aspects 1 to 45 or any example, configuration, concept, aspect or embodiment described herein.

[0180] 71. The antibody, fragment, composition, kit, method or use of any preceding aspect, for treating or preventing an inflammatory or autoimmune disease or condition in a human or for reducing or preventing angiogenesis in a human.

[0181] 72. The antibody, fragment, composition, kit, method or use of any preceding aspect, wherein the disease or condition is selected from the group consisting of an inflammatory bowel disease (IBD), Chrohn's disease, rheumatoid arthritis, psoriasis, bronchiolitis, gingivitis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), asthma, adult respiratory distress syndrome (ARDS), septic shock, ulcerative colitis, Sjorgen's syndrome, airway inflammation, systemic lupus erythematosus (SLE), diabetes, contact hypersensitivity, multiple sclerosis and atherosclerosis.

[0182] 72a. The antibody, fragment, composition, kit, method or use of any preceding aspect, wherein the disease or condition is selected from the group consisting of an inflammatory bowel disease (IBD), Chrohn's disease, rheumatoid arthritis, psoriasis, bronchiolitis, gingivitis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), asthma, adult respiratory distress syndrome (ARDS), septic shock, ulcerative colitis, Sjorgen's syndrome, airway inflammation, systemic lupus erythematosus (SLE), uveitis, pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis, diabetes, contact hypersensitivity, multiple sclerosis and atherosclerosis.

[0183] In any aspect, configuration, concept or embodiment, the human is suffering from or at risk of a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

[0184] In an example, the disease or condition is an OX40L-mediated disease or condition disclosed in US7812133 or EP1791869.

[0185] In an example, the disease or condition is an inflammatory or autoimmune disease or condition. In an example, the disease or condition is transplant rejection.

[0186] As used herein, inflammatory disease or condition refers to pathological states resulting in inflammation, for example caused by neutrophil chemotaxis. Examples of such disorders include inflammatory skin diseases including psoriasis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); ischemic reperfusion; adult respiratory distress syndrome; dermatitis; meningitis; encephalitis; uveitis; autoimmune diseases such as rheumatoid arthritis, Sjorgen's syndrome, vasculitis; diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma; alcoholic hepatitis, bacterial pneumonia, antigen-antibody complex mediated diseases; inflammations of the lung, including pleurisy, alveolitis, vasculitis, pneumonia, chronic bronchitis, bronchiectasis, and cystic fibrosis; etc. The preferred indications are bacterial pneumonia and inflammatory bowel disease such as ulcerative colitis. The invention is thus in an example provided for treating or preventing any one or more of such conditions.

[0187] In an example, the disease or condition is cancer.

[0188] In an example, the disease is uveitis, such as systemic uveitis or autoimmune/non-infectious uveitis.

[0189] 73. An antibody or a fragment thereof, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

[0190] The features of the antibodies of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply *mutatis mutandis* to these anitbodies, e.g the antibody may be a human antibody or chimeric antibody having functional features as described herein. Competition may be determined as described in any aspect, embodiment, example, concept or configuration described herein, e.g. as determined by SPR, ELISA, HTRF or FACS.

[0191] In one embodiment, the antibody or fragment competes with the variable regions of 02D10 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 34 and the light chain variable region of SEQ ID No:48). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:62 and a light chain amino acid sequence of SEQ ID No:64.

[0192] In another embodiment, the antibody or fragment additionally or alternatively competes with 10A7. In one embodiment, the antibody or fragment competes with the variable regions of 10A7 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 2 and the light chain variable region of SEQ ID No:16). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:30 and a light chain amino acid sequence of SEQ ID No:32.

[0193] In one embodiment, the amino acid is any naturally-occurring amino acid.

[0194] 74. The antibody or fragment according to aspect 73, where X is a neutral amino acid, optionally P or G.

[0195] In an embodiment, X is P or G. In an embodiment, X is selected from P, N, A or G. In another embodiment, X is selected from P, G or N. In another embodiment, X is selected from P, G or A.

[0196] 75. An antibody or a fragment thereof, optionally according to aspect 73 or 74, that specifically binds to hOX40L and competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises the HCDR3 sequence of SEQ ID NO:40 or 46 or the HCDR3 sequence of SEQ ID NO:40 or 46 comprising less than 5 amino acid substitutions.

[0197] The features of the antibodies of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply *mutatis mutandis* to these antibodies, e.g the antibody may be a human antibody or chimeric antibody having functional features as described herein. Competition may be determined as described in any aspect, embodiment, concept, example or configuration described herein, e.g. as determined by SPR, ELISA, HTRF or FACS.

[0198] In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR3 sequence of SEQ ID NO:40 or 46 comprises less than 2 amino acid substitutions (i.e. one substitution).

[0199] In one embodiment, the antibody or fragment competes with the variable regions of 02D10 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 34 and the light chain variable region of SEQ ID No:48). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:62 and a light chain amino acid sequence of SEQ ID No:64.

[0200] In another embodiment, the antibody or fragment additionally or alternatively competes with 10A7. In one embodiment, the antibody or fragment competes with the variable regions of 10A7 (e.g. competes with an antibody comprising the heavy chain variable region of SEQ ID No: 2 and the light chain variable region of SEQ ID No:16). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:30 and a light chain amino acid sequence of SEQ ID No:32.

[0201] 76. An antibody or fragment according to any one of aspects 73 to 75, the VH domain comprising a HCDR3 of from 16 to 27 amino acids and which is derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

[0202] In an embodiment, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02, IGHJ6*03 and IGHJ6*04. In another embodiment, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02 and IGHJ6*04. In another embodiment, the JH gene segment is IGHJ6*02.

[0203] In a further embodiment, the human VH gene segment is IGHV3-23, for example selected from IGHV3-23*01, IGHV3-23*02, IGHV3-23*03, IGHV3-23*04 or IGHV3-23*05. In another embodiment, the human VH gene segment is IGHV3-23*01 or IGHV3-23*04, in particular IGHV3-23*04.

[0204] In a further embodiment, the human DH gene segment is IGHD3-10, for example selected from IGHD3-10*01 or IGHD3-10*02. In one embodiment, the human DH gene segment is IGHD3-10*01. In one embodiment, the human DH gene segment is IGHD3-10*02.

[0205] 77. The antibody or fragment according to any one of aspects 73 to 76, the VH domain comprising the HCDR1 sequence of SEQ ID NO:36 or 42 or the HCDR1 sequence of SEQ ID NO:36 or 42 comprising less than 4 amino acid substitutions.

[0206] In an embodiment, the HCDR1 sequence of SEQ ID NO:36 or 42 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR1 sequence of SEQ ID NO:36 or 42 comprises less than 2 amino acid substitutions (i.e. one substitution).

[0207] 78. The antibody or fragment according to any one of aspects 73 to 77, the VH domain comprising the HCDR2 sequence of SEQ ID NO:38 or 44, or the HCDR2 sequence of SEQ ID NO:38 or 44 comprising less than 5 amino acid substitutions.

[0208] In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the HCDR2 sequence of SEQ ID NO:38 or 44 comprises less than 2 amino acid substitutions (i.e. one substitution).

[0209] 79. The antibody or fragment according to any one of aspects 73 to 78, the VH domain comprising an amino acid sequence of SEQ ID NO: 34, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%) identical to SEQ ID NO:34.

[0210] In an embodiment, the heavy chain variable domain amino acid sequence is at least 85%, at least 90%, at least 95%, least 96% at least 97% at least 98% or at least 99% identical to SEQ ID NO:34.

[0211] 80. The antibody or fragment according to any one of aspects 73 to 79 comprising first and second copies of said VH domain.

[0212] 81. The antibody or fragment according to any one of aspects 73 to 80, comprising a VL domain which comprises the LCDR1 sequence of SEQ ID NO:54 or 60, or the LCRD3 sequence of SEQ ID NO:54 or 60 comprising less than 5 amino acid substitutions.

[0213] In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 4 amino acid substitutions (i.e. 3 or fewer). In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the LCRD3 sequence of SEQ ID NO:54 or 60 comprises less than 2 amino acid substitutions (i.e. one substitution).

[0214] 82. The antibody or fragment according to any one of aspects 73 to 81, comprising a or said VL domain, which VL domain comprises the LCDR2 sequence of SEQ ID NO:52 or 58, or the LCRD2 sequence of SEQ ID NO:52 or 58 comprising less than 2 amino acid substitutions.

[0215] 83. The antibody or fragment according to any one of aspects 73 to 82, comprising a or said VL domain, which VL domain comprises the LCDR1 sequence of SEQ ID NO:54 or 60, or the LCRD1 sequence of SEQ ID NO:54 or 60 comprising less than 4 amino acid substitutions.

[0216] In an embodiment, the LCDR1 sequence of SEQ ID NO:54 or 60 comprises less than 3 amino acid substitutions (i.e. 2 or 1 substitutions). In an embodiment, the LCDR1 sequence of SEQ ID NO:54 or 60 comprises less than 2 amino acid substitutions (i.e. one substitution).

[0217] 84. The antibody or fragment according to any one of aspects 73 to 83, comprising a or said VL domain, which VL domain comprises an amino acid sequence of SEQ ID NOs: 48, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%) identical to SEQ ID NO:48.

[0218] In an embodiment, the light chain variable domain amino acid sequence is at least 85%, at least 90%, at least 95%, least 96% at least 97% at least 98% or at least 99% identical to SEQ ID NO:48.

[0219] 85. The antibody or fragment according to any one of aspects 81 to 84, comprising first and second copies of said VL domain.

[0220] 86. The antibody or fragment according to any one of aspects 81 to 85, wherein the antibody or fragment comprises a kappa light chain.

[0221] In another embodiment, the VL domain is a kappa VL domain. In an embodiment, the kappa VL domain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39. In another embodiment, the VL gene segment is IGKV1D-39*01.

[0222] In a further embodiment, the human JL gene segment is IGKJ1 or IGKJ3. In another embodiment, the JL gene segment is IGKJ1*01. In another embodiment, the JL gene segment is IGKJ3*01.

[0223] 87. The antibody or fragment according to any one of aspects 75 to 86 wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

1. 1) Alanine (A), Serine (S), Threonine (T);
2. 2) Aspartic acid (D), Glutamic acid (E);
3. 3) Asparagine (N), Glutamine (Q);
4. 4) Arginine (R), Lysine (K);
5. 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
6. 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W)

[0224] In an embodiment, the conservative amino acid substitutions are as described herein. For example, the substitution may be of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P. In another embodiment, the conservative amino acid substitutions may be wherein Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V.

[0225] 88. The antibody or fragment according to any one of aspects 73 to 87, wherein the antibody or fragment comprises a constant region, e.g. an IgG4 constant region, optionally wherein the constant region is IgG4-PE (Seq ID No: 128).

[0226] In another example of any aspect herein, the antibody of fragment comprises a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation (i.e. where the wild type leucine residue is mutated to a glutamic acid residue). In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability.

[0227] 89. The antibody according to any one of aspects 73 to 88, wherein the antibody comprises a heavy chain and a light chain, the heavy chain amino acid sequence consisting of the sequence of SEQ ID No:62 and the light chain amino acid sequence consisting of the sequence of SEQ ID No:64.

[0228] 90. An antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 for use in treating or preventing a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

[0229] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply *mutatis mutandis* to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this use.

[0230] 91. Use of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplantfnost rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

[0231] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply *mutatis mutandis* to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this use.

[0232] 92. A method of treating or preventing a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD in a human, comprising administering to said human a therapeutically effective amount of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

[0233] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments as described herein optionally apply *mutatis mutandis* to this method. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this method.

[0234] 93. The antibody or fragment according to aspect 90, the use according to aspect 91, or the method according to aspect 92, wherein the hOX40L-mediated disease or condition is GvHD.

[0235] In another embodiment, the antibody or fragment is capable of treating or preventing GvHD.

[0236] 94. The antibody or fragment, the use or the method according to any one of aspects 90 to 93, wherein the antibody is administered prophylactically.

[0237] In an embodiment, the prophylaxis prevents the onset of the disease or condition or of the symptoms of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening, or onset, of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening of the disease or condition.

[0238] In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

[0239] In another embodiment, said antibody is administered 1-4 days before transplant, e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

[0240] In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine *et al*, *"A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study"*, Lancet Haematol 2015; 2:e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

[0241] 95. A human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L for treating or preventing a hOX40L-mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD (e.g. wherein the antibody is for the prevention of GvHD).

[0242] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply *mutatis mutandis* to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this use.

[0243] 96. Use of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L in the manufacture of a medicament for administration to a human for treating or preventing a hOX40L mediated disease or condition in the human selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD.

[0244] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply *mutatis mutandis* to this use. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this use.

[0245] 97. A method of treating or preventing a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis or atherosclerosis, in particular GvHD in a human, comprising administering to said human a therapeutically effective amount of a human antibody or fragment thereof comprising a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02), which specifically binds to hOX40L, wherein the hOX40L mediated disease or condition is thereby treated or prevented.

[0246] The features of the antibodies, and the hOX40L-mediated disease of any of the aspects, configurations, concepts, examples or embodiments optionally apply *mutatis mutandis* to this method. Any of the compositions, dosing schedules or modes of administration as described in any aspect, configuration, concept, example or embodiment herein optionally apply *mutatis mutandis* to this method.

[0247] In an embodiment of any one of aspects 95 to 97, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02, IGHJ6*03 and IGHJ6*04. In another embodiment of any one of aspects 95 to 97, the human JH gene segment is selected from IGHJ6*01, IGHJ6*02 and IGHJ6*04. In another embodiment of any one of aspects 95 to 97, the JH gene segment is IGHJ6*02.

[0248] In a further embodiment of any one of aspects 95 to 97, the human VH gene segment is IGHV3-23, for example selected from IGHV3-23*01, IGHV3-23*02, IGHV3-23*03, IGHV3-23*04 or IGHV3-23*05. In another embodiment of any one of aspects 95 to 97 the human VH gene segment is IGHV3-23*01 or IGHV3-23*04, in particular IGHV3-23*04.

[0249] In a further embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10, for example selected from IGHD3-10*01 or IGHD3-10*02. In one embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10*01. In one embodiment of any one of aspects 95 to 97, the human DH gene segment is IGHD3-10*02.

[0250] In an embodiment of any one of aspects 90 to 97, the antibody is capable of treating or preventing GvHD. In another embodiment of any one of aspects 90 to 97, the antibody or fragment is used for the treatment or prevention of a disease other than GvD, but the antibody or fragment is capable of treating or preventing GvHD.

[0251] 98. The antibody or fragment according to aspect 86, or the antibody or fragment according to aspect 95, the use according to aspect 96, or the method according to aspect 97, wherein the antibody or fragment comprises a kappa light chain, e.g. wherein the VL domain of the light chain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39 (e.g. IGKV1D-39*01), and optionally the human JL gene segment is IGKJ1 (e.g. IGKJ1*01) or IGKJ3 (e.g. IGKJ3*01).

[0252] In another embodiment, the VL domain is a kappa VL domain. In an embodiment, the kappa VL domain is derived from the recombination of a human VL gene segment, and a human JL gene segment, wherein the human VL gene segment is IGKV1D-39. In another embodiment, the VL gene segment is IGKV1D-39*01.

[0253] In a further embodiment, the human JL gene segment is IGKJ1. In another embodiment, the JL gene segment is IGKJ1*01. In a futher embodiment, the human JL gene segment is IGKJ3. In another embodiment, the JL gene segment is IGKJ3*01

[0254] 99. The antibody or fragment according to any one of aspects 73 to 89, 98, 101 or 102, or the antibody or fragment use or method according to any one of aspects 90 to 98, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a Rhesus macaque model of haploidentical hematopoietic stem cell transplantation, optionally wherein the antibody is for the prevention of GvHD.

[0255] In another aspect, there is provided an antibody or fragment, use or method according to any one of aspects 95 to 98, wherein the antibody or fragment is for treating or preventing transplant rejection (e.g. GvHD) in a human by enabling greater than 80% stem cell donor chimerism by day 12 in said human following donor human hematopoietic stem cell transplantation.

[0256] In another embodiment, there is provided an antibody or fragment according to any one of aspects 73 to 89, 98, 101 or 102, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

[0257] In one embodiment, the chimerism is T cell ($CD3^+/CD20^-$) chimerism. In another embodiment, the chimerism is peripheral blood chimerism. In another embodiment, the chimerism is peripheral blood or T cell ($CD3^+/CD20^-$) chimerism.

[0258] In one embodiment, the stem cell donor chimerism (e.g. the peripheral blood or T cell ($CD3^+/CD20^-$) chimerism) is determined using divergent donor- and recipient-specific MHC-linked microsatellite markers, by comparing peak heights of the donor- and recipient-specific amplicons. In another embodiment, stem cell donor chimerism is determined as described in Kean, LS, et al., "Induction of chimerism in rhesus macaques through stem cell transplant and costimulation blockade-based immunosuppression", Am J Transplant. 2007 Feb;7(2):320-35. In another embodiment, stem cell donor chimerism is determined as described in Example 7.

[0259] In one embodiment, the *Rhesus macaque* model of haploidentical haematopoietic stem cell is performed by the transplant (HSCT) recipient animals undergoing a conditioning procedure together with anti-OX40L antibody administration, followed by infusion of a peripheral blood product isolated from a half-sibling donor animal, following which animals continue to receive weekly doses of the anti-OX40L antibody of the invention, and blood samples are taken and analysed for chimerism.

[0260] In another embodiment, in the HSCT model, recipient animals receive a conditioning radiation dose of 1020 cGy in 4 dose fractions over 2 days (experimental Day -2 and Day -1) to ablate the host haematopoietic system before intravenous administration of an anti-OX40L antibody of the invention (Day -2,with subsequent intravenous doses on Days 5, 12, 19, 26, 33, 40, 47) and transplant of white blood cell- and stem cell-enriched peripheral blood from an MHC half-matched (half-sibling) donor animal to reconstitute the recipient's immune system, together with provision of continuous supportive care, blood sampling and monitoring for signs of GVHD.

[0261] In one embodiment, the antibody or fragment, use or method is for the prevention of GvHD.

[0262] In an embodiment, the anti-hOX40L antibody of the invention is administered prophylactically. In one embodiment, the prophylactic treatment prevents the worsening or onset of the disease or condition.

[0263] In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered intravenously. In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

[0264] In another embodiment, said antibody is administered 1-4 days before transplant, e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

[0265] In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine et al., "A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study", Lancet Haematol 2015; 2: e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

[0266] In a further embodiment, the HSCT model is conducted as described in Miller, Weston P., et al. "GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ T cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression." Blood, 116, 24(2010):5403-5418. In a further embodiment, the HSCT model is carried out as described in Example 7.

[0267] 100. The antibody or fragment, use or method according to any one of aspects 95 to 99, wherein the antibody is as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

[0268] 101. The antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 102, or the antibody or fragment, use or method according to any one of aspects 90 to 100, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-XceedTM at level greater than 1.5g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

[0269] In one embodiment, the expression level is greater than 1.0g/L, greater than 1.1g/L, greater than 1.2g/L, greater than 1.3g/L or greater than 1.4g/L.

[0270] 102. An antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 101, or the antibody or fragment, use or method according to any one of aspects 90 to 101, wherein the antibody or fragment maintains a naive population of $CD4^+$ T-cells of >20% of total $CD4^+$ T cell population at day 12 in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation.

[0271] In another aspect, there is provided an antibody or fragment according to any one of aspects 73 to 89, 98, 99 or 101, or an antibody or fragment, use or method according to any one of aspects 90 to 101, wherein the antibody or fragment is for treating or preventing transplant rejection in a human by maintaining a naive population of donor $CD4^+$ T-cells of >20% of total $CD4^+$ T cell population at day 12 in said human following donor human hematopoietic stem cell transplantation

[0272] In one embodiment, the HSCT model is as described in any embodiment contemplated hereinabove, e.g. as described in connection with aspect 99.

[0273] In another embodiment, the naive population is measured by evaluating the relative proportion of specific T cell phenotypes using flow cytometry where cell subsets are identified by labelling with fluorescent antibody probes and whereby naive CD4 or CD8 T-cells are labelled $CD4^+/CD28^+/CD95^-$ or $CD8^+/CD28^+/CD95^-$, respectively, central memory CD4 or CD8 T-cells are labelled $CD4^+/CD28^+/CD95^+$ or $CD8^+/CD28^+/CD95^+$, respectively, and effector memory CD4 or CD8 T-cells are labelled $CD4^+/CD28^-/CD95^+$ or $CD8^+/CD28^-/CD95^+$, respectively.

[0274] 103. The antibody or fragment, use or the method according to any one of aspects 90 to 102, further comprising administering to the human a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0275] In one embodiment, the further therapeutic agent is an anti-inflammatory drug. In aother embodiment, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies.

[0276] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0277] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basiliximab, daclizumab).

[0278] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus). In another embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

[0279] 104. The antibody or fragment, use or the method according to aspect 103, wherein the further therapeutic agent is administered sequentially or simultaneously with the anti-hOX40L antibody or fragment.

[0280] 105. A pharmaceutical composition comprising an antibody of fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102 and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0281] The pharmaceutically acceptable excipients, diluents or carriers as described herein apply *mutatis mutandis* to these compositions.

[0282] In one embodiment, the further therapeutic agent is an anti-inflammatory drug. In aother embodiment, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone), anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab) or anti-TNFa antibodies/TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab, certolizumab pegol). In an example, the anti-inflammatory drug is independently selected from the group consisting of corticosteroids (e.g. methylprednisolone) and anti-LFA1 antibodies.

[0283] In one embodiment, the further therapeutic agent is independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0284] In one embodiment, the further therapeutic agent is independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basiliximab, daclizumab).

[0285] In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In another embodiment, the further therapeutic agent is tacrolimus. In another embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In another embodiment, the further therapeutic agent is ciclosporin. In another embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In another embodiment, the further therapeutic agent is cyclophosphamide. In another embodiment, the further therapeutic agent is mycophenolate mofetil

[0286] 106. A pharmaceutical composition according to aspect 105, or a kit comprising a pharmaceutical composition as defined in aspect 105, wherein the composition is for treating and/or preventing a hOX40L-mediated condition or disease selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

[0287] The hOX40L-mediated diseases of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply *mutatis mutandis* to this combination.

[0288] 107. A pharmaceutical composition according to aspect 105 or aspect 106 in combination with, or kit according to aspect 106 comprising a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

[0289] The labels, instructions, hOX40L-mediated diseases and conditions of any of the aspects, configurations, concepts, examples or embodiments described herein optionally apply *mutatis mutandis* to this combination.

[0290] 108. A nucleic acid that encodes the HCDR3 of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

[0291] 109. A nucleic acid that encodes a VH domain and/or a VL domain of an antibody or fragment as defined in any one of aspects 73 to 89, 98, 99, 101 or 102.

[0292] 110. A nucleic acid according to aspect 109 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO: 33 and/or SEQ ID NO: 47.

[0293] In an example, the nuecleotide sequence is at least 85% identical, at least 90% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical or at least 99% identical to the sequence of SEQ ID NO: 33 and/or SEQ ID NO: 47.

[0294] 111. A nucleic acid that encodes a heavy chain or a light chain of an antibody recited in any one of aspects 73 to 89, 98, 99, 101 or 102.

[0295] 112. A vector comprising the nucleic acid of any one of aspects 108 to 111; optionally wherein the vector is a CHO or HEK293 vector.

[0296] 113. A host comprising the nucleic acid of any one of aspects 108 to 111 or the vector of aspect 112.

[0297] The present invention furthermore relates to the following concepts.

Concept 1. A method of reducing the proportion of (e.g. of depleting or decreasing the level of) $CD45RA^+CCR7^+CD95^+OX40^+$ memory stem T-cells (Tscm) comprising combining said cells with an agent (such as an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of said Tscm cells is reduced (e.g. whereby the level of said Tscm cells is decreased or depleted).

[0298] $CD45RA^+CCR7^+CD95^+OX40^+$ memory stem T-cells (Tscm) are thought to be a newly-defined subset of stem cell memory T-cells which are long-lived and have the capacity for self-renewal. Therefore, these cells may be detrimental in various diseases, such as GvHD and autoimmune disorders, because they are the source of a persistent and multipotent population of potentially self-reactive effector T-cells. It is known that T-cells develop through a pathway beginning with naive T-cells (Tn), through stem cell memory T-cells (Tscm), through central memory T-cells (Tcm) and effector memory T-cells (Tem), before developing into short-lived effector T-cells (Teff), as described in Gattinoni and Restifo (2013), Inside Blood, 121(4), 567-568. At these various stages, different markers are expressed on the surface of the T-cells, which reflect the activation status of the T-cells, their tissue localisation and their responsiveness to various stimuli such as inflammatory cytokines.

[0299] Tscm cells as defined herein are characterised as $CD45RA^+CCR7^+CD95^+OX40^+$. For alternative prior art classifications of different T-cell types, see the figure in Gattinoni and Restifo (2013). Further markers may be present or absent, but Tscm cells must at a minimum be $CD45RA^+CCR7^+CD95^+OX40^+$. The various cell-surface markers are, in one embodiment, identified using flow cytometry using methods which are well-known to those of skill in the art. In one embodiment, the Tscm cells may additionally be $CD8^+$. In another embodiment, the Tscm cells may additionally be $CD62L^+$. Flow cytometry techniques are well-known to those skilled in the art. Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000), Journal of Immunological Methods, 243, 77-97. (see concept 25 hereinbelow).

[0300] In a particular embodiment, the Tscm cells are characterised as being $CD4^+CD45RA^+$ $CCR7^+CD95^+OX40^+$.

[0301] Without being bound by theory, it is thought that reducing this Tscm population will have a number of benefits in various diseases, as set out herein. In one embodiment, the Tscm cells are active Tscm cells.

[0302] Throughout concepts 1 to 83 herein, the proportion or levels of Tscm cells may be reduced in a sample, or indeed in (a sample of) the blood of a subject. The proportion or levels of Tscm cells may be determined relative to the entire T-cell population in the sample. In one embodiment, the proportion or level of Tscm cells is determined relative to other T-cells in the sample. T-cells generally may be identified as being $CD3^+$, and include Tn cells, Tscm cells, Tcm cells, Tem cells and Teff cells. In a particular embodiment, the proportion or level of Tscm cells is determined relative to Tn cells (as defined hereinbelow) in the sample. The proportion or level of Tscm cells may be altered by depletion or by a decrease. In one embodiment, a ratio of T-cell types may be the same as a proportion of Tscm cells (e.g. as for concept 2 hereinbelow). In another embodiment, a level of T-cell types may be the same as a proportion of Tscm cells. In one embodiment, the ratio or proportion of Tscm:Tn is greater than 50:50. Particular ratios and proportions are as described in concepts 23 and 24.

[0303] As used in concepts 1 to 83 herein "depleting" and "depletes" describes an active effect following combination with an agent (such as an antibody) on the desired target to kill or remove the target cells (e.g. Tscm cells). When the agent is an antibody, this is usually achieved through effector functions, such as ADC, ADCC or CDC. Alternatively, the target may be killed or removed by a toxin, which may be conjugated to a drug or targeting moiety (such as an anti-OX40 or an anti-OX40L antibody). Such toxins will selectively kill or remove the cell to which they are targeted. Suitable immunoconjugates are described on

page 90, and on pages 114 to 118, and 134 (in particular pages 114 to 116) herein.

[0304] "Decreasing" or "decreases" as used in concepts 1 to 83 herein refers to a mechanism other than depletion, which reduces the absolute number of cells in a given population. This may be achieved indirectly, for example through a blocking or neutralising agent (such as an antibody) against a target which indirectly results in the killing of a target cell (such as a Tscm), or prevents the expansion or growth of the target cells, resulting in an apparent decrease in proportions relative to another type of cell (such as Tn cells).

[0305] As used in concepts 1 to 83 herein, a "level" of a T-cell population may refer to the absolute number, or to the relative proportion of a type of T-cell.

[0306] Throughout the various concepts 1 to 83 described herein, an agent which reduces the proportion of Tscm cells may be, for example, an antibody or fragment thereof, a short interfering RNA (SiRNA), a zinc finger, a DARPin, an aptamer, a Spiegelmer, an ant-calin, a receptor-Fc fusion, a ligand-Fc fusion or a small molecule. In one embodiment, the agent targets OX40 (e.g. human OX40), or ligands of OX40. In another embodiment, the agent targets OX40L (e.g. human OX40L), or receptors of OX40L. In one example, the agent may be an OX40-Fc fusion protein (e.g. hOX40-Fc fusion), or may be an OX40L-Fc fusion protein (e.g. hOX40L-Fc fusion), both including functional fragments of OX40 and OX40L. These types of constructs are known to those skilled in the art. In another embodiment, the agent targets OX40 (e.g. human OX40). In another embodiment, the agent targets OX40L (e.g. human OX40L).

[0307] In a particular embodiment, the agent is an antibody or fragment thereof. Formats and structures of antibodies and fragments are described elsewhere herein and may be applied to any of the concepts disclosed herein. The antibody or fragment may be any of the constructs as described herein (for example, as in any one of concepts 52 to 64 herein). In a particular embodiment, the agent is an anti-human OX40 antibody or fragment thereof. In another particular embodiment, the agent is an anti-human OX40L antibody, such as an antibody comprising the amino acid sequence of 02D10 described herein or an antibody comprising the amino acid sequence of oxelumab.

[0308] Concept 2. A method of altering the ratio of cell types in a T-cell population in a sample, the method comprising:

1. a. providing said population, wherein the population comprises a mixture of different T-cell types, wherein the population comprises CD45RA+CCR7+CD95+OX40+Tscm cells,
2. b. providing an agent which reduces the proportion of Tscm cells (or providing an anti-OX40 or an anti-OX40L antibody or fragment thereof); and
3. c. combining said cell population with an amount of said agent (e.g. antibody or fragment thereof) effective to alter the ratio (e.g. to reduce the proportion) of Tscm cells in said population.

[0309] Throughout concepts 1 to 83 herein, the ratio of T-cell types may be altered in a sample, for example by increasing the proportion of naive T-cells (Tn, as defined hereinbelow). In another embodiment, the ratio of T-cell types may be altered by decreasing the proportion of Tscm cells. The ratio of Tscm cells may be determined relative to the entire sample. In one embodiment, the ratio of T-cells is determined by comparing the proportion of naive T-cells or Tscm cells relative to other T-cells in the sample. T-cells generally may be identified as being CD3+, and include Tn cells, Tscm cells, Tcm cells, Tem cells and Teff cells. In a particular embodiment, the ratio of T-cells is determined as the ratio of Tscm cells relative to naive T-cells in the sample. The ratio of T-cells may be altered by depletion or by a decrease of Tscm cells. The ratio of T-cells may be altered by an increase or expansion of naive T-cells.

[0310] Concept 3. A method according to concept 2, wherein in step a), the population further comprises CD45RA+CCR7+CD95- naive T-cells (Tn).

[0311] Naive T-cells (Tn) as defined in concepts 1 to 83 herein are characterised as CD45RA+CCR7+CD95-. Further markers may be present or absent, but Tn cells must at a minimum be CD45RA+CCR7+CD95-. In one embodiment, Tn cells may additionally be CD8+ or CD4+, in particular CD4+. It is thought that Tn are beneficial because these represent the entire pool of T-cells from which adaptive T-cell immune responses can develop to protect an indiviudal when exposed to potentially harmful pathogens and malignant cells.

[0312] Concept 4. A method according to concept 3 wherein the ratio of Tscm:Tn in the population of step a) is greater than 50:50.

[0313] Concept 5. A method according to any one of concepts 1 to 4, wherein the method is carried out *ex vivo* in a sample of blood extracted from a human donor subject.

[0314] Concept 6. A method according to concept 5, wherein blood produced by said method is reintroduced to a recipient human subject.

[0315] In one embodiment, the recipient human subject is the same donor human subject from whom the sample was removed. In another embodiment, the recipient human subject is different to the donor human subject. When the recipient is different to the donor, it is preferable that the donor is of the same gender as the recipient subject. In another embodiment, the donor may be of a similar age and ethnicity as the recipient subject. In another embodiment, the donor may have the same or similar allotype markers as the recipient subject.

[0316] In another embodiment, the recipient human donor may receive more than one transfusion of donor blood, according to the severity of the disease to be treated.

[0317] Concept 7. A method according to any one of concepts 1 to 4, wherein the method is carried out *in vivo* in a human subject.

[0318] Concept 8. A method according to concept 7, wherein the subject has or is at risk of a Tscm-mediated disease or condition.

[0319] As used herein, a subject may be indentified as being "at risk of a Tscm-mediated disease or condition" when the cellular changes in their T-cell population have begun to take place, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease by any conventional method. Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases. In one embodiment, the disease is prevented (i.e. the treatment is prophylactic).

[0320] In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. Potential transplant therapies are envisaged in concept 78 hereinbelow.

[0321] In any of concepts 1 to 83 described herein, a Tscm-mediated disease may be as defined in any of concepts 71 to 80 hereinbelow.

[0322] Concept 9. A method of treating or reducing the risk of a Tscm-mediated disease or condition in a subject, the method comprising combining a population of T-cells with an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of CD45RA+CCR7+CD95+OX40+Tscm cells is reduced in the population (e.g. whereby the level of said Tscm cells is decreased or depleted in said population).

[0323] As used in concepts 1 to 83 herein, the "treatment" of a Tscm-mediated disease includes the reduction of one or more symptom(s) of said Tscm-mediated disease. The "prevention" of a Tscm-mediated disease includes the prevention of one or more symptom(s) of said Tscm-mediated disease.

[0324] Concept 10. A method according to any one of concepts 7 to 9, wherein the agent (e.g. antibody or fragment thereof) is combined by administering said agent (e.g. antibody or fragment) in a therapeutically effective amount to said subject, whereby said Tscm-mediated disease or condition is treated or the risk of said Tscm-mediated disease or condition is reduced in said subject.

[0325] In one embodiment, the administration is prophylactic to reduce the risk of a Tscm-mediated disease.

[0326] In any of the concepts described herein, a therapeutically effective or prophylactically effective amount of the antibody or fragment is as described elsewhere (see page 29, 73, 105 to 107 for therapy, and pages 72, and 102 to 103 for prophylaxis). In any of the concepts described herein, modes and compositions for administration may be as described elsewhere (see pages 118 to 142 herein). In one embodiment, the antibody or fragment is administered by bolus injection (e.g. intravenously).

[0327] Concept 11. A method of treating or reducing the risk of a Tscm-mediated disease or condition in a subject comprising administering to said subject a therapeutically effectve amount of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), and whereby the proportion of CD45RA+CCR7+CD95+OX40+Tscm cells is reduced (e.g. whereby the level of said Tscm cells is decreased or depleted), wherein the Tscm-mediated disease or condition is thereby treated or the risk of said Tscm-mediated disease or condition is reduced.

[0328] Concept 12a. An agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for use in treating or reducing the risk of a Tscm-mediated disease or condition in a subject; or concept 12b. An anti-OX40 or an anti-OX40L antibody or fragment thereof for use in treating or reducing the risk of a Tscm-mediated disease or condition in a subject.

[0329] Concept 13a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 13b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

[0330] Concept 14a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) in the manufacture of a medicament for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 14b. The use of an anti-OX40 or an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

[0331] Concept 15a. A composition comprising an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for the treatment or prevention of a Tscm-mediated disease or condition in a subject; or concept 15b. A composition comprising an anti-OX40 or an anti-OX40L antibody or fragment thereof for the treatment or prevention of a Tscm-mediated disease or condition in a subject.

[0332] Concept 16. A method of treating a disease or condition in a subject in need thereof, comprising:

1. a. Performing an assay to measure the level of CD45RA+CCR7+CD95- Tn cells and the level of CD45RA+CCR7+CD95+OX40+ Tscm cells in a sample obtained from the subject; and
2. b. Administering an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), such as an anti-OX40 or an anti-OX40L antibody or fragment thereof, to the subject when the ratio of Tscm:Tn cells in the sample is determined in the assay to be greater than 50:50.

[0333] Concept 17a. An agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for use in therapy of a subject, wherein the agent is to be administered to a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+Tscm cells:CD45RA+CCR7+ CD95- Tn cells of greater than 50:50; or concept 17b. An anti-OX40 or an anti-OX40L antibody or fragment thereof for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+ Tscm cells:CD45RA+CCR7+CD95- Tn cells of greater than 50:50.

[0334] Concept 18a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) for therapy of a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+ Tscm cells: CD45RA+CCR7+CD95- Tn cells of greater than 50:50; or concept 18b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof for therapy of a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+ Tscm cells: CD45RA+CCR7+CD95- Tn cells of greater than 50:50.

[0335] Concept 19a. Use of an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells) in the manufacture of a medicament for use in therapy of a subject, wherein the agent is to be administered to a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+ Tscm cells:CD45RA+CCR7+CD95- Tn cells of greater than 50:50; or concept 19b. Use of an anti-OX40 or an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for use in therapy of a subject, wherein the antibody or fragment thereof is to be administered to a subject who has, or has been determined to have, a ratio of CD45RA+CCR7+CD95+OX40+Tscm cells:CD45RA+ CCR7+CD95- Tn cells of greater than 50:50.

[0336] In any of concepts 17 to 19, the ratio is determined in a sample, for example, in a sample of blood obtained from said subject.

[0337] Concept 20. A method according to concept 16a or b, an agent or an antibody or fragment for the use according to concept 17a or b, or the use according to concept 18a or b or concept 19 a or b, wherein the therapy is the treatment or prevention of a Tscm-mediated disease or condition, preferably wherein the therapy is the treatment of a Tscm-mediated disease or condition.

[0338] In another embodiment, the subject has or is at risk of a Tscm-mediated disease or condition. The Tscm-mediated disease or condition may be as defined in any one of concepts 71 to 80 hereinbelow.

[0339] Concept 21. A method of classifying a subject as having or as being at risk of a Tscm-mediated disease or condition (e.g. which disease or condition is suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof), comprising:

1. a. performing an assay that detects (i) CD45RA+CCR7+CD95+OX40+Tscm cells, and (ii) CD45RA+CCR7+CD95- Tn cells in a sample obtained from said subject; and
2. b. classifying the subject as having, or as being at risk of a Tscm-mediated disease or condition if the ratio of Tscm:Tn cells in the sample is greater than 50:50.

[0340] Concept 22. A method according to concept 21 further comprising the step of:
c. administering to said subject an anti-OX40 or an anti-OX40L antibody or fragment thereof which reduces the proportion of said Tscm cells in the blood of said subject, (e.g. which depletes or decreases the level of said Tscm cells) if said subject has been classified as having or as being at risk of a Tscm-mediated disease or condition in step b).

[0341] Tscm-mediated diseases or conditions which may be suitable for treatment with an anti-OX40 or an anti-OX40L antibody or fragment thereof are as described in any one of concepts 71 to 80 herein below.

[0342] Concept 23. A method according to any one of concepts 4, 16, or 20 to 22, an agent or an antibody or fragment for the use according to concept 17 or 20, or the use according to any one of concepts 18 to 20, wherein the ratio of Tscm:Tn cells is (or is determined or classified to be) greater than 60:40, or is greater than 70:30, or is greater than 75:25, such as greater than 70:30.

[0343] In another embodiment, the ratio is (or is determined or classified to be) greater than 55:45. In another embodiment, the ratio is (or is determined or classified to be) greater than 65:35.

[0344] Concept 24. A method, agent or an antibody or fragment for the use, or the use according to concept 23, wherein the ratio of Tscm:Tn cells is (or is determined or classified to be) greater than 80:20, or is greater than 85:15, for example greater than 90:10, e.g. greater than 95:5.

[0345] Concept 25. A method according to any one of concepts 4, 16, or 20 to 24, an agent or an antibody or fragment for the use according to any one of concepts 17, 20, 23 or 24, or the use according to any one of concepts 18 to 20, 23 or 24, wherein the ratio of Tscm:Tn cells is determined (or is determinable) by flow cytometry.

[0346] Flow cytometry techniques are well-known to those skilled in the art, as discussed above. Agents which may be used in flow cytometry techniques are defined in Example 7 below. In one embodiment, the flow cytometry is carried out as described in Example 7 below. In another embodiment, the flow cytometry is carried out as described in Baumgarth & Roederer (2000).

[0347] Concept 26. A method for treating or reducing the risk of a Tscm-mediated disease or condition with an agent (e.g. an anti-OX40 or an anti-OX40L antibody or fragment thereof) which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof, comprising the steps of:

1. a. determining whether the subject is a candidate for treatment by detecting the presence of OX40 on the surface of CD45RA+CCR7+CD95+Tscm cells obtained from a sample from the subject; and
2. b. administering said agent, such as said antibody or fragment, to the subject if the subject is identified as a candidate for treatment.

[0348] Concept 27. A method according to concept 26, wherein the presence of OX40 on the surface of the Tscm cells is determined using flow cytometry.

[0349] In one embodiment, the subject is a human and the OX40 is human OX40.

[0350] Concept 28. A method, comprising:

1. a. obtaining at least two T-cell samples derived from a subject who has or is at risk of a Tscm-mediated disease or condition, wherein said at least two samples comprise a first sample and a second sample,
2. b. determining levels of CD45RA+CCR7+CD95+OX40+ Tscm cells in said first and second samples;
3. c. treating said subject to reduce the proportion of CD45RA+CCR7+CD95+OX40+ Tscm cells (e.g. to deplete or decrease the level of Tscm cells) by administering an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, if the levels of Tscm cells in said second sample are elevated as compared to said first sample, in order to treat or reduce the risk of said Tscm-mediated disease or condition.

[0351] The levels of Tscm in said first and second samples in step b. may be either the absolute number of Tscm cells, or may be the relative proportions of Tscm (e.g. the ratio of Tscm:Tn, or Tscm:total T-cell count). The levels of Tscm cells may be elevated in the second sample if they are statistically significantly higher than the levels in the first sample.

[0352] Concept 29. A method according to concept 28, wherein said first sample is collected:

1. i. before the onset of said disease or condition; or
2. ii. after the onset of said disease or condition; and

optionally wherein said second sample is collected no longer than one month, e.g. no longer than one week after the first sample.

[0353] As used in the concepts herein, a subject may be determined to be "before the onset of a Tscm-mediated disease or condition" if the subject is presenting no symptoms which would conventionally be associated with said disease or condition or if the subject would not be diagnosed as having such a disease or condition by any conventional method. For example, the presence of signs and symptoms of acute GvHD may be staged and graded according to a standardised scale such as described in Przepiorka et al. (1995), 1994 Consensus Conference on Acute GvHD Grading Bone Marrow Transplant 1995; 15, 825-828. Similar disease grading scales are also in routine clinical use for other relevant diseases, such as rheumatoid arthritis and inflammatory bowel diseases.

[0354] Concept 30. A method according to concept 28 or concept 29, wherein the Tscm-mediated disease or condition is a transplant, and wherein in step c) the treatment is in order to reduce the risk of transplant rejection, optionally wherein the first sample is taken before the transplant, and the second sample is taken after the transplant.

[0355] The first sample may be taken pre-operatively, e.g. after the subject has been identified as a candidate for treatment. The second sample is taken after the transplant and may be used by physicians as a method of monitoring the acceptance of the transplant. Thus, it may be that the physician may take more than one sample after the transplant, e.g. a daily blood sample to monitor the subject for changes in the proportion of Tscm:Tn or the levels of Tscm in the sample. The samples may be taken every other day, weekly, monthly or longer (including yearly) according to the likelihood of transplant rejection. For example, if the transplant is autologous, then the likelihood of transplant rejection may be reduced as compared to an allogeneic transplant, and therefore the time period between sample collections post-transplant may be longer than with an allogeneic transplant, where the risk of rejection is higher.

[0356] Concept 31. A method according to concept 30, wherein in step a), the first sample is collected no longer than a week, e.g. no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days before said transplant.

[0357] Concept 32. A method according to any one of concepts 28 to 31, wherein the second sample is collected no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, such as no longer than 2 days after the first sample or after said transplant.

[0358] Concept 33. A method according to any one of concepts 28 to 32, wherein in step c), the levels of Tscm cells in said second sample are greater than double the levels as compared to said first sample, for example are greater than three times the level, or preferably are greater than 4 times the levels as compared to said first sample.

[0359] In one embodiment, in step c), the levels of Tscm cells in said second sample are greater than 4 times (e.g. greater than 4.5 times) the levels as compared to said first sample. In another embodiment, in step c), the levels of Tscm cells in said second sample are greater than 5 times the levels as compared to said first sample.

[0360] Concept 34. A method according to any one of concepts 30 to 33, wherein the subject is given a prophylactic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a prophylactic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, before said transplant, and the first sample is taken before administration of said agent, or antibody or fragment thereof, and wherein the second sample is taken after the transplant or after administration of the agent, or the antibody or fragment thereof (preferably, where in the second sample is taken after the transplant).

[0361] In one embodiment, the prophylactic dose is an effective prophylactic dose. By "effective", it is meant that the dose is effective to reduce the proportion or level of Tscm as described herein, or effective to prevent or reduce the risk of a Tscm-mediated disease or condition.

[0362] The methods as described herein may be used to correct an already-abberent level of Tscm cells, by administration of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administration of an anti-OX40 or an anti-OX40L antibody or fragment thereof, before a transplant, in order to reduce the risk of transplant rejection after the transplant. Therefore, multiple samples may be taken after administration of the agent (or of the anti-OX40 or an anti-OX40L antibody or fragment thereof), but before the transplant. Comparison may be made between the collected samples and a sample obtained from a healthy donor.

[0363] Concept 35. A method according to any one of concepts 30 to 33, wherein the subject is given a therapeutic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the transplant.

[0364] In one embodiment, the therapeutic dose is an effective therapeutic dose. By "effective", it is meant that the dose is effective to reduce the proportion or level of Tscm as described herein, or effective to treat a Tscm-mediated disease or condition.

[0365] In one embodiment, the second sample is taken after the administration of the agent, or antibody or fragment thereof. This would enable a physician to check that the levels or proportion of Tscm cells remain "normal", i.e. as compared to the first sample, or to a sample obtained from a healthy donor.

[0366] Concept 36. A method according to any one of concepts 30 to 33, wherein the subject is given a therapeutic dose of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or is given a therapeutic dose of an anti-OX40 or an anti-OX40L antibody or fragment thereof, after the transplant, and wherein the first sample is taken before said transplant, and the second sample is taken after the administration of said agent, or of said antibody or fragment thereof.

[0367] Concept 37. A method according to any one of concepts 34 to 36, further comprising the steps of:

d. obtaining a third sample derived from said subject;

e. determining the levels of CD45RA+CCR7+CD95+OX40+ Tscm cells in said third sample;

f. treating said subject to reduce the proportion of CD45RA+CCR7+CD95+OX40+ Tscm cells (e.g. to deplete or decrease the level) of Tscm cells by administering an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or by administering an anti-OX40 or an anti-OX40L antibody or fragment thereof, if the levels of Tscm cells in said third sample are elevated as compared to said second or said first sample.

[0368] The levels are considered to be "elevated" as described hereinabove (e.g. as for concept 28 or 33).

[0369] Concept 38. A method according to concept 37, wherein steps d) to f) are repeated as necessary until the levels of Tscm cells remain at a therapeutically-effective, or at a prophylactically-effective levels, e.g. at a substantially constant level in said subject.

[0370] As used in the concepts herein, a "substantially constant level" may be described as within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In another embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples.

[0371] Concept 39. A method according to any one of concepts 28 to 38, wherein the second sample is taken no longer than one month after the first sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the first sample, and optionally wherein the third sample is taken no longer than one month after the second sample, such as no longer than one week, no longer than 6 days, no longer than 5 days, no longer than 4 days, or no longer than 3 days, e.g. no longer than 2 days after the second sample.

[0372] Timepoints for taking any of the samples described in these concepts will depend on a number of factors, such as the likelihood of the subject having or being at risk of a Tscm-mediated disease (e.g. GvHD or transplant rejection), the level determined in the previous sample, the type of transplant, etc. A person skilled in the art will be able to determine appropriate time points as necessary or desired. The timepoints may be monthly, every other month, quarterly, half-yearly or yearly, if desired.

[0373] Concept 40. *In vitro* use of CD45RA+CCR7+CD95+OX40+Tscm cells, as a diagnostic for a Tscm-mediated disease or condition in a subject (for example, which disease or condition can be treated or prevented with an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof in the subject).

[0374] In one embodiment, there is provided biomarker of an autoimmune disease, HIV-1, and a T-cell malignancy, wherein the biomarker is a CD45RA+CCR7+CD95+OX40+ Tscm cell. In another embodiment, the biomarker is of any of the diseases described in concepts 71 to 80 hereinbelow. In another embodiment, the Tscm cell is a CD4+CD45RA+CCR7+CD95+OX40+ Tscm cell.

[0375] Concept 41. Use of a biomarker of a Tscm-mediated disease or condition, wherein the biomarker is CD45RA+CCR7+CD95+OX40+ Tscm cells, *in vitro* as a diagnostic for a Tscm-mediated disease or condition (e.g. which disease or condition can be treated or prevented with an an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof in the subject).

[0376] In one embodiment, the Tscm-mediated diseases are any of those described in concepts 71 to 80 hereinbelow.

[0377] Concept 42. A method of maintaining CD45RA+CCR7+CD95- Tn cells, whilst decreasing CD45RA+CCR7+CD95+OX40+ Tscm cells in a population of T-cells in a sample, said method comprising contacting said sample with an effective amount of an agent which reduces the proportion of Tscm cells (e.g. which depletes or decreases the level of said Tscm cells), or with an anti-OX40 or an anti-OX40L antibody or fragment thereof.

[0378] As used in concepts 1 to 83 herein, "maintains" or "maintaining" with respect to a level or a proportion may be described as substantially constant. A substantially constant level may be within 30% variance between samples. In one embodiment, a substantially constant level is within 20% variance between samples. In one embodiment, a substantially constant level is within 15% variance between samples, such as within 10% variance between samples, e.g. within 5% variance between samples. In another embodiment, a substantially constant level is one which does not show a statistically significant change in level. In one embodiment, a substantially constant level is one which reaches the 95% confidence level (e.g greater than 97% or greater than 99%). "Statistically significant" may be as defined above in concept 28 herein.

[0379] Concept 43. A method according to concept 42, wherein the level of said Tn cells are at least maintained, whilst the levels of said Tscm cells are decreased in said sample, optionally wherein the sample is from a subject.

[0380] Concept 44. A method according to any one of concepts 2 to 8, 10, 16, 20, 21, 23 to 39, 42 or 43, an agent or an antibody or fragment thereof for the use according to any one of concepts 12, 17, 20, 21 or 23 to 25, the use according to any one of concepts 13, 14, 18 to 20 or 23 to 25, or the composition according to concept 15, wherein agent (e.g. the antibody or fragment thereof) reduces the proportion of CD45RA+CCR7+CD95+OX40+ Tscm cells (e.g.depletes or decreases the level of Tscm cells).

[0381] Concept 45. A method or fragment thereof according to any one of concepts 1 to 8, 10, 16, 20, 21, 23 to 39 or 42 to 44, an agent or an antibody or fragment thereof for the use according to any one of concepts 12, 17, 20, 21, 23 to 25, or 44, the use according to any one of concepts 13, 14, 18 to 20 or 23 to 25 or 44, or the composition according to concept 15 or concept 44, wherein the agent (e.g. the antibody or fragment thereof) maintains CD45RA+CCR7+CD95- Tn cells.

[0382] Concept 46. A method according to concept 42 or 45, an agent or an antibody or fragment thereof for the use according to concept 45, the use according to concept 45, or the composition according to concept 45, wherein the Tn cells are maintained at a level of not below 50% of the level of said Tn cells in a sample from a healthy donor or from said subject before the onset of disease.

[0383] The healthy donor is preferably of the same species at the subject, for example, wherein the subject is a human, the donor is most preferably also a human. The donor is also preferably of the same gender as the subject. The donor is preferably of a similar age and ethnicity as the subject.

[0384] Concept 47. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 46, wherein the Tn cells are maintained at a level of not below 55% (such as not below 60%, for example not below 65%, e.g. not below 70%).

[0385] Concept 48. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 47, wherein the Tn cells are maintained at a level of not below 75% (such as not below 80%, for example not below 85%, e.g. not below 90%)

[0386] Concept 49. A method according to any one of concepts 1 to 8, or 42 to 48, an agent or an antibody or fragment thereof for the use according to any one of concepts 44 to 48, the use according to any one of concepts 38 to 41, or the composition according to any one of concepts 44 to 48, wherein the Tscm cells are depleted or decreased to a level of less than 50% of the level of said Tscm cells in a sample from a healthy donor or from said subject before the onset of disease.

[0387] Concept 50. A method, an antibody or fragment for the use, a use or a composition according to concept 49, wherein the Tscm cells are depleted or decreased to a level of less than 45% (such as less than 40%, for example less than 35%, e.g. less than 30 % or less than 25%).

[0388] Concept 51. A method, an antibody or fragment for the use, a use or a composition according to concept 50, wherein the Tscm cells are depleted or decreased to a level of less than 20% (such as less than 15%, for example less than 10%.

[0389] Concept 52. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment is a depleting antibody or fragment that specifically binds OX40 (in particular human OX40), optionally wherein the antibody is engineered for enhanced ADC, ADCC and/or CDC.

[0390] The potency of Fc-mediated effects may be enhanced by engineering the Fc domain by various established techniques. Such methods increase the affinity for certain Fc-receptors, thus creating potential diverse profiles of activation enhancement. This can achieved by modification of one or several amino acid residues (e.g. as described in Lazar et al., 2006, Proc. Natl. Acad. Sci. U.S.A., Mar 14; 103(11):4005-10.) or by altering the natural glycosylation profile of the Fc domain by, for example, generating under fucosylated or de-fucosylated variants (as described in Natsume etal., 2009, Drug Des Devel Ther.;3:7-16). For example, to increase ADCC, residues in the hinge region can be altered to increase binding to Fc-gamma RIII (see, for example, Shields et al, 2001, J Biol Chem., Mar 2; 276(9):6591-604.).

[0391] Equally, the enhancement of CDC may be achieved by amino acid changes that increase affinity for C1q, the first component of the classic complement activation cascade (see Idusogie et al., J. Immunol., 2001;166:2571-2575). Another approach is to create a chimeric Fc domain created from human IgG1 and human IgG3 segments that exploit the higher affinity if IgG3 for C1q (Natsume et al., 2008, Cancer Res., 68: 3863-3872).

[0392] The antibody may be a targeting antibody (such as an anti-OX40 or an anti-OX40L antibody) which exhibits its effects through a toxin, to which the antibody may be conjugated. Such toxins will selectively kill or remove the cell to which they are targeted. Suitable immunoconjugates are described on page 90, and on pages 114 to 118, and 134 (in particular pages 114 to 116) herein.

[0393] Thus, in one embodiment, the antibody or fragment thereof is de-fucosylated. In another embodiment, the antibody or fragment thereof contains one or more mutations in the hinge or Fc region which enhances the ADCC and/or the CDC functionality.

[0394] Methods for determining depletion and/or ADCC and/or CDC functionality may be as described herein, or as well-known by those skilled in the art.

[0395] The OX40 antibodies may be as described in WO2014/148895 (Biocerox Products & Janssen Pharmaceuticals; see claims on pages 138 to 139 for specific sequences), WO2013/068563 (Biocerox Products & Janssen Pharmaceuticals; see claims on pages 138 to 139 for specific sequences), WO2013/130102 and WO2013/119202 (Providence Health & Services - Oregon, see mAb 9B12 as described in Weinberg, A.D., et al., J. Immunother., 29, 575-585 (2006), and fusions with IL-2), WO2013/038191 (Bioceros B.V.; see claims 4 to 11 for specific antibody sequences), WO2013/026231 (Board of Regents, the University of Texas System; see claims 1 to 12 for specific antibody sequences), WO2013/008171 (Glenmark Pharmaceuticals S.A.; see claims 1, 2, 5 to 12, 16 to 21 and 28 to 29 for specific antibody sequences), WO2012/027328 (Board of Regents, the University of Texas System; see claims 1 to 11 for specific antibody sequences), WO2010/096418 (UCB Pharma S.A.; see claims 1 to 9 and 11 to 14 for specific antibody sequences), WO2009/079335 (Medarex, Inc & Pfizer, Inc; see claims 1 to 9 and 14 to 17 for specific antibody sequences), WO2008/106116 (Genentech, Inc; see claims 1 to 12 for specific antibody sequences), WO2007/062245 (Kirin Beer Kabushiki Kaisha & La Jolla Institute for Allergy and Immunology; see claim 12 for specific antibody deposit numbers, and claim 16 for specific antibody sequences) WO03/106498 (Crucell Holland B.V.; see claims 3 and 4 for specific antibody sequences).

[0396] More generally anti-OX40 antibodies are described in WO99/42585, WO95/21251, WO95/21915 and WO95/12673.

[0397] Concept 53. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is an antagonistic or blocking antibody.

[0398] Methods for determining antagonism or blocking functionality may be as described herein, or as well-known by those skilled in the art. For example, *in vitro* techniques include SPR and/or ELISA, which are described elsewhere herein.

[0399] Concept 54. A method, an antibody or fragment for the use, a use or a composition according to concept 53, wherein the antibody specifically binds to OX40L (in particular human OX40L).

[0400] The OX40L antibodies may be any antibody or fragment as described herein. In one embodiment, the OX40L antibody is the antagonist anti-human OX40L (gp34) antibody ik-1 described by Matsumura et al., J Immunol. (1999), 163:3007.

[0401] Concept 55. A method, an antibody or fragment for the use, a use or a composition according to concept 56, wherein the antibody antagonises specific binding of OX40 to OX40L, e.g. as determined using SPR or ELISA.

[0402] SPR and ELISA methods may be as described elsewhere herein.

[0403] Concept 56. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is a humanized, human or fully human antibody.

[0404] Other antibody constructs may be as described herein.

[0405] Concept 57. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

[0406] Concept 58. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a Rhesus macaque model of haploidentical hematopoietic stem cell transplantation.

[0407] Concept 59. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-XceedTM at level greater than 1.5g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

[0408] Concept 60. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

[0409] Concept 61. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 selected from:

1. a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);
2. b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No:14);
3. c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);
4. d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No:106);
5. e. a CDR3 of any of the nanobodies disclosed in WO2011/073180 (Ablynx; Seq ID Nos: 161 to 167 therein);
6. f. an HCDR3 of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech, Seq ID Nos: 33 to 38 therein); or
7. g. an HCDR3 of any of the antibodies disclosed in US7,812,133 (Genentech, Seq ID Nos: 11 or 12 therein).

[0410] Concept 62. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises:

1. a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:60 or SEQ ID No:66 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
2. b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);
3. c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);
4. d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No:116 for CDRL1, SEQ ID No:112 or SEQ ID No:118 for CDRL2 and SEQ ID No:114 or SEQ ID No:120 for CDRL3);
5. e. the CDRs of any of the nanobodies disclosed in WO2011/073180 (Ablynx; Seq ID Nos: 161 to 167 therein for CDR3; Seq ID Nos: 147 to 153 therein for CDR2; and Seq ID Nos: 133 to 139 therein for CDR1);
6. f. the CDRs of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech: Seq ID Nos: 33 to 38 therein for CDRH3; Seq ID Nos: 21 to 25 therein for CDRH1 and Seq ID Nos: 26 to 32 therein for CDRH2; SEQ ID NOs: 39 to 44 therein for CDRL1; SEQ ID NOs: 45 to 50 therein for CDRL2; and SEQ ID NOs: 51 to 57 therein for CDRL3); or
7. g. the CDRs of any of the antibodies disclosed in US7,812,133 (Genentech: Seq ID Nos: 11 or 12 therein for CDRH3, Seq ID Nos: 7 or 8 therein for CDRH1 and Seq ID Nos: 9 or 10 therein for CDRH2; SEQ ID NOs: 1 or 2 therein for CDRL1; SEQ ID NOs: 3 or 4 therein for CDRL2; and SEQ ID NOs: 5 or 6 therein for CDRL3).

[0411] Concept 63. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

1. a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);
2. b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);
3. c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);
4. d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No: 108 for VL);
5. e. a VH domains of any of the nanobodies disclosed in WO2011/073180 (Ablynx; Seq ID Nos: 177 to 185, 199 to 226 therein [reproduced herein as Seq ID Nos: 177 to 213]);
6. f. the VH and/or VL domains of any of the antibodies disclosed in WO2006/029879 (Roche/Genentech, Seq ID Nos: 2, 4, 6, 8, 10, 12, 17, 19 and 20 therein for VH domains; and Seq ID Nos: 1, 3, 5, 7, 9, 11, 16 and 18 therein for VL domains [reproduced herein as Seq ID Nos: 214 to 230]); or
7. g. the VH and/or VL domains of any of the antibodies disclosed in US7,812,133 (Genentech, Seq ID Nos: 15 and 16 therein for VH domains; and Seq ID Nos: 13 and 14 therein for VL domains [reproduced herein as Seq ID Nos: 231 to 234]).

[0412] Concept 64. A method, an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the antibody is oxelumab.

[0413] Concept 65. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, where in the Tscm cells and/or the Tn cells are CD4+.

[0414] In another embodiment, the Tscm cells and/or the Tn cells are CD8+.

[0415] Concept 66. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 64, wherein the Tscm cells and/or the Tn cells are circulating T-cells.

[0416] Concept 67. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 65, wherein the Tscm cells and/or the Tn cells are in a sample of blood , e.g. peripheral blood.

[0417] Whereas T-cells present in blood are relatively straightforward to isolate and characterise, T-cells which are present in the tissues of a subject are generally more difficult to isolate. That said, it may be possible to isolate T-cells from various tissues (such as skin, tissues of the GI tract, e.g. bowel, and from inflamed joints, e.g. synovium)

[0418] Concept 68. A method according to any one of concepts 9 to 11, 16, 20 to 39 or 43 to 67, an agent or an antibody or fragment for the use according to any one of concepts 12, 17, 20, 21, 23 to 25 or 44 to 67, a use according to any one of concepts 13, 14, 18 to 20 or 23 to 25 or 44 to 67, or a composition according to any one of concepts 15 or 44 to 67, wherein the subject is a human patient.

[0419] Concept 69. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 68, wherein the subject is at risk of a Tscm-mediated disease or condition.

[0420] Concept 70. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 68, wherein the subject has a Tscm-mediated disease or condition.

[0421] Concept 71. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the Tscm-mediated disease or condition is mediated by CD45RA+CCR7+CD95+OX40+ Tscm cells.

[0422] Concept 72. A method, an agent or an antibody or fragment for the use, a use or a composition according to any one of concept 68 to 70, wherein the Tscm-mediated disease or condition is characterised by having a ratio of CD45RA+CCR7+CD95+OX40+Tscm cells:CD45RA+CCR7+CD95- Tn cells of greater than 50:50.

[0423] In another embodiment, the disease or condition is characterised by having a ratio of Tscm cells:Tn cells as set out in any of concepts 23 to 25.

[0424] Concept 73. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 72, wherein the Tscm-mediated disease or condition is characterised by having a ratio of Tscm:Tn of greater than 60:40, or greater than 70:30, or greater than 75:25, such as greater than 70:30.

[0425] Concept 74. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 73, wherein the Tscm-mediated disease or condition is characterised by having a ratio of Tscm:Tn of greater than 80:20, or greater than 85:15, for example greater than 90:10, e.g. greater than 95:5.

[0426] Concept 75. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, wherein the Tscm-mediated disease or condition is selected from an autoimmune disease, HIV-1, and a T-cell malignancy.

[0427] Concept 76. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 75, wherein the Tscm-mediated disease or condition is selected from GvHD, transplant rejection, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, juvenile dermatomyositis, T-cell lymphoma and T-cell leukemia.

[0428] Concept 77. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is GvHD or transplant rejection.

[0429] Concept 78. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the transplant is a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

[0430] In one embodiment, the transplant is a CAR T-cell transplant (chimeric antigen receptor).

[0431] Concept 79. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is a T-cell lymphoma selected from T-cell non-Hodgkin's lymphoma, peripheral T-cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL), angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma, blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma (T-LBL) and nasal NK/T-cell lymphoma.

[0432] Concept 80. A method, an agent or an antibody or fragment for the use, a use or a composition according to concept 76, wherein the Tscm-mediated disease or condition is a T-cell leukemia selected from large granular lymphocytic leukemia (LGLL), T-cell prolymphocytic leukemia (T-PLL), T-cell acute lymphoblastic leukemia (T-ALL) and Sezary syndrome.

[0433] Concept 81. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, in particular rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0434] In one embodiment, the further therapeutic agent is independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0435] In one embodiment, the further therapeutic agent is independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basiliximab, daclizumab).

[0436] In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In another embodiment, the further therapeutic agent is tacrolimus. In another embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In another embodiment, the further therapeutic agent is ciclosporin. In another embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In another embodiment, the further therapeutic agent is cyclophosphamide. In another embodiment, the further therapeutic agent is mycophenolate mofetil.

[0437] Concept 82. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount of rapamycin.

[0438] Concept 83. A method, an agent or an antibody or fragment for the use, a use or a composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount of tacrolimus.

[0439] The inventors have surprisingly found that an anti-OX40L antibody may provide synergistic effects when administered as part of a combination therapy with a further therapeutic agent. To that end, further concepts are provided below:

Concept 101. An anti-OX40L antibody or fragment thereof for use in treating or reducing the risk of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 102. Use of an anti-OX40L antibody or fragment thereof for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basilixumab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 103. Use of an anti-OX40L antibody or fragment thereof in the manufacture of a medicament for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor

antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 104. A composition comprising an an anti-OX40L antibody or fragment thereof for the treatment or prevention of an OX40L-mediated disease or condition in a subject in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

Concept 105. A method of treating or preventing an OX40L-mediated disease or condition in a subject comprising administering to said human a therapeutically effective amount of an anti-OX40L antibody or fragment thereof in combination with a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the OX40L-mediated disease or condition is thereby treated or prevented.

[0440] In any of the concepts herein, the combination may be used in the prevention of an OX40L-mediated disease. In any of the concepts, the combination may be used to reduce the risk of an OX40L-mediated disease. In any of the concepts, the combination may be used in the treatment of an OX40L-mediated disease.

[0441] A "combination" as described here may be as defined elsewhere herein, for example on page 100, on pages 105 to 107, and on pages 119 to 120. In one embodiment, the disease is rheumatoid arthritis or psoriasis, and the further therapeutic agent is an anti-IL-17 antibody (such as brodalumab, secukinumab and ixekizumab). Combinations may be administered concomitantly or sequentially. Administration may be *via* any of the methods disclosed herein, for example, as discussed in the section entitled "Methods of Administration and Dosing" beginning on page 130 herein.

[0442] As used in any of the concepts herein, the "treatment" of an OX40L-mediated disease includes the reduction of one or more symptom(s) of said OX40L-mediated disease. Treatment may be interpreted as described elsewhere herein, for example on page 107, and in the section entitled "Kits" (beginning on page 149, in particular page 152)

[0443] Immunosuppressive drug intervention in the management of GvHD associated with hematopoietic stem cell transplant (HSCT) may be administered to treat patients with confirmed disease. GvHD grading may be determined as described below.

[0444] In one embodiment, the administration is prophylactic to reduce the risk of an OX40L-mediated disease. As used in the concepts herein, "prevention" (or "prevent" or "preventing" and the like) of an OX40L-mediated disease includes the prevention of one or more symptom(s) of said OX40L-mediated disease. Preventing may refer to the total or partial inhibition of the development, recurrence, onset or spread of an OX40L-mediated disease and/or symptom related thereto, resulting from the administration combination of therapies provided herein (e.g., a combination of prophylactic and/or therapeutic agents). Preventing may be interpreted as disclosed elsewhere herein.

[0445] Immunosuppressive drug intervention in the management of GvHD associated with hematopoietic stem cell transplant (HSCT) may be administered to prevent disease in patients known to be at risk.

[0446] Thus, in one embodiment, a prophylactically-effective dose is administered before the onset of an OX40L-mediated disease or condition. As used in the concepts herein, a subject may be determined to be "before the onset of an OX40L-mediated disease or condition" if the subject is presenting no symptoms which would conventionally be associated with said disease or condition or if the subject would not be diagnosed as having such a disease or condition by any conventional method. In another embodiment, administration which is before the onset of disease may be termed "pre-emptive treatment", which refers to the use of further therapeutic agents (such as immunosuppressant agents) and/or an anti-OX40L antibody of the invention in individuals at risk of developing disease and where there may be early signs that emergence of clinically-relevant GvHD is imminent. For example, an experimental or predictive serum or cellular biomarker may indicate the optimal time for initiation of pre-emptive GvHD treatment.

[0447] For example, the presence of signs and symtpoms of acute GvHD in a human may be staged and graded according to a standardised scale such as described in Przepiorka *et al.* In a primate, such as a rhesus macaque monkey, the presence of signs and symtpoms of acute GvHD may be staged and graded according to a standardised scale such as described herein in Example 7. Similar disease grading scales are also in routine clinical use for other relevant diseases, such as rheumatoid arthritis and inflammatory bowel diseases.

[0448] "Prevention" or "prophylaxis" may be as described in aspect 94 herein, with dosages and timings of administration of the anti-OX40L antibody as described. A prophylactic agent may be used in any of the methods described on page 102 to 103.

[0449] The OX40L-mediated diseases or conditions may be any of the diseases or conditions mentioned herein, including those which are defined elsewhere herein as Tscm-mediated diseases or conditions (see concepts 75 to 80 hereinabove). In one embodiment, the OX40L-mediated diseases or conditions are as described in any of aspects 12, 12a, 69, 69a, 71, 72, 72a, 90 to 93 as described herein. In one embodiment, the OX40L-mediated diseases or conditions are as described in any of aspects 12, 12a, 69, 69a, 71, 72, 72a, 90 to 93 as described herein. In one embodiment, the OX40L-mediated disease or condition is a hOX40L- mediated disease or condition as described herein, for example on pages 103 to 104, or on page 131. In another embodiment, the OX40L-mediated diseases or conditions are as described in the section entitled "Methods of Administration and Dosing" beginning on page 130 herein. In a preferred embodiment, the disease or condition is GvHD or transplant rejection, in particular, GvHD. In another embodiment, the OX40L-mediated disease of condition is Chron's disease. In another embodiment, the OX40L-mediated disease of condition is inflammatory bowel disease (IBD). In another embodiment, the OX40L-mediated disease of condition is ulcerative colitis. In another embodiment, the OX40L-mediated disease of condition is psoriasis.

[0450] In any of concepts described herein, the anti-OX40L antibody and/or the further therapeutic agent are administered to the subject. Administration may be by any method described herein, for example as described on page 93, or in the sections entitled "Pharmaceutical compositions" and "Methods of Administration" beginning on pages 118 and 130 respectively. In one embodiment, the anti-OX40L antibody of the invention is administered intravenously. In one embodiment, the anti-OX40L antibody of the invention is administered subcutaneously.

[0451] In one embodiment, the further therapeutic agent is rapamycin (sirolimus) and is administered orally. In one embodiment, the further therapeutic agent is tacrolimus and is administered orally. In one embodiment, the further therapeutic agent is methotrexate and is administered orally and/or intravenously. In one embodiment, the further therapeutic agent is ciclosporin and is administered intravenously and/or orally. In one embodiment, the further therapeutic agent is cyclophosphamide and is administered intravenously and/or orally. In one embodiment, the further therapeutic agent is methyl prednisolone and is administered orally and/or intravenously.

[0452] Concept 106. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein the subject has a post-treatment or post-prophylaxis survival time of at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days.

[0453] Concept 107. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein post-prophylaxis, the subject has at least 7 days, or at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days disease-free.

[0454] Concept 108. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 105, wherein post-treatment, the subject has at least 7 days, or at least 14 days, or at least 21 days, or at least 28 days, or at least 40 days, or at least 50 days, or at least 60 days disease progression-free.

[0455] Concept 109. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 106 to 108, wherein the number of days of survival, the number of disease free days, or the number of disease-progression free days is at least 2 months, or at least 3 months, or at least 4 months, e.g. at least 5 months, such as at least 6 months.

[0456] Concept 110. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 109, wherein the number of days of survival, the number of disease free days, or the number of disease-progression free days is at least 9 months, or at least one year.

[0457] Concept 111. A method of preventing the onset of an OX40L-mediated disease or condition in a subject by administering a prophylactically-effective amount of an anti-OX40L antibody and administering a prophylactically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is prevented.

[0458] By "prophylactically-effective", it is meant that the dose is effective to prevent or reduce the risk of an OX40L-mediated disease or condition.

[0459] In one embodiment, the combination may be used to reduce the risk of an OX40L-mediated disease or condition. In concept 111, the anti-OX40L antibody of the invention and the further therapeutic agent may be administered to the patient prophylactically, which administration may be sequential or simultaneous. The dosing regimens and modes of administration may be those which are normal or traditionally administered by physicians for the further therapeutic agent. The dosing regimens and modes of administration may be those which are normal or traditionally administered by physicians for the anti-OX40L antibody of the invention. However, the concurrent use of both agents is expected to result in an improved prophylaxis as compared to either agent alone.

[0460] Concept 112. A method of treating an OX40L-mediated disease or condition in a subject by administering a prophylactically-effective amount of an anti-OX40L antibody and administering a therapeutically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

[0461] By "therapeutically effective", it is meant that the dose is effective to treat an OX40L-mediated disease or condition. Effective may be as defined on pages 96 to 97, or pn page 152 herein, and may provide serum concentrations as described in the section entitled "Parmacetical Compositions" starting on page 118 herein.

[0462] In concept 112, the anti-OX40L antibody of the invention may be administered to the patient, but despite prophylaxis, the onset of the OX40L-mediated disease or condition occurs (the onset may be delayed by a number of days or weeks, as compared with a patient who had not been receiving the antibody of the invention). In this case, a therapeutically-effective amount of a further therapeutic agent may be administered to treat the disease or condition.

[0463] Concept 113. A method of treating an OX40L-mediated disease or condition in a subject by administering a therapeutically-effective amount of an anti-OX40L antibody and administering a prophylactically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

[0464] In concept 113, the further therapeutic agent may be administered to the patient, but despite prophylaxis, the onset of the OX40L-mediated disease or condition occurs (the onset may be delayed by a number of days or weeks, as compared with a patient who had not been receiving the further therapeutic agent). In this case, a therapeutically-effective amount of an anti-OX40L antibody of the invention may be administered to treat the disease or condition.

[0465] Concept 114. A method of treating an OX40L-mediated disease or condition in a subject by administering a therapeutically-effective amount of an anti-OX40L antibody and administering a therapeutically-effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the onset of the OX40L-mediated disease or condition is treated.

[0466] In concept 114, both the anti-OX40L antibody of the invention and the further therapeutic agent are not administered until there are clinical signs of the OX40L-mediated disease or condition. The combination treatment of both agents may provide further benefits as compared to either agent alone.

[0467] Concept 115. A method according to concept 111 or concept 113, wherein the further therapeutic agent is independently selected from rapamycin (sirolimus), tacrolimus, a combination of tacrolimus and methotrexate, cyclophosphamide, ciclosporin, and a combination of ciclosporin and methotrexate.

[0468] In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is tacrolimus. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is cyclophosphamide. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is ciclosporin. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and the further therapeutic agent is mycophenolate mofetil.

[0469] In one embodiment, the anti-OX40L antibody is administered to a patient who is already receving rapamycin (sirolimus). In another embodiment, embodiment, the anti-OX40L antibody is administered to a patient who is already receiving tacrolimus. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving a combination of tacrolimus and methotrexate. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving a combination of ciclosporin and methotrexate. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving ciclosporin. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving cyclophosphamide. In another embodiment, the anti-OX40L antibody is administered to a patient who is already receiving mycophenolate mofetil.

[0470] These further therapeutic agents may be used prophylactically in the treatment of OX40L-mediated diseases or conditions. For example, in GvHD, preventive therapy (prophylaxis) is typically administered around the time of HSCT and is continued for a period of time following transplant to maintain immunosuppression during the period of greatest risk of developing acute GvHD. Specific drug regimens differ between transplant centres, but as an example prophylaxis with calcineurin inhibitors such as ciclosporin or tacrolimus, or with rapamycin (sirolimus) may be initiated within the 7 day period preceding transplant (such as Day -3, or Day -1 pre-HSCT), or immediately following the HSCT procedure (e.g. on Day 0, or Day +1 after transplant). Prophylaxis with mycophenolate mofetil is typically dosed following HSCT, for example starting between Day +1 to Day +5 post-transplant. Prophylaxis with these agents may be continued, for example, between 28 to 180 days or longer following transplant, with daily dosages calculated to maintain serum levels in the range to achieve effective immunosuppression without limiting side effects. In addition to calcineurin inhibitors, methotrexate is often used as an adjunct to prophylaxis, typically being administered on Days+1, +3, +6, and +11 post-transplant.

[0471] An anti-OX40L antibody of the invention may be used as prophylaxis in combination with tacrolimus, ciclosporin, a combination of tacrolimus and methotrexate, a combination of ciclosporin and methotrexate, cyclophosphamide, mycophenolate mofetil or rapamycin, where prophylaxis with any of these agents is started before or around the time of HSCT, or immediately following the transplant procedure, for example within the period 7 days before, to 7 days after transplant. Tacrolimus, or ciclosporin, or rapamycin may then be administered at therapeutically effective dose and frequency, for example daily, for up to 180 days following the transplant. An anti-OX40L antibody of the invention may be administered concurrently, starting before or around the time of HSCT, or immediately following the transplant procedure, for example within the period 7 days before, to 7 days after transplant. The anti-OX40L antibody may then be dosed at a therapeutically effective dose and frequency, for example biweekly or monthly, for up to 180 days following the transplant. Under these circumstances the combined activity of the anti-OX40L antibody and the additional prophylactic agent would be expected to display a synergistic effect in preventing the onset and / or severity of GvHD.

[0472] Concept 116. A method according to concept 112 or concept 114, wherein the further therapeutic agent is a corticosteroid (e.g. methylprednisolone).

[0473] In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is methylprednisolone.

[0474] In cases where breakthrough GvHD occurs (for example, even despite prophylaxis), treatment may be initiated immediately upon confirmation of Grade II or higher GvHD disease. Systemic corticosteroids such as methylprednisolone are the first-line treatment of choice, administered concurrently with ongoing prophylaxis with, for example, a calcineurin inhibitor such as ciclosporin or tacrolimus.

[0475] Where first-line treatment or prophylaxis fails to control GvHD, "salvage therapy" may be attempted in which case additional previously unused immunosuppressants such as rapamycin or mycophenolate mofetil may be administered. Thus, in one embodiment, a therapeutically effective amount of an anti-OX40L antibody of the invention is administered to a patient who is refractory to prophylaxis or treatment with any of: rapamycin, tacrolimus, tacrolimus in combination with methotrexate, cyclophosphamide, ciclosporin, ciclosporin in combination with methotrexate, or corticosteroids (e.g. methylprednisolone). In another embodiment, a therapeutically effective amount of an anti-OX40L antibody of the invention is administered to a patient who is refractory to prophylaxis or treatment with any of the further therapeutic agents mentioned herein. In another embodiment, an anti-OX40L antibody of the invention is administered as a salvage therapy.

[0476] Concept 117. A method of prolonging survival in a subject having or at risk of an OX40L-mediated disease or condition by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab); anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

[0477] In one embodiment, then OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. A number of factors affect the severity and disease progression in GvHD, such as the pre-transplant conditioning regimen (e.g. myeoablation by irradiation, preparative chemotherapy), degree of donor-recipient tissue matching (HLA matching, and/or relationship of donor-recipient), and therapeutic or prophylactic treatment regimens.

[0478] In general, however, in primates, such as rhesus macaque that have received haploidential stem cell transplants, the mean survivial time (MST) post-transplant and in the absence of therapy is 8 days.

[0479] Concept 118. A method according to concept 117, wherein survival is increased by at least 7 days, or by at least 14 days, or by at least 20 days, or by at least 30 days or by at least 40 days, or by at least 50 days, or by at least 60 days, or by at least 70 days.

[0480] Concept 119. A method of increasing the number of disease-free, or disease-progression free, days in a a subject having or at risk of an OX40L-mediated disease or condition by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab); anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

[0481] In one embodiment, then OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In humans, the presence of signs and symtpoms of acute GvHD may be staged and graded according to a standardised scale such as described in Przepiorka *et al.* In primates, such as *rhesus macaques*, the presence of signs and symtpoms of acute GvHD may be staged and graded according to a standardised scale such as described herein in Example 7.

[0482] Thus, the number of disease free days may be measured by absence of clinical grading symptoms. The number of disease-progression free days may be measures as the number of days where the clinical grading score does not change.

[0483] Concept 120. A method according to concept 119, wherein the number of disease-free, or disease-progression free, days is at least 7 days, or at least 14 days, or at least 21 days, or at least 28 or at least 40 days, or at least 50 days, or by at least 60 days, or at least 70 days.

[0484] Concept 121. A method according to concept 120, wherein the number of disease free, or disease-progression free, days is at least 90 days, at least 180 days or at least 365 days.

[0485] Concept 122. A method of treating or reducing the risk of transplant rejection or GvHD in a subject by administering a therapeutic or prophylactic combination of an anti-OX40L antibody and a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab); anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat, wherein the combination results in an increased survival in a *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation as compared to either the antibody or the further therapeutic agent as a monotherapy.

[0486] In one embodiment, the method is a method of preventing an OX40L-mediated disease or condition.

[0487] In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a rapamycin (sirolimus). In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is tacrolimus. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is cyclophosphamide. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is ciclosporin. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD, and the further therapeutic agent is mycophenolate mofetil.

[0488] The *Rhesus macaque* model of haploidentical hematopoietic stem cell transplantation may be as described in aspect 99 herein.

[0489] Concept 123. A method according to any one of concepts 106, 109, 110, 117, 119, or 122, wherein the survival is increased by at least 7 days, or by at least 14 days, or by at least 21 days, or by at least 28 days, or by at least 40 days, or by at least 50 days, or by at least 60 days, or by at least 70 days as compared to either the antibody or the further therapeutic agent as a monotherapy.

[0490] Concept 124. A method according to any one of concepts 106, 109, 110, 117, 119, or 122, wherein survival is at least doubled, e.g tripled, as compared to either the antibody or the further therapeutic agent as a monotherapy.

[0491] Concept 125. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceeding concept, wherein the antibody specifically binds to human OX40L (hOX40L).

[0492] The hOX40L may be as described in aspect 28 or aspect 30 described herein.

[0493] In any of the concepts provided herein, the anti-OX40L antibody may be as described elsewhere herein. In one embodiment, the anti-OX40L antibody is as described in any of aspects 1 to 11, 13 to 27, 29, 31 to 43 or 45 described herein. In another embodiment, the anti-OX40L antibody is as described in aspects 73 to 89, or as in any of aspects 95 to 102 described herein. In another embodiment, the anti-OX40L antibody is as described in any of concepts 53 to 64 hereinabove. Other properties of anti-OX40L antibodies are described on pages 86 to 89, in the section entitled "bispecifics" beginning on page 90 herein, in the section entited "Antibodies" beginning on page 108 herein and in the section entitled "Methods of Administration and Dosing" beginning on page 130 herein.

[0494] Concept 126. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 125, which competes for binding to said hOX40L with an antibody selected from the group consisting of 02D10, 10A07, 09H04 and 19H01.

[0495] Competition between antibodies may be determined as described in aspect 13 or aspect 73, for example as determined by SPR, ELISA, HTRF or FACS. Methods related to the measurement methods are disclosed herein, including in the Examples.

[0496] Concept 127. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 126, which competes for binding to said hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY, wherein X is any amino acid.

[0497] Concept 128. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceeding concept, wherein the antibody antagonises specific binding of OX4D to OX40L, e.g. as determined using SPR or ELISA.

[0498] Antagonism and inhibition may be carried out as defined on page 94 to 95.

[0499] Concept 129. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is a humanized, human or fully human antibody.

[0500] Concept 130. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is a fragment of an antibody selected from the list of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments thereof.

[0501] Concept 131. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment enables greater than 80% stem cell donor chimerism by day 12 in a Rhesus macaque model of haploidentical hematopoietic stem cell transplantation.

[0502] Concept 132. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment expresses as a stably transfected pool in Lonza GS-XceedTM at level greater than 1.5g/L in a fed batch overgrow culture using Lonza version 8 feed system with an overgrow period of 14 days.

[0503] Concept 133. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g. IGHJ6*02).

[0504] Concept 134. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises a CDR selected from:

1. a. the HCDR3 of antibody 2D10 (Seq ID No:40 or Seq ID No:46);
2. b. the HCDR3 of antibody 10A7 (Seq ID No:8 or SEQ ID No:14);
3. c. the HCDR3 of antibody 09H04 (Seq ID No:72 or Seq ID No:78);
4. d. the HCDR3 of antibody 19H01 (Seq ID No:100 or Seq ID No:106);
5. e. a CDR3 of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
6. f. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or
7. g. an HCDR3 of any of the antibodies having the variable region amino acid sequence of Seq ID Nos: 232 or 234.

[0505] Concept 135. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises:

1. a. the CDRs of antibody 2D10 (Seq ID No:40 or Seq ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
2. b. the CDRs of antibody 10A7 (Seq ID No:8 or SEQ ID No:14 for CDRH3, SEQ ID No:6 or SEQ ID No:12 for CDRH2, SEQ ID No:4 or SEQ ID No:10 for CDRH1, SEQ ID No:18 or SEQ ID No:24 for CDRL1, SEQ ID No:20 or SEQ ID No:26 for CDRL2 and SEQ ID No:22 or SEQ ID No:28 for CDRL3);
3. c. the CDRs of antibody 09H04 (Seq ID No:72 or Seq ID No:78 for CDRH3, SEQ ID No:70 or SEQ ID No:76 for CDRH2, SEQ ID No:68 or SEQ ID No:74 for CDRH1, SEQ ID No:82 or SEQ ID No:88 for CDRL1, SEQ ID No:84 or SEQ ID No:90 for CDRL2 and SEQ ID No:86 or SEQ ID No:92 for CDRL3);
4. d. the CDRs of antibody 19H01 (Seq ID No:100 or Seq ID No:106 for CDRH3, SEQ ID No:98 or SEQ ID No:104 for CDRH2, SEQ ID No:96 or SEQ ID No:102 for CDRH1, SEQ ID No:110 or SEQ ID No: 116 for CDRL1, SEQ ID No: 112 or SEQ ID No: 118 for CDRL2 and SEQ ID No: 114 or SEQ ID No:120 for CDRL3);
5. e. the CDRs of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
6. f. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 214, 216, 218, 220, 222, 224, 226 or 228; or
7. g. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

[0506] Concept 136. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

1. a. the VH and/or VL domains of antibody 2D10 (Seq ID No:34 for VH and/or Seq ID No:48 for VL);
2. b. the VH and/or VL domains of antibody 10A7 (Seq ID No:2 for VH and/or Seq ID No:16 for VL);
3. c. the VH and/or VL domains of antibody 09H04 (Seq ID No:66 for VH and/or Seq ID No:80 for VL);
4. d. the VH and/or VL domains of antibody 19H01 (Seq ID No:94 for VH and/or Seq ID No:108 for VL);
5. e. a VH domain of any of the nanobodies having the variable region amino acid sequence of Seq ID Nos: 177 to 213;
6. f. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos: 214, 216, 218, 220, 222, 224, 226 or 228; or
7. g. a VH domain of any of the antibodies having the heavy chain variable region amino acid sequence of Seq ID Nos: 232 or 234, and a VL domain of any of the antibodies having the light chain variable region amino acid sequence of Seq ID Nos:231 or 233.

[0507] Concept 137. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the antibody is oxelumab.

[0508] Concept 138. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is a primate.

[0509] The term "subject" may be other subjects as described herein, for example as described on page 104. In one embodiment, the primate is a *rhesus macaque* monkey.

[0510] Concept 139. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is a human.

[0511] In one embodiment, the subject is a human patient.

[0512] Concept 140. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the subject is at risk of an OX40L-mediated disease or condition.

[0513] In one embodiment, a subject may be indentified as being "at risk of an OX40L-mediated disease or condition" if the subject has been previously identified as having an increased risk, e.g. by genotyping and/or phenotyping, but the subject has not yet presented symptoms or would not be diagnosed as having such a disease or condition by any conventional method. Thus, the methods and uses disclosed herein may aid in the early identification of patients who will develop such diseases or conditions. In one embodiment, the disease or condition is prevented (i.e. the treatment is prophylactic).

[0514] In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. In a particular embodiment, the subject is at risk of GvHD or transplant rejection when they are pre-operative for a transplant. In particular, a subject is at risk of GvHD or tansplant rejection when they have commenced a pre-transplant conditioning regimen (e.g. myeoablation by irradiation, preparative chemotherapy), and when degree of donor-recipient tissue matching (HLA matching, and/or relationship of donor-recipient) is not 100%. Potential transplant therapies are envisaged in concept 78 hereinabove.

[0515] Concept 141. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 40, wherein the method, antibody or fragment for the use, the use or the composition is for the prevention of the OX40L-mediated disease or condition.

[0516] Concept 142. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 101 to 139, wherein the subject has an OX40L-mediated disease or condition.

[0517] A subject has an OX40L-mediated disease or condition if the subject is presenting symptoms which would conventionally be associated with said disease or condition or if the subject would be diagnosed as having such a disease or condition by any conventional method. In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, particularly GvHD, and a subject may be determined to have the disease by any of the methods mentioned in concepts 101 to 105 and 119 hereinabove.

[0518] Concept 143. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 142, wherein the method, antibody or fragment for the use, the composition for the use, or the use is for the treatment of the OX40L-mediated disease or condition.

[0519] In one embodiment, treatment is commenced when the OX40L-mediated disease or condition has been diagnosed as a confirmed disease or condition.

[0520] In one embodiment, the OX40L-mediated disease or condition is GvHD or transplant rejection, in particular GvHD. GvHD grading may be determined as described herein (see concepts 101 to 105 and 119 hereinabove). In one embodiment, the subject is a human having Grade II clinical symptoms of GvHD.

[0521] Concept 144. A method, an antibody or fragment for the use, a composition for the use, or the use according to any preceding concept, wherein the OX40L-mediated disease or condition is selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection.

[0522] Concept 145. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 144, wherein the OX40L-mediated disease or condition is selected from inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis.

[0523] Concept 146. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 145, wherein the OX40L-mediated disease or condition is GvHD or transplant rejection.

[0524] Concept 147. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 146, wherein the OX40L-mediated disease or condition is GvHD.

[0525] Concept 148. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 146, wherein the transplant is a cell, tissue or organ transplant (e.g. liver, lung, heart, kidney or bowel), or a blood transplant (e.g. autologous or allogeneic), for example where the blood is bone marrow-derived, is cord-blood derived (umbilical), or is peripheral-blood derived.

[0526] Concept 149. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 146 to 148, wherein the anti-OX40L antibody or fragment thereof is administered before transplant.

[0527] Concept 150. A method, an antibody or fragment for the use, a composition for the use, or the use according to any one of concepts 146 to 148, wherein the anti-OX40L antibody or fragment thereof is administered after transplant.

[0528] Concept 151. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 149 or concept 150, wherein the further therapeutic agent is administered after transplant.

[0529] In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the further therapeutic agent is tacrolimus. In one embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the further therapeutic agent is cyclophosphamide. In one embodiment, the further therapeutic agent is ciclosporin. In one embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the further therapeutic agent is mycophenolate mofetil. In one embodiment, the further therapeutic agent is methyl prednisolonel.

[0530] Concept 152. A method, an antibody or fragment for the use, a composition for the use, or the use according to concept 149 or concept 150, wherein the further therapeutic agent is administered before transplant.

[0531] In one embodiment, the further therapeutic agent is rapamycin (sirolimus). In one embodiment, the further therapeutic agent is tacrolimus. In one embodiment, the further therapeutic agent is a combination of tacrolimus and methotrexate. In one embodiment, the further therapeutic agent is cyclophosphamide. In one embodiment, the further therapeutic agent is ciclosporin. In one embodiment, the further therapeutic agent is a combination of ciclosporin and methotrexate. In one embodiment, the further therapeutic agent is mycophenolate mofetil.

[0532] Concept 153. A pharmaceutical composition comprising an anti-OX40L antibody or fragment thereof and a pharmaceutically acceptable excipient, diluent or carrier and further comprising a further therapeutic agent independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa /TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat.

[0533] In one embodiment, there is provided a composition or kit for treating and/or preventing a OX40L-mediated condition or disease, the composition or kit comprising an antibody or fragment of the invention in combination with a further therapeutic agent optionally in combination with a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

[0534] The composition may be as described in aspect 105, 106 or 107 herein. Excipients for use in pharmaceutical formulations are well-known to the skilled person and may be as defined on page 97 herein, or in the section entitled "Pharmaceutical Compositions" beginning on page 118 herein, or in the section entitled "Methods of Administration and Dosing" beginning on page 130 herein.

[0535] Concept 154. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, wherein the further therapeutic agent is independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0536] Other combinations may be with the anti-inflammatory drugs described in aspect 46 herein, or as described in aspect 103. Other combinations are as described in concepts 81 to 83 hereinabove, or in any of concepts 101 to 153 hereinabove.

[0537] Concept 155. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin, tacrolimus, ciclosporin, cyclophosphamide, corticosteroids (e.g. methylprednisolone), methotrexate or mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept) and anti-thymocyte globulins.

[0538] Concept 156. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of rapamycin, tacrolimus, ciclosporin, cyclophosphamide, corticosteroids (e.g. methylprednisolone), methotrexate and mycophenolate mofetil.

[0539] Concept 157. A method, an antibody or fragment for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of an immunosuppressant that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus)), and anti-CD25 antibodies (e.g. basiliximab, daclizumab).

[0540] Concept 158. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a further therapeutic agent independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0541] Concept 159. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of rapamycin.

[0542] Concept 160. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of tacrolimus.

[0543] Concept 161. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of tacrolimus and methotrexte.

[0544] Concept 162. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of ciclosporin.

[0545] Concept 163. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of ciclosporin and methotrexte.

[0546] Concept 164. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of cyclophosphamide.

[0547] Concept 165. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of mycophenolate mofetil.

[0548] Concept 166. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, further comprising administering to the human a therapeutically effective amount, or a prophylactically effective amount of a corticosteroid (e.g. methyl prednisolone).

[0549] Concept 167. A method, an antibody or fragment for the use, a composition for the use, the use or the composition according to any preceding concept, wherein the further therapeutic agent is administered sequentially or simultaneously with the anti-hOX40L antibody or fragment.

[0550] As explained in the examples, the inventors devised a set of criteria that is particularly useful for identifying antibodies and fragments of the invention, these criteria being:-

1. (a) The ability of the antibody or fragment to bind cell-surface hOX40L on CHO-S cells (optionally transfected with full length human OX40L) and/or bind recombinant hOX40L in a HTRF assay;
2. (b) The ability of the antibody or fragment to neutralise human OX40 (e.g. neutralise human OX40L binding to human OX40 Receptor) in a receptor neutralisation HTRF assay and/or a flow cytometry receptor neutralisation assay; and
3. (c) The ability of the antibody or fragment to specifically bind both human and rhesus monkey OX40L (useful so that the PK, PD, efficacy and other parameters of the antibody or fragment can be assessed in the rhesus model as a surrogate for humans).

[0551] Thus, in an example of the invention the antibody or fragment meets criteria (a), (b) and (c).

[0552] In an example, criterion (a) is set so that the antibody or fragment shows <70% receptor binding by FACS to hOX40L expressed by CHO-S cells.

[0553] In an example, criterion (a) is set so that the antibody or fragment shows <90% of receptor binding to OX40L in the HTRF assay.

[0554] In an example, criterion (a) is set so that the antibody or fragment shows at least a 20% effect in the HTRF assay.

[0555] In an example, OX40 is used in criterion (b).

[0556] In an embodiment, assaying or testing of an antibody or fragment of the invention is carried out at or substantially at pH7 (e.g., for *in vitro* tests and assays) and at or substantially at rtp.

[0557] Optionally, the antibody or fragment specifically binds hOX40L with an affinity (apparent affinity, Kd) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1mM to 1pM (e.g., 1mM to 100pM; 10nM to 100pM; 1nM to 10pM; or 100pM to 1pM) as determined by SPR, e.g., under SPR conditions disclosed herein). Additionally or alternatively, the antibody or fragment specifically binds rhesus monkey OX40L with an affinity (apparent affinity, Kd) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1mM to 1pM (e.g., 1mM to 100pM; 10nM to 100pM; 1nM to 10pM; or 100pM to 1pM) as determined by SPR, e.g., under SPR conditions disclosed herein). Such binding measurements can be made using a variety of binding assays known in the art, e.g., using surface plasmon resonance (SPR), such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®), using KinExA® (Sapidyne Instruments, Inc), or using ForteBio Octet (Pall ForteBio Corp.).

[0558] OX40L binding ability, specificity and affinity (Kd, K_{off} and/or K_{on}) can be determined by any routine method in the art, e.g., by surface plasmon resonance (SPR). The term "Kd", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0559] In one embodiment, the surface plasmon resonance (SPR) is carried out at 25°C. In another embodiment, the SPR is carried out at 37°C.

[0560] In one embodiment, the SPR is carried out at physiological pH, such as about pH7 or at pH7.6 (e.g., using Hepes buffered saline at pH7.6 (also referred to as HBS-EP)).

[0561] In one embodiment, the SPR is carried out at a physiological salt level, e.g., 150mM NaCl.

[0562] In one embodiment, the SPR is carried out at a detergent level of no greater than 0.05% by volume, e.g., in the presence of P20 (polysorbate 20; e.g., Tween-20™) at 0.05% and EDTA at 3mM.

[0563] In one example, the SPR is carried out at 25°C or 37°C in a buffer at pH7.6, 150mM NaCl, 0.05% detergent (e.g., P20) and 3mM EDTA. The buffer can contain 10mM Hepes. In one example, the SPR is carried out at 25°C or 37°C in HBS-EP. HBS-EP is available from Teknova Inc (California; catalogue number H8022).

[0564] In an example, the affinity of the antibody or fragment is determined using SPR by

1. 1. Coupling anti-mouse (or other relevant human, rat or non-human vertebrate antibody constant region species-matched) IgG (e.g., Biacore™ BR-1008-38) to a biosensor chip (e.g., GLM chip) such as by primary amine coupling;
2. 2. Exposing the anti-mouse IgG (or other matched species antibody) to a test IgG antibody to capture test antibody on the chip;
3. 3. Passing the test antigen over the chip's capture surface at 1024nM, 256nM, 64nM, 16nM, 4nM with a 0nM (i.e. buffer alone); and
4. 4. And determining the affinity of binding of test antibody to test antigen using surface plasmon resonance, e.g., under an SPR condition discussed above (e.g., at 25°C in physiological buffer). SPR can be carried out using any standard SPR apparatus, such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®).

[0565] Regeneration of the capture surface can be carried out with 10mM glycine at pH1.7. This removes the captured antibody and allows the surface to be used for another interaction. The binding data can be fitted to 1:1 model inherent using standard techniques, e.g., using a model inherent to the ProteOn XPR36™ analysis software.

[0566] In an example, the antibody or fragment of the invention is contained in a medical container, e.g., a vial, syringe, IV container or an injection device (e.g., an intraocular or intravitreal injection device). In an example, the antibody or fragment is *in vitro*, e.g., in a sterile container. In an example, the invention provides a kit comprising the antibody or fragment of the invention, packaging and instructions for use in treating or preventing or diagnosing in a human a disease or condition mediated by the OX40L. In an example, the instructions indicate that the human should be genotyped for an OX40L variant sequence of the invention before administering the antibody or fragment to the human. In an example, the instructions indicate that the human should be phenotyped for an OX40L variant of the invention before administering the antibody or fragment to the human. In an example, the human is of Chinese (e.g., Han or CHS) ethnicity and the instructions are in Chinese (e.g., Mandarin).

[0567] In an example the binding site(s) of the antibody or fragment are selected from a plurality (e.g., library) of binding sites. For example, the plurality of binding sites comprises or consists of a plurality of 4-chain antibodies or fragments thereof, e.g., dAbs, Fabs or scFvs. Suitable methods for producing pluralities of binding sites for screening include phage display (producing a phage display library of antibody binding sites), ribosome display (producing a ribosome display library of antibody binding sites), yeast display (producing a yeast display library of antibody binding sites), or immunisation of a non-human vertebrate (e.g., a rodent, e.g., a mouse or rat, e.g., a Velocimouse™, Kymouse™, Xenomouse™, Alka Mouse™, HuMab Mouse™, Omnimouse™, Omnirat™ or MeMo Mouse™) with hOX40L or a hOX40L epitope and isolation of a repertoire of antibody-producing cells (e.g., a B-cell, plasma cell or plasmablast repertoire) and/or a repertoire of isolated antibodies, fragments or binding sites.

[0568] The term "epitope" is a region of an antigen that is bound by an antibody or fragment. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0569] The term "isolated" with reference to any aspect of the invention, e.g., an antibody or fragment, means that a subject antibody or fragment etc. (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same

species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. Typically, an "isolated" antibody, fragment, etc. constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50%, 60%, 70%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or >99% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated antibody, fragment, etc. Preferably, the isolated antibody, fragment, etc. is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

[0570] For example, an "isolated" antibody is one that has been identified, separated and/or recovered from a component of its production environment (e.g., naturally or recombinantly). Preferably, the isolated polypeptide is free of association with all other components from its production environment, e.g., so that the antibody has been isolated to an FDA-approvable or approved standard. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated polypeptide or antibody will be prepared by at least one purification step.

Immunoconjugates

[0571] The invention encompasses the antibody or fragment conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxin agents include any agent that is detrimental to cells. Examples of suitable cytotoxin agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Bispecifics

[0572] The antibodies and fragments of the present invention may be monospecific, bispecific, or multispecific. Multispecific mAbs may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., (1991) J. Immunol. 147:60-69. The human anti-hOX40L antibodies or fragments can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity.

[0573] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig CH3 domain binds Protein A and the second Ig CH3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second CH3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT, N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

[0574] In certain embodiments, the antibody or OX40L binding fragment thereof comprises less than six CDRs. In some embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3. In specific embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3).

[0575] In specific embodiments, an antibody of the invention is a fully human antibody, a monoclonal antibody, a recombinant antibody, an antagonist antibody, a hOX40L-neutralising antibody or any combination thereof or the invention provides a hOX40L binding fragment thereof. In an example, the antibody is a chimaeric antibody comprising human variable domains and non-human (e.g., mouse or rat or rabbit) constant domains. In particular embodiments, the antibody is a fully human antibody, such as a fully human monoclonal antibody, or antigen binding fragment thereof, that specifically binds to hOX40L. In preferred embodiments, the antibody is an antagonist antibody. In preferred embodiments, the antibody is a neutralising antibody.

[0576] In an example, the antibody or fragment is a lambda-type antibody or fragment (i.e., whose variable domains are lambda variable domains). Optionally, the antibody or fragment also comprises lambda constant domains.

[0577] In certain embodiments, the antibody competes (e.g., in a dose dependent manner) with OX40 or a fusion protein thereof (e.g., Fc:OX40), for binding to hOX40L, such as a cell surface-expressed hOX40L or soluble hOX40L. Exemplary competitive blocking tests are provided in the Examples herein.

[0578] In another aspect, provided herein are isolated nucleic acids encoding antibodies that specifically bind to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L), a hOX40L polypeptide fragment, or a hOX40L epitope. In certain embodiments, the nucleic acid encodes a VH chain, VL chain, VH domain, VL domain, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as disclosed in the sequence listing (i.e. Seq ID No:30 or Seq ID No:62 for VH chains; Seq ID No:32 or Seq ID No:64 for VL chains; Seq ID No: Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34 for VH domains; Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48 for VL domains; Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3).

[0579] In another aspect, provided herein are vectors and host-cells comprising nucleic acids encoding antibodies or fragments of the invention.

[0580] In certain embodiments, the antibody specifically binds to one or more single nucleotide polymorphism (SNP) variants of hOX40L. In an example of any aspect of the invention, the hOX40L is a trimer of monomers.

[0581] In an aspect, provided herein is a method for decreasing (e.g., by at least 20, 30, 40 50 or 60%, or 70%, 80%, 90%, 95% or >90%) or completely inhibiting binding of hOX40L to OX40 in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L).

[0582] In an aspect, provided herein is a method of treating or preventing a hOX40L-mediated disease or condition in a subject (e.g., a human subject), the method comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L), wherein the disease or condition is treated or prevented by the antibody or fragment. In an example, the method comprises decreasing or inhibiting a hOX40L biological activity, such as secretion of one, more or all of IL-2, IL-8, TNF alpha and interferon gamma, in the subject. In an example, the biological activity is selected from the secretion of one, more or all of IL-2, TNF alpha and interferon gamma. In an example, the biological activity is selected from the secretion of one, more or all of IL-8, CCL20 and RANTES.

[0583] In an aspect, provided herein is a method of decreasing or inhibiting a hOX40L biological activity, such as secretion of one, more or all of IL-2, IL-8, TNF alpha and interferon gamma, in a subject (e.g., a human subject), the method comprising administering to the subject an effective amount of an antibody or fragment thereof of the invention that specifically binds to hOX40L (e.g., a cell surface-expressed or soluble hOX40L), wherein hOX40L biological activity is decreased by the antibody or fragment. In an example, the biological activity is selected from the secretion of one, more or all of IL-2, TNF alpha and interferon gamma. In an example, the biological activity is selected from the secretion of one, more or all of IL-8, CCL20 and RANTES.

[0584] The term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% (or 4%, or 3% or 2%, or, in an example, 1% or less) of a given value or range.

[0585] As used herein, "administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (e.g., an anti-hOX40L antibody provided herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease, or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof.

[0586] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=number of identical overlapping positions/total number of positions×100%). In one embodiment, the two sequences are the same length.

[0587] 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 preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264-2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol. 215:403. 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 of the present invention. 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 of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389-3402. 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 preferred, 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. 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.

[0588] 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.

[0589] As used herein, an "antagonist" or "inhibitor" of hOX40L refers to a ligand (e.g., antibody or fragment) that is capable of inhibiting or otherwise decreasing one or more of the biological activities of hOX40L, such as in a cell expressing hOX40L or in a cell expressing a hOX40L ligand. For example, in certain embodiments, antibodies of the invention are antagonist antibodies that inhibit or otherwise decrease secretion of CCL20, IL-8 and/or RANTES from a cell having a cell surface-expressed OX40 when said antibody is contacted with said cell. In some embodiments, an antagonist of hOX40L (e.g., an antagonistic antibody of the invention) may, for example, act by inhibiting or otherwise decreasing the activation and/or cell signalling pathways of the cell expressing OX40L, thereby inhibiting a hOX40L-mediated biological activity of the cell the relative to the hOX40L-mediated biological activity in the absence of antagonist. In certain embodiments, the antibodies provided herein are fully human, antagonistic anti-hOX40L antibodies, preferably fully human, monoclonal, antagonistic anti-hOX40L antibodies.

[0590] The term "antibody" and "immunoglobulin" or "Ig" may be used interchangeably herein. An antibody or a fragment thereof that specifically binds to a hOX40L antigen may be cross-reactive with related antigens. Preferably, an antibody or a fragment thereof that specifically binds to a hOX40L antigen does not cross-react with other antigens (but may optionally cross-react with OX40L of a different species, e.g., rhesus, or murine). An antibody or a fragment thereof that specifically binds to a hOX40L antigen can be identified, for example, by immunoassays, BIAcore™, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a hOX40L antigen when it binds to a hOX40L antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 times background. See, e.g., Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

[0591] Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (e.g., including monospecific, bispecific, etc.), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. In particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., antigen binding domains or molecules that contain an antigen-binding site that specifically binds to a hOX40L antigen (e.g., one or more complementarity determining regions (CDRs) of an anti-hOX40L antibody). The antibodies of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, in particular IgG4), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. In preferred embodiments, the hOX40L antibodies are fully human, such as fully human monoclonal hOX40L antibodies. In certain embodiments, antibodies of the invention are IgG antibodies, or a class (e.g., human IgG1 or IgG4) or subclass thereof. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

[0592] The term "antigen binding domain,""antigen binding region," "antigen binding fragment," and similar terms refer to that portion of an antibody which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (e.g., the complementarity determining regions (CDRs)). The antigen binding region can be derived from any animal species, such as rodents (e.g., rabbit, rat or hamster) and humans. Preferably, the antigen binding region will be of human origin.

[0593] As used herein, the term "composition" is intended to encompass a product containing the specified ingredients (e.g., an antibody of the invention) in, optionally, the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts.

[0594] In the context of a polypeptide, the term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or an antibody that specifically binds to a hOX40L polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or an antibody that specifically binds to a hOX40L polypeptide which has been chemically modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may be chemically modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. A derivative of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may be chemically modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a hOX40L polypeptide, a fragment of a hOX40L polypeptide, or a hOX40L antibody described herein.

[0595] The term "effective amount" as used herein refers to the amount of a therapy (e.g., an antibody or pharmaceutical composition provided herein) which is sufficient to reduce and/or ameliorate the severity and/or duration of a given disease and/or a symptom related thereto. This term also encompasses an amount necessary for the reduction or amelioration of the advancement or progression of a given disease, reduction or amelioration of the recurrence, development or onset of a given disease, and/or to improve or enhance the prophylactic or therapeutic effect(s) of another therapy (e.g., a therapy other than anti-hOX40L antibody provided herein). In some embodiments, the effective amount of an antibody of the invention is from about 0.1 mg/kg (mg of antibody per kg weight of the subject) to about 100 mg/kg. In certain embodiments, an effective amount of an antibody provided therein is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg (or a range therein). In some embodiments, "effective amount" as used herein also refers to the amount of an antibody of the invention to achieve a specified result (e.g., inhibition of a hOX40L biological activity of a cell, such as inhibition of secretion of CCL20, IL-8 or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ from the cell).

[0596] The term "epitope" as used herein refers to a localized region on the surface of an antigen, such as hOX40L polypeptide or hOX40L polypeptide fragment, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human, that is capable of eliciting an immune response. An epitope having immunogenic activity is a portion of a polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody specifically binds as determined by any method well known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. A region of a polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. In certain embodiments, a hOX40L epitope is a three-dimensional surface feature of a hOX40L polypeptide (e.g., in a trimeric form of a hOX40L polypeptide). In other embodiments, a hOX40L epitope is linear feature of a hOX40L polypeptide (e.g., in a trimeric form or monomeric form of the hOX40L polypeptide). Antibodies provided herein may specifically bind to an epitope of the monomeric (denatured) form of hOX40L, an epitope of the trimeric (native) form of hOX40L, or both the monomeric (denatured) form and the trimeric (native) form of hOX40L. In specific embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hOX40L but do not specifically bind the monomeric form of hOX40L.

[0597] The term "excipients" as used herein refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes, but not limited to, proteins (e.g., serum albumin, etc.), amino acids (e.g., aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (e.g., alkyl sulfonates, caprylate, etc.), surfactants (e.g., SDS, polysorbate, nonionic surfactant, etc.), saccharides (e.g., sucrose, maltose, trehalose, etc.) and polyols (e.g., mannitol, sorbitol, etc.). See, also, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa..

[0598] In the context of a peptide or polypeptide, the term "fragment" as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative RNA splicing or from in vivo protease activity. In certain embodiments, hOX40L fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues of the amino acid sequence of a hOX40L polypeptide or an antibody that specifically binds to a hOX40L polypeptide. In a specific embodiment, a fragment of a hOX40L polypeptide or an antibody that specifically binds to a hOX40L antigen retains at least 1, at least 2, or at least 3 functions of the polypeptide or antibody.

[0599] The terms "fully human antibody" or "human antibody" are used interchangeably herein and refer to an antibody that comprises a human variable region and, most preferably a human constant region. In specific embodiments, the terms refer to an antibody that comprises a variable region and constant region of human origin. "Fully human" anti-hOX40L antibodies, in certain embodiments, can also encompass antibodies which bind hOX40L polypeptides and are encoded by nucleic acid sequences which are naturally occurring somatic variants of human germline immunoglobulin nucleic acid sequence. In a specific embodiment, the anti-hOX40L antibodies provided herein are fully human antibodies. The term "fully human antibody" includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat et al. (1991) Sequences of

Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Exemplary methods of producing fully human antibodies are provided, e.g., in the Examples herein, but any method known in the art may be used.

[0600] The phrase "recombinant human antibody" includes human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (e.g., a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (see e.g., Taylor, L. D. et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies can have variable and constant regions derived from human germline immunoglobulin sequences (See Kabat, E. A. et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0601] The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (i.e., a polypeptide or protein not normally a part of the antibody (e.g., a non-anti-hOX40L antigen antibody)). The term "fusion" when used in relation to hOX40L or to an anti-hOX40L antibody refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative thereof, with a heterologous peptide or polypeptide. Preferably, the fusion protein retains the biological activity of the hOX40L or anti-hOX40L antibody. In certain embodiments, the fusion protein comprises a hOX40L antibody VH domain, VL domain, VH CDR (one, two or three VH CDRs), and/or VL CDR (one, two or three VL CDRs), wherein the fusion protein specifically binds to a hOX40L epitope.

[0602] The term "heavy chain" when used in reference to an antibody refers to five distinct types, called alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant domain. These distinct types of heavy chains are well known and give rise to five classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG1, IgG3 and IgG4. Preferably the heavy chain is a human heavy chain. In one example, the heavy chain is a disabled IgG isotype, e.g. a disabled IgG4. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

[0603] The term "host" as used herein refers to an animal, preferably a mammal, and most preferably a human.

[0604] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0605] The term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, as used herein refer to an agent that modulates a host's immune system. In certain embodiments, an immunomodulatory agent is an immunosuppressant agent. In certain other embodiments, an immunomodulatory agent is an immunostimulatory agent. In accordance with the invention, an immunomodulatory agent used in the combination therapies of the invention does not include an anti-hOX40L antibody or antigen-binding fragment. Immunomodulatory agents include, but are not limited to, small molecules, peptides, polypeptides, proteins, fusion proteins, antibodies, inorganic molecules, mimetic agents, and organic molecules.

[0606] As used herein, the term "in combination" in the context of the administration of other therapies refers to the use of more than one therapy. The use of the term "in combination" does not restrict the order in which therapies are administered to a subject with a disease. A first therapy can be administered before (e.g., 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks), concurrently, or after (e.g., 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks) the administration of a second therapy to a subject which had, has, or is susceptible to a hOX40L-mediated disease. Any additional therapy can be administered in any order with the other additional therapies. In certain embodiments, the antibodies of the invention can be administered in combination with one or more therapies (e.g., therapies that are not the antibodies of the invention that are currently administered to prevent, treat, manage, and/or ameliorate a hOX40L-mediated disease. Non-limiting examples of therapies that can be administered in combination with an antibody of the invention include analgesic agents, anesthetic agents, antibiotics, or immunomodulatory agents or any other agent listed in the U.S. Pharmacopoeia and/or Physician's Desk Reference.

[0607] An "isolated" or "purified" antibody is for example substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. 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%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is preferably 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 have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a preferred embodiment, antibodies of the invention are isolated or purified.

[0608] An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source 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. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody of the invention is isolated or purified.

[0609] The term "human OX40L," "hOX40L" or "hOX40L polypeptide" and similar terms refers to the polypeptides ("polypeptides," "peptides" and "proteins" are used interchangeably herein) comprising the amino acid sequence in the sequence listing and related polypeptides, including SNP variants thereof. Related polypeptides include allelic variants (e.g., SNP variants); splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies homologs, preferably, which retain hOX40L activity and/or are sufficient to generate an anti-hOX40L immune response. Also encompassed are soluble forms of hOX40L which are sufficient to generate an anti-hOX40L immunological response. As those skilled in the art will appreciate, an anti-hOX40L antibody of the invention can bind to a hOX40L polypeptide, polypeptide fragment, antigen, and/or epitope, as an epitope is part of the larger antigen, which is part of the larger polypeptide fragment, which, in turn, is part of the larger polypeptide hOX40L can exist in a trimeric (native) or monomeric (denatured) form.

[0610] The terms "Kabat numbering," and like terms are recognized in the art and refer to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) Ann. NY Acad. Sci. 190:382-391 and, Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region typically ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3.

[0611] The term "monoclonal antibody" refers to an antibody obtained from a population of homogenous or substantially homogeneous antibodies, and each monoclonal antibody will typically recognize a single epitope on the antigen. In preferred embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody specifically binds to only a hOX40L epitope as determined, e.g., by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. The term "monoclonal" is not limited to any particular method for making the antibody. For example, monoclonal antibodies of the invention may be made by the hybridoma method as described in Kohler et al.; Nature, 256:495 (1975) or may 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 et al., eds., John Wiley and Sons, New York). Other exemplary methods of producing other monoclonal antibodies are provided in the Examples herein.

[0612] The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated by a human being.

[0613] The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

[0614] "Polyclonal antibodies" as used herein refers to an antibody population generated in an immunogenic response to a protein having many epitopes and thus includes a variety of different antibodies directed to the same and to different epitopes within the protein. Methods for producing polyclonal antibodies are known in the art (See, e.g., see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel et al., eds., John Wiley and Sons, New York).

[0615] As used herein, the term "polynucleotide," "nucleotide," nucleic acid" "nucleic acid molecule" and other similar terms are used interchangeable and include DNA, RNA, mRNA and the like.

[0616] As used herein, the terms "prevent," "preventing," and "prevention" refer to the total or partial inhibition of the development, recurrence, onset or spread of a hOX40L-mediated disease and/or symptom related thereto, resulting from the administration of a therapy or combination of therapies provided herein (e.g., a combination of prophylactic or therapeutic agents, such as an antibody of the invention).

[0617] As used herein, the term "prophylactic agent" refers to any agent that can totally or partially inhibit the development, recurrence, onset or spread of a hOX40L-mediated disease and/or symptom related thereto in a subject. In certain embodiments, the term "prophylactic agent" refers to an antibody of the invention. In certain other embodiments, the term "prophylactic agent" refers to an agent other than an antibody of the invention. Preferably, a prophylactic agent is an agent which is known to be useful to or has been or is currently being used to prevent a hOX40L-mediated disease and/or a symptom related thereto or impede the onset, development, progression and/or severity of a hOX40L-mediated disease and/or a symptom related thereto. In specific embodiments, the prophylactic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

[0618] In an embodiment, the prophylaxis prevents the onset of the disease or condition or of the symptoms of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening, or onset, of the disease or condition. In one embodiment, the prophylactic treatment prevents the worsening of the disease or condition.

[0619] In another embodiment, an anti-OX40L antibody of the invention is administered intravenously (e.g. before or concomitantly with a transplant, e.g. blood or organ transplant). In another embodiment, said antibody is administered at a dose of about 5-10 mg/kg (e.g. at about 8 mg/kg). In another embodiment, said antibody is administered at a dose selected from about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg, in particular about 1 mg/kg, or about 3 mg/kg.

[0620] In another embodiment, said antibody is administered 1-4 days before transplant (e.g. of blood or organs), e.g. 1-3 days before transplant or 1-2 days before transplant. In another embodiment, said antibody is administered weekly, bi-weekly or monthly following transplant, e.g. bi-weekly. In a further embodiment, said antibody is administered intravenously prophylactically 1-3 days before transplant at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg) and then intravenously, bi-weekly at a dose of about 5-10 mg/kg (e.g. about 8 mg/kg).

[0621] In another embodiment, the patient is monitored periodically post-transplant, for the presence of a biomarker predictive for the development of transplant rejection or of GvHD (e.g. acute GvHD), and the anti-OX40L antibody of the invention is administered once the biomarker levels are such that the patient is determined to be at risk of developing transplant rejection or of GvHD (e.g. acute GvHD). This strategy would avoid unnecessary dosing of drug and unnecessary suppression of the immune system. Examples of biomarkers which may be useful as predictive biomarkers of actue GvHD may be those identified in Levine et al., "A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study", Lancet Haematol 2015; 2:e21-29. These biomarkers include, but are not limited to TNFR1, ST-2, elafin and IL2Rα and Reg3α.

[0622] A region of a hOX40L contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. A localized region on the surface of a hOX40L antigen that is capable of eliciting an immune response is a hOX40L epitope. The epitope may or may not be a three-dimensional surface feature of the antigen.

[0623] A "hOX40L-mediated disease" and "hOX40L-mediated condition" are used interchangeably and refer to any disease or condition that is completely or partially caused by or is the result of hOX40L. In certain embodiments, hOX40L is aberrantly (e.g., highly) expressed on the surface of a cell. In some embodiments, hOX40L may be aberrantly upregulated on a particular cell type. In other embodiments, normal, aberrant or excessive cell signaling is caused by binding of hOX40L to a hOX40L ligand. In certain embodiments, the hOX40L ligand is OX40, for example, that is expressed on the surface of a cell, such as a colonic epithelial cell. In certain embodiments, the hOX40L-mediated disease is an inflammatory bowel disease (IBD), such as Crohn's disease (CD) or ulcerative colitis (UC). In other embodiments, the hOX40L-mediated disease is graft-versus-host disease (GVHD). In other embodiments, the hOX40L-mediated disease is selected from pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome, non-infectious scleritis and uveitis (non-infectious/autoimmune and/or systemic). In other embodiments, a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

[0624] The terms "hOX40L receptor" or "hOX40L binding receptor" are used interchangeably herein and refer to a receptor polypeptide that binds to hOX40L. In specific embodiments, the hOX40L receptor is Hox40. In some embodiments, the hOX40L receptor is expressed on the surface of a cell, such as a colonic epithelial cell; or on graft or transplant tissue or on host tissue.

[0625] As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, a subject is preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats, etc.) or a primate (e.g., monkey and human), most preferably a human. In one embodiment, the subject is a mammal, preferably a human, having a hOX40L-mediated disease. In another embodiment, the subject is a mammal, preferably a human, at risk of developing a hOX40L-mediated disease.

[0626] As used herein "substantially all" refers to refers to at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

[0627] The term "substantially free of surfactant" as used herein refers to a formulation of an antibody that specifically binds to a hOX40L antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants.

[0628] The term "substantially free of salt" as used herein refers to a formulation of an antibody that specifically binds to a hOX40L antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

[0629] The term "surfactant" as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

[0630] As used herein, the term "tag" refers to any type of moiety that is attached to, e.g., a polypeptide and/or a polynucleotide that encodes a hOX40L or hOX40L antibody or antigen binding fragment thereof. For example, a polynucleotide that encodes a hOX40L, hOX40L antibody or antigen binding fragment thereof can contain one or more additional tag-encoding nucleotide sequences that encode a, e.g., a detectable moiety or a moiety that aids in affinity purification. When translated, the tag and the antibody can be in the form of a fusion protein. The term "detectable" or "detection" with reference to a tag refers to any tag that is capable of being visualized or wherein the presence of the tag is otherwise able to be determined and/or measured (e.g., by quantitation). A non-limiting example of a detectable tag is a fluorescent tag.

[0631] As used herein, the term "therapeutic agent" refers to any agent that can be used in the treatment, management or amelioration of a hOX40L-mediated disease and/or a symptom related thereto. In certain embodiments, the term "therapeutic agent" refers to an antibody of the invention. In certain other embodiments, the term "therapeutic agent" refers to an agent other than an antibody of the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management or amelioration of a hOX40L-mediated disease or one or more symptoms related thereto. In specific embodiments, the therapeutic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

[0632] The combination of therapies (e.g., use of prophylactic or therapeutic agents) which is more effective than the additive effects of any two or more single therapy. For example, a synergistic effect of a combination of prophylactic and/or therapeutic agents permits the use of lower dosages of one or more of the agents and/or less frequent administration of said agents to a subject with a hOX40L-mediated disease. The ability to utilize lower dosages of prophylactic or therapeutic therapies and/or to administer said therapies less frequently reduces the toxicity associated with the administration of said therapies to a subject without reducing the efficacy of said therapies in the prevention, management, treatment or amelioration of a hOX40L-mediated disease. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention, or in the management, treatment or amelioration of a hOX40L-mediated disease. Finally, synergistic effect of a combination of therapies (e.g., prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

[0633] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD2B antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat. In another embodiment the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD2B antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0634] In some embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0635] In further embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basiliximab, daclizumab).

[0636] Without being bound by theory, it is thought that the mechanism of action of an anti-OX40L antibody of the invention is complementary to further therapeutic agents which modulate immune function. In particular, agents that modulate IL-2 signalling or that inhibit IL-2/IL-2R-mediated T cell proliferation may synergistically combine with an anti-OX40L antibody resulting in greater immune modulation than would be observed with either agent alone. As shown in Examples 7 and 9 hereinbelow, both tacrolimus and rapamycin display immune modulating activity. Tacrolimus and rapamycin are both agents which are known to modulate IL-2 signalling. In particular, rapamycin is known to act as an mTOR inhibitor, which reduces IL-2 and IL2R transcription, and inhibits cell cycle progression evoked by IL2R activation, but there may be other mechanisms on proliferation of T cells by which mTOR inhibitors may function (Thomson et al, Nat. Rev. Immunol., 2009, 9(6), 324-337; Scheffert & Raza, J. Thorac. Dis., 2014, 6(8), 1039-1053). Figure 6 herein shows that the mechanism of an anti-OX40L anbody is different with regards to Tscm population to both these agents, and Figure 7 shows a synergistic effect on survival of an anti-OX40L antibody of the invention in combination with rapamycin. It is therefore thought that other agents having a similar mechanism of action to rapamycin and/or tacrolimus will also result in a synergistic effect when used in combination with the anti-OX40L antibodies of the invention.

[0637] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus).

[0638] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a combination of tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cicllosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

[0639] As used herein, the term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease (e.g., IBD or GVHD). In certain embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease known to one of skill in the art such as medical personnel.

[0640] As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a hOX40L-mediated disease (e.g., IBD or GVHD) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents, such as an antibody of the invention). In specific embodiments, such terms refer to the reduction or inhibition of the binding of hOX40L to OX40, the reduction or inhibition of the production or secretion of CCL20 from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of IL-8 from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of RANTES from a cell expressing hOX40 or hOX40L, and/or the inhibition or reduction of one or more symptoms associated with a hOX40L-mediated disease, such as an IBD or GVHD. In specific embodiments, such terms refer to the reduction or inhibition of the binding of hOX40L to OX40, the reduction or inhibition of the production or secretion of INF-γ from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of TNF-α from a cell expressing hOX40 or hOX40L, the reduction or inhibition of the production or secretion of IL-2 from a cell expressing hOX40 or hOX40L, and/or the inhibition or reduction of one or more symptoms associated with a hOX40L-mediated disease, such as an IBD or GVHD (in particular GvHD). In an example, the cell is a human cell. In specific embodiments, a prophylactic agent is a fully human anti-hOX40L antibody, such as a fully human anti-hOX40L monoclonal antibody.

[0641] The term "variable region" or "variable domain" refers to a portion of the OX40L and heavy chains, typically about the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complimentarily determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). The CDRs of the OX40L and heavy chains are primarily responsible for the interaction of the antibody with antigen. Numbering of amino acid positions used herein is according to the EU Index, as in Kabat et al. (1991) Sequences of proteins of immunological interest. (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed. ("Kabat et al."). In preferred embodiments, the variable region is a human variable region.

Antibodies

[0642] Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (e.g., including monospecific, bispecific, etc.), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

[0643] In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds to a hOX40L antigen. The immunoglobulin molecules provided herein can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In a specific embodiment, an antibody provided herein is an IgG antibody, preferably an IgG1 or IgG4. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

[0644] Variants and derivatives of antibodies include antibody fragments that retain the ability to specifically bind to an epitope. Preferred fragments include Fab fragments; Fab' (an antibody fragment containing a single anti-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); $F(ab')_2$ (two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain Fab chain comprising a variable region, also known as, a sFv; a disulfide-linked Fv, or dsFv; a camelized VH (the variable, antigen-binding determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific sFv (a sFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (a dimerized sFv formed when the VH domain of a first sFv assembles with the VL domain of a second sFv and the VL domain of the first sFv assembles with the VH domain of the second sFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (a trimerized sFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen binding domains may be directed towards the same or different epitopes). Derivatives of antibodies also include one or more CDR sequences of an antibody combining site. The CDR sequences may be linked together on a scaffold when two or more CDR sequences are present. In certain embodiments, the antibody to be used with the invention comprises a single-chain Fv ("scFv"). scFvs are antibody fragments comprising the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFvs see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

[0645] The antibodies of the invention may be from any animal origin including birds and mammals (e.g., human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). In certain embodiments, the antibodies of the invention are human or humanized monoclonal antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice that express antibodies from human genes.

[0646] In preferred embodiments, the antibodies of the invention are fully human antibodies, such as fully human antibodies that specifically bind a hOX40L polypeptide, a hOX40L polypeptide fragment, or a hOX40L epitope. Such fully human antibodies would be advantageous over fully mouse (or other full or partial non-human species antibodies), humanized antibodies, or chimeric antibodies to minimize the development of unwanted or unneeded side effects, such as immune responses directed toward non-fully human antibodies (e.g., anti-hOX40L antibodies derived from other species) when administered to the subject.

[0647] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a hOX40L polypeptide or may be specific for both a hOX40L polypeptide as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. In preferred embodiments, the antibodies provided herein are monospecific for a given epitope of a hOX40L polypeptide and do not specifically bind to other epitopes.

[0648] Also provided herein is a B-cell (e.g., an immortalised B-cell) or a hybridoma that produces an anti-hOX40L antibody or fragment described herein.

[0649] In certain embodiments, an isolated antibody is provided herein that specifically binds to a hOX40L epitope wherein the binding to the hOX40L epitope by the antibody is competitively blocked (e.g., in a dose-dependent manner) by an antibody or fragment of the invention. The antibody may or may not be a fully human antibody. In preferred embodiments, the antibody is a fully human monoclonal anti-hOX40L antibody, and even more preferably a fully human, monoclonal, antagonist anti-hOX40L antibody. Exemplary competitive blocking tests that can be used are provided in the Examples herein.

[0650] In some embodiments, the antibody or fragment of the invention competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to cell surface-expressed hOX40L. In other embodiments, the antibody or fragment of the invention competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to soluble hOX40L. Exemplary competitive binding assays that can be used are provided in the Examples herein. In one embodiment, the antibody or fragment partially or completely inhibits binding of hOX40 to cell surface-expressed OX40L, such as hOX40L. In another embodiment, the antibody partially or completely inhibits binding of hOX40 to soluble hOX40L. In some embodiments, the antibody or fragment partially or completely inhibits the secretion of CCL20, IL-8, and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ from a cell having cell surface-expressed OX40. In certain embodiments, the cell expressing the OX40 is a colonic epithelial cell.

[0651] Preferably, the antibodies of the invention are fully human, monoclonal antibodies, such as fully human, monoclonal antagonist antibodies, that specifically bind to hOX40L.

[0652] In some embodiments, the antibody or fragment provided herein binds to a hOX40L epitope that is a three-dimensional surface feature of a hOX40L polypeptide (e.g., in a trimeric form of a hOX40L polypeptide). A region of a hOX40L polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide A hOX40L epitope may be present in (a) the trimeric form ("a trimeric hOX40L epitope") of hOX40L, (b) the monomeric form ("a monomeric hOX40L epitope") of hOX40L, (c) both the trimeric and monomeric form of hOX40L, (d) the trimeric form, but not the monomeric form of hOX40L, or (e) the monomeric form, but not the trimeric form of hOX40L.

[0653] For example, in some embodiments, the epitope is only present or available for binding in the trimeric (native) form, but is not present or available for binding in the monomeric (denatured) form by an anti-hOX40L antibody. In other embodiments, the hOX40L epitope is linear feature of the hOX40L polypeptide (e.g., in a trimeric form or monomeric form of the hOX40L polypeptide). Antibodies provided herein may specifically bind to (a) an epitope of the monomeric form of hOX40L, (b) an epitope of the trimeric form of hOX40L, (c) an epitope of the monomeric but not the trimeric form of hOX40L, (d) an epitope of the trimeric but not the monomeric form of hOX40L, or (e) both the monomeric form and the trimeric form of hOX40L. In preferred embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hOX40L but do not specifically bind to an epitope the monomeric form of hOX40L.

[0654] The present invention also provides antibodies that specifically bind to a hOX40L epitope, the antibodies comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that specifically bind to a hOX40L antigen. The present invention also provides antibodies comprising derivatives of antibodies disclosed in the Examples, wherein said antibodies specifically bind to a hOX40L epitope. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In another embodiment, the derivatives have conservative amino acid substitutions. In a preferred embodiment, the derivatives have conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

[0655] In another embodiment, an antibody that specifically binds to a hOX40L epitope comprises a variable domain amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a variable domain amino acid sequence of the sequence listing.

[0656] In specific embodiments, the antibody is a fully human anti-human antibody, such as a fully human monoclonal antibody. Fully human antibodies may be produced by any method known in the art. Exemplary methods include immunization with a hOX40L antigen (any hOX40L polypeptide capable of eliciting an immune response, and optionally conjugated to a carrier) of transgenic animals (e.g., mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production; see, e.g., Jakobovits et al., (1993) Proc. Natl. Acad. Sci., 90:2551; Jakobovits et al., (1993) Nature, 362:255 258 (1993); Bruggermann et al., (1993) Year in Immunol., 7:33. Other methods of producing fully human anti-hOX40L antibodies can be found in the Examples provided herein.

[0657] Alternatively, fully human antibodies may be generated through the in vitro screening of phage display antibody libraries; see e.g., Hoogenboom et al., J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991). Various antibody-containing phage display libraries have been described and may be readily prepared by one skilled in the art. Libraries may contain a diversity of human antibody sequences, such as human Fab, Fv, and scFv fragments, that may be screened against an appropriate target.

[0658] The antibodies and fragments of the invention include antibodies and fragments that are chemically modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been chemically modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Additionally, the antibody may contain one or more non-classical amino acids.

[0659] The present invention also provides antibodies that specifically bind to a hOX40L antigen which comprise a framework region known to those of skill in the art (e.g., a human or non-human fragment). The framework region may, for example, be naturally occurring or consensus framework regions. Most preferably, the framework region of an antibody of the invention is human (see, e.g., Chothia et al., 1998, J. Mol. Biol. 278:457-479 for a listing of human framework regions). See also Kabat et al. (1991) Sequences of Proteins of Immunological Interest (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed.

[0660] In a specific embodiment, the present invention provides for antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of one or more of the CDRs in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3) and human framework regions with one or more amino acid substitutions at one, two, three or more of the following residues: (a) rare framework residues that differ between the murine antibody framework (i.e., donor antibody framework) and the human antibody framework (i.e., acceptor antibody framework); (b) Vernier zone residues when differing between donor antibody framework and acceptor antibody framework; (c) interchain packing residues at the VH/VL interface that differ between the donor antibody framework and the acceptor antibody framework; (d) canonical residues which differ between the donor antibody framework and the acceptor antibody framework sequences, particularly the framework regions crucial for the definition of the canonical class of the murine antibody CDR loops; (e) residues that are adjacent to a CDR; (g) residues capable of interacting with the antigen; (h) residues capable of interacting with the CDR; and (i) contact residues between the VH domain and the VL domain. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprising the human framework regions with one or more amino acid substitutions at one, two, three or more of the above-identified residues are antagonistic hOX40L antibodies.

[0661] The present invention encompasses antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of the VH domain and/or VL domain in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34 for VH domains; Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48 for VL domains) but having mutations (e.g., one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprise the amino acid sequence of the VH domain and/or VL domain or an antigen-binding fragment thereof of an antibody disclosed in the Examples with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains.

[0662] In some embodiments, antibodies provided herein decrease or inhibit binding of hOX40L hOX40, and/or decrease or inhibit a hOX40L biological activity, such as secretion of CCL20, IL8 and/or RANTES , or INF-γ, TNF-α or IL-2, in particular INF-γ, in subject (e.g., a human subject). In certain embodiments, antibodies provided herein, such as a human monoclonal anti-hOX40L antibody, decreases or inhibits binding of a soluble or cell-surface expressed hOX40L to hOX40, and/or decreases or inhibits secretion of CCL20 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ after contact with a soluble or cell-surface expressed hOX40L, in a subject. Blocking activity of an antibody provided herein of hOX40L binding to hOX40 can be detected using an assay as described in the Examples. Inhibition of biological activity of cells expressing OX40 by a hOX40L antibody provided herein can be detected using an assay as described in the Examples.

[0663] The present invention also provides for fusion proteins comprising an antibody provided herein that specifically binds to a hOX40L antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed hOX40L.

Antibody Conjugates and Fusion Proteins

[0664] The following discussion on conjugates and fusion proteins also applies to fragments so that disclosure mentioning antibodies can also apply *mutatis mutandis* to fragments of the invention.

[0665] In some embodiments, antibodies of the invention are conjugated or recombinantly fused to a diagnostic, detectable or therapeutic agent or any other molecule. The conjugated or recombinantly fused antibodies can be useful, e.g., for monitoring or prognosing the onset, development, progression and/or severity of a hOX40L-mediated disease as part of a clinical testing procedure, such as determining the efficacy of a particular therapy.

[0666] Such diagnosis and detection can be accomplished, for example, by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113}In, ^{112}In, and ^{111}In), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[0667] The present invention further encompasses uses of the antibodies of the invention conjugated or recombinantly fused to a therapeutic moiety (or one or more therapeutic moieties). The antibody may be conjugated or recombinantly fused to a therapeutic moiety, such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Therapeutic moieties include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine); alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP), and cisplatin); anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin); antibiotics (e.g., d actinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)); Auristatin molecules (e.g., auristatin PHE, bryostatin 1, and solastatin 10; see Woyke et al., Antimicrob. Agents Chemother. 46:3802-8 (2002), Woyke et al., Antimicrob. Agents Chemother. 45:3580-4 (2001), Mohammad et al., Anticancer Drugs 12:735-40 (2001), Wall et al., Biochem. Biophys. Res. Commun 266:76-80 (1999), Mohammad et al., Int. J. Oncol. 15:367-72 (1999)); hormones (e.g., glucocorticoids, progestins, androgens, and estrogens), DNA-repair enzyme inhibitors (e.g., etoposide or topotecan), kinase inhibitors (e.g., compound ST1571, imatinib mesylate (Kantarjian et al., Clin Cancer Res. 8(7):2167-76 (2002)); cytotoxic agents (e.g., paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogues or homologs thereof and those compounds disclosed in U.S. Pat. Nos. 6,245,759, 6,399,633, 6,383,790, 6,335,156, 6,271,242, 6,242,196, 6,218,410, 6,218,372, 6,057,300, 6,034,053, 5,985,877, 5,958,769, 5,925,376, 5,922,844, 5,911,995, 5,872,223, 5,863,904, 5,840,745, 5,728,868, 5,648,239, 5,587,459); farnesyl transferase inhibitors (e.g., R115777, BMS-214662, and those disclosed by, for example, U.S. Pat. Nos. 6,458,935, 6,451,812, 6,440,974, 6,436,960, 6,432,959, 6,420,387, 6,414,145, 6,410,541, 6,410,539, 6,403,581, 6,399,615, 6,387,905, 6,372,747, 6,369,034, 6,362,188, 6,342,765, 6,342,487, 6,300,501, 6,268,363, 6,265,422, 6,248,756, 6,239,140, 6,232,338, 6,228,865, 6,228,856, 6,225,322, 6,218,406, 6,211,193, 6,187,786, 6,169,096, 6,159,984, 6,143,766, 6,133,303, 6,127,366, 6,124,465, 6,124,295, 6,103,723, 6,093,737, 6,090,948, 6,080,870, 6,077,863, 6,071,935, 6,066,738, 6,063,930, 6,054,466, 6,051,582, 6,051,574, and 6,040,305); topoisomerase inhibitors (e.g., camptothecin; irinotecan; SN-38; topotecan; 9-aminocamptothecin; GG-211 (GI 147211); DX-8951f; IST-622; rubitecan, pyrazoloacridine; XR-5000; saintopin; UCE6; UCE1022; TAN-1518A; TAN 1518B; KT6006; KT6528; ED-110; NB-506; ED-110; NB-506; and rebeccamycin); bulgarein; DNA minor groove binders such as Hoescht dye 33342 and Hoechst dye 33258; intidine; fagaronine; epiberberine; coralyne, beta-lapachone; BC-4-1; bisphosphonates (e.g., alendronate, cimadronte, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate) HMG-CoA reductase inhibitors, (e.g., lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin, statin, cerivastatin, lescol, lupitor, rosuvastatin and atorvastatin); antisense oligonucleotides (e.g., those disclosed in the U.S. Pat. Nos. 6,277,832, 5,998,596, 5,885,834, 5,734,033, and 5,618,709); adenosine deaminase inhibitors (e.g., Fludarabine phosphate and 2-Chlorodeoxyadenosine); ibritumomab tiuxetan (Zevalin®); tositumomab (Bexxar®)) and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

[0668] Further, an antibody of the invention may be conjugated or recombinantly fused to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, γ-interferon, α-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-γ, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, J. Immunol., 6:1567-1574), and VEGF (see, International Publication No. WO 99/23105), an anti-angiogenic agent, e.g., angiostatin, endostatin or a component of the coagulation pathway (e.g., tissue factor); or, a biological response modifier such as, for example, a lymphokine (e.g., interferon gamma, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-5 ("IL-5"), interleukin-6 ("IL-6"), interleukin-7 ("IL-7"), interleukin 9 ("IL-9"), interleukin-10 ("IL-10"), interleukin-12 ("IL-12"), interleukin-15 ("IL-15"), interleukin-23 ("IL-23"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (e.g., growth hormone ("GH")), or a coagulation agent (e.g., calcium, vitamin K, tissue factors, such as but not limited to, Hageman factor (factor XII), high-molecular-weight kininogen (HMWK), prekallikrein (PK), coagulation proteins-factors II (prothrombin), factor V, XIIa, VIII, XIIIa, XI, XIa, IX, IXa, X, phospholipid, and fibrin monomer).

[0669] The present invention encompasses antibodies of the invention recombinantly fused or chemically conjugated (covalent or non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90 or about 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of an antibody of the invention (e.g., a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. In one embodiment, the heterologous protein, polypeptide, or peptide that the antibody is fused to is useful for targeting the antibody to a particular cell type, such as a cell that expresses hOX40L or an hOX40L receptor. For example, an antibody that specifically binds to a cell surface receptor expressed by a particular cell type (e.g., an immune cell) may be fused or conjugated to a modified antibody of the invention.

[0670] A conjugated or fusion protein of the invention comprises any antibody of the invention described herein and a heterologous polypeptide. In one embodiment, a conjugated or fusion protein of the invention comprises the variable domains of an antibody disclosed in the Examples and a heterologous polypeptide.

[0671] In addition, an antibody of the invention can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In, ^{131}Lu, ^{131}Y, ^{131}Ho, ^{131}Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4(10):2483-90; Peterson et al., 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman et al., 1999, Nucl. Med. Biol., 26(8):943-50.

[0672] Moreover, antibodies of the invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc.), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767), and the "FLAG" tag.

[0673] Methods for fusing or conjugating therapeutic moieties (including polypeptides) to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), Thorpe et al., 1982, Immunol. Rev. 62:119-58; U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,783,181, 5,908,626, 5,844,095, and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi et al., Proc. Natl. Acad. Sci. USA, 88: 10535-10539, 1991; Traunecker et al., Nature, 331:84-86, 1988; Zheng et al., J. Immunol., 154:5590-5600, 1995; Vil et al., Proc. Natl. Acad. Sci. USA, 89:11337-11341, 1992.

[0674] Fusion proteins may be generated, for example, through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention (e.g., antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson etal., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313. Antibodies, or the encoded antibodies, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0675] An antibody of the invention can also be conjugated to a second antibody to form an antibody heteroconjugate as described in U.S. Pat. No. 4,676,980.

[0676] The therapeutic moiety or drug conjugated or recombinantly fused to an antibody of the invention that specifically binds to a hOX40L antigen should be chosen to achieve the desired prophylactic or therapeutic effect(s). In certain embodiments, the antibody is a modified antibody. A clinician or other medical personnel should consider the following when deciding on which therapeutic moiety or drug to conjugate or recombinantly fuse to an antibody of the invention: the nature of the disease, the severity of the disease, and the condition of the subject.

[0677] Antibodies of the invention may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Pharmaceutical Compositions

[0678] The following discussion on compositions also applies to fragments so that disclosure mentioning antibodies can also apply *mutatis mutandis* to fragments of the invention.

[0679] Therapeutic formulations containing one or more antibodies of the invention provided herein can be prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[0680] The antibodies of the invention provided herein can also, for example, be formulated in liposomes. Liposomes containing the molecule of interest are prepared by methods known in the art, such as described in Epstein et al. (1985) Proc. Natl. Acad. Sci. USA 82:3688; Hwang et al. (1980) Proc. Natl. Acad. Sci. USA 77:4030; and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

[0681] Particularly useful immunoliposomes can be generated by the reverse phase evaporation method with a lipid composition containing phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of an antibody provided herein can be conjugated to the liposomes as described in Martin et al. (1982) J. Biol. Chem. 257:286-288 via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome; See Gabizon et al., (1989) J. National Cancer Inst. 81(19): 1484.

[0682] Formulations, such as those described herein, can also contain more than one active compound as necessary for the particular indication being treated. In certain embodiments, formulations comprise an antibody of the invention and one or more active compounds with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. For example, an antibody of the invention can be combined with one or more other therapeutic agents. Such combined therapy can be administered to the patient serially or simultaneously or in sequence.

[0683] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, anti-IL12/IL-23 antibodies (e.g. ustekinumab), anti-CD20 antibodies (e.g.rituximab), anti-CD30 antibodies (e.g. brentuximab), CTLA4-Fc molecules (e.g. abatacept), CCR5 receptor antagonists (e.g. maraviroc), anti-CD40L antibodies, anti-VLA4 antibodies (e.g. natalizumab), anti-LFA1 antibodies, fludarabine, anti-CD52 antibodies (e.g. alemtuzumab), anti-CD45 antibodies, cyclophosphamide, anti-thymocyte globulins, anti-complement C5 antibodies (e.g. eculizumab), anti-a4b7 integrin antibodies (e.g. vedolizumab), anti-IL6 antibodies (e.g. tocilizumab), anti-IL2R antibodies (e.g. basiliximab), anti-CD25 antibodies (e.g. daclizumab), anti-TNFa / TNFa-Fc molecules (e.g. etanercept, adalimumab, infliximab, golimumab or certolizumab pegol) and Vorinostat. In another embodiment the combination comprises an anti-OX40L antibody of the invention and a further therapeutic agents independently selected from the group consisting of rapamycin (sirolimus), tacrolimus, ciclosporin, corticosteroids (e.g. methylprednisolone), methotrexate, mycophenolate mofetil, anti-CD28 antibodies, CTLA4-Fc molecules (e.g. abatacept), anti-CD40L antibodies, anti-LFA1 antibodies, anti-CD52 antibodies (e.g. alemtuzumab), cyclophosphamide and anti-thymocyte globulins.

[0684] In some embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of calcineurin inhibitors (e.g. tacrolimus, ciclosporin), mTOR inhibitors (e.g. rapamycin (sirolimus)), and antiproliferative agents (e.g. mycophenolate mofetil, cyclophosphamide).

[0685] In further embodiments the combination comprises an anti-OX40L antibody of the invention and further therapeutic agents independently selected from the group consisting of immunosuppressants that modulate IL-2 signalling (e.g. tacrolimus, ciclosporin, rapamycin (sirolimus), and anti-CD25 antibodies (e.g. basiliximab, daclizumab)

[0686] In one embodiment, the combination comprises an anti-OX40L antibody of the invention and rapamycin (sirolimus). In one embodiment, the combination comprises an anti-OX40L antibody of the invention and tacrolimus. In one embodiment, the combination comprises an anti-OX40L antibody of the invention and a combination of tacrolimus and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and ciclosporin and methotrexate. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and cyclophosphamide. In another embodiment, the combination comprises an anti-OX40L antibody of the invention and mycophenolate mofetil.

[0687] An antibody of the invention can also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.

[0688] The formulations to be used for in vivo administration can be sterile. This is readily accomplished by filtration through, e.g., sterile filtration membranes.

[0689] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antagonist, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0690] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the antibodies of the invention provided herein, and optionally one or more additional prophylactic of therapeutic agents, in a pharmaceutically acceptable carrier. Such pharmaceutical compositions are useful in the prevention, treatment, management or amelioration of a hOX40L-mediated disease, such as an inflammatory bowl disease, transplant rejection, GvHD or one or more of the symptoms thereof.

[0691] Pharmaceutical carriers suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[0692] In addition, the antibodies of the invention may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients (such as one or more other prophylactic or therapeutic agents).

[0693] The compositions can contain one or more antibodies of the invention. In one embodiment, the antibodies are formulated into suitable pharmaceutical preparations, such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. In one embodiment, the antibodies described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, e.g., Ansel (1985) Introduction to Pharmaceutical Dosage Forms, 4th Ed., p. 126).

[0694] In the compositions, effective concentrations of one or more antibodies or derivatives thereof is (are) mixed with a suitable pharmaceutical carrier. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates a hOX40L-mediated disease or symptom thereof.

[0695] In one embodiment, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected carrier at an effective concentration such that the treated condition is relieved, prevented, or one or more symptoms are ameliorated.

[0696] An antibody of the invention is included in the pharmaceutically acceptable carrier in an effective amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration can be determined empirically by testing the compounds in in vitro and in vivo systems using routine methods and then extrapolated therefrom for dosages for humans.

[0697] The concentration of antibody in the pharmaceutical composition will depend on, e.g., the physicochemical characteristics of the antibody, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

[0698] In one embodiment, a therapeutically effective dosage produces a serum concentration of antibody of from about 0.1 ng/ml to about 50-100 µg/ml. The pharmaceutical compositions, in another embodiment, provide a dosage of from about 0.001 mg to about 2000 mg of antibody per kilogram of body weight per day. Pharmaceutical dosage unit forms can be prepared to provide from about 0.01 mg, 0.1 mg or 1 mg to about 500 mg, 1000 mg or 2000 mg, and in one embodiment from about 10 mg to about 500 mg of the antibody and/or a combination of other optional essential ingredients per dosage unit form.

[0699] The antibody can be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and can be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values can also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens can be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[0700] Upon mixing or addition of the antibody, the resulting mixture can be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0701] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The antibody is, in one embodiment, formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the antibody sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms can be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[0702] In preferred embodiments, one or more anti-hOX40L antibodies of the invention are in a liquid pharmaceutical formulation. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

[0703] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa.

[0704] Dosage forms or compositions containing antibody in the range of 0.005% to 100% with the balance made up from non-toxic carrier can be prepared. Methods for preparation of these compositions are known to those skilled in the art.

[0705] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[0706] In certain embodiments, the formulations are solid dosage forms. In certain embodiments, the formulations are capsules or tablets. The tablets, pills, capsules, troches and the like can contain one or more of the following ingredients, or compounds of a similar nature: a binder; a lubricant; a diluent; a glidant; a disintegrating agent; a colouring agent; a sweetening agent; a flavouring agent; a wetting agent; an emetic coating; and a film coating. Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, molasses, polyvinylpyrrolidine, povidone, crospovidones, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Colouring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended

on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavours. Flavouring agents include natural flavours extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0707] The antibodies of the invention can be provided in a composition that protects itfrom the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition can also be formulated in combination with an antacid or other such ingredient.

[0708] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colourings and flavours.

[0709] The antibody can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is an antibody or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[0710] In all embodiments, tablets and capsules formulations can be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

[0711] In preferred embodiments, the formulations are liquid dosage forms. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

[0712] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives.

[0713] Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Colouring and flavouring agents are used in all of the above dosage forms.

[0714] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Colouring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavouring agents include natural flavours extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[0715] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is, in one embodiment, encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, can be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

[0716] Alternatively, liquid or semi-solid oral formulations can be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. RE28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[0717] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[0718] Parenteral administration, in one embodiment, is characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[0719] Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Pat. No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The antibody diffuses through the outer polymeric membrane in a release rate controlling step. The amount of antibody contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0720] Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[0721] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0722] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anaesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0723] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0724] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

[0725] The unit-dose parenteral preparations can be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration can be sterile, as is known and practiced in the art.

[0726] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[0727] Injectables are designed for local and systemic administration. In one embodiment, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, in certain embodiments more than 1% w/w of the active compound to the treated tissue(s).

[0728] The antibody can be suspended in micronized or other suitable form. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

[0729] In other embodiments, the pharmaceutical formulations are lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[0730] The lyophilized powder is prepared by dissolving an antibody provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4° C. to room temperature.

[0731] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[0732] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0733] The antibodies of the invention can be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[0734] The compounds can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0735] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts.

[0736] Other routes of administration, such as transdermal patches, including iontophoretic and electrophoretic devices, and rectal administration, are also contemplated herein.

[0737] Transdermal patches, including iotophoretic and electrophoretic devices, are well known to those of skill in the art. For example, such patches are disclosed in U.S. Pat. Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[0738] For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by moulding. The weight of a rectal suppository, in one embodiment, is about 2 to 3 gm.

[0739] Tablets and capsules for rectal administration can be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

[0740] The antibodies and other compositions provided herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, e.g., U.S. Pat. Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In some embodiments, the anti-hOX40L antibodies of the invention are targeted (or otherwise administered) to the colon, such as in a patient having or at risk of having an IBD. In some embodiments, the anti-hOX40L antibodies of the invention are targeted (or otherwise administered) to the eye, such as in a patient having or at risk of having uveitis.

[0741] In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumour-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art. For example, liposome formulations can be prepared as described in U.S. Pat. No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLVs) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

Methods of Administration and Dosing

[0742] The present invention further provides for compositions comprising one or more antibodies or fragments of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease (or symptom thereof). Discussion in respect of antibodies also applies *mutatis mutandis* to fragments of the invention. In an alternative, the present invention further provides for compositions comprising one or more antibodies or fragments of the invention for use in the prevention, management, treatment and/or amelioration of an OX40L-mediated disease (or symptom thereof) in a subject, wherein the OX40L is non-human (e.g., canine, feline, equine, bovine, ovine or porcine) and the subject is respectively a dog, cat, horse, cow, sheep or pig.

[0743] In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as IBD (e.g., ulcerative colitis or Crohn's disease), or a symptom thereof. IBD symptoms may range from mild to severe and generally depend upon the part of the intestinal tract involved. Exemplary symptoms of IBD include abdominal cramps and pain, bloody diarrhoea, severe urgency to have a bowel movement, fever, loss of appetite, weight loss, anaemia, fatigue, and/or sores on lower legs, ankles, calves, thighs, and arms. Exemplary intestinal complications of IBD include profuse bleeding from the ulcers, perforation or rupture of the bowel, strictures and obstruction, fistulae (abnormal passage) and perianal disease, toxic megacolon (e.g., acute nonobstructive dilation of the colon), and/or malignancy (e.g., cancer of the colon or small intestine). Exemplary extraintestinal complications of IBD include arthritis, skin conditions, inflammation of the eye, liver and kidney disorders, and/or bone loss. Any combination of these symptoms may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0744] In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of an hOX40L-mediated disease, such as GVHD, or a symptom thereof. GVHD generally occurs following allogeneic or matched unrelated bone marrow transplants (BMT).

[0745] In some embodiments, the GVHD is acute GVHD. The symptoms of acute GVHD can happen quickly and can be mild or severe. In certain instances, acute GVHD develops within about three months after transplant, such as when blood counts recover after transplant. It certain instances, the acute GVHD affects the skin, gastrointestinal (GI) tract and/or liver. For example, in some patients, acute skin GVHD begins with a rash, for example, on the palms of the patient's hands, soles of the feet, or shoulders. However, the rash can become widespread, and may be itchy and painful and/or might blister and peel. Acute liver GVHD may affect normal functions of the liver, such as liver enzymes, and may in turn, cause jaundice. Acute liver GVHD may also cause the patient's abdomen to become swollen and painful if the liver becomes enlarged. Finally, symptoms of acute gut GVHD (or GVHD of the digestive system) can include diarrhoea, mucus or blood in the stool, cramping or abdominal pain, indigestion, nausea and/or loss of appetite. Other general symptoms of acute GVHD can include anaemia, low grade fever, and/or being more prone to infections. Any combination of these symptoms of acute GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0746] In other embodiments, the GVHD is chronic GVHD. Chronic GVHD can occur from about three months to about a year or longer after transplant. Chronic GVHD can be mild or severe, and generally includes symptoms similar to those of acute GVHD. Chronic GVHD can affect the skin and digestive system, including the liver but can also involve other organs and the immune system (e.g., making the patient more prone to infections) and/or connective tissues. Symptoms of chronic skin GVHD include a rash, dry skin, tight skin, itchy skin, darkening of the colour of the skin, thickening of the skin, and/or may affect hair (e.g., hair loss, turning grey) or nails (e.g., hard or brittle nails). Chronic gut GVHD can affect the digestive system, mouth, oesophagus, lining of the stomach, and/or lining of the bowel, and symptoms can include diarrhoea, dry or sore mouth, painful swallowing, low nutrient absorption by the stomach, bloating, stomach cramps. Chronic liver GVHD can cause damage and scarring of the liver (cirrhosis). Chronic GVHD of the eyes can affect the glands that make tears, causing eyes to become dry, burning and painful or difficult to tolerate bright light. Chronic lung GVHD can cause shortness of breath, wheezing, persistent

cough, and/or being more prone to chest infections. Chronic GVHD affects tendons (e.g., inflammation) that connect muscle to bone causing difficulty straightening or bending your arms and legs. Any combination of these symptoms of chronic GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0747] In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as uveitis, or a symptom thereof.

[0748] In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease, such as pyoderma gangrenosum, giant cell arteritis, Schnitzler syndrome or non-infectious scleritis.

[0749] In certain embodiments provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hOX40L mediated disease or condition selected from an autoimmune disease or condition, a systemic inflammatory disease or condition, or transplant rejection; for example inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, transplant rejection, allogeneic transplant rejection, graft-versus-host disease (GvHD), ulcerative colitis, systemic lupus erythematosus (SLE), diabetes, uveitis, ankylosing spondylitis, contact hypersensitivity, multiple sclerosis and atherosclerosis, in particular GvHD.

[0750] In a specific embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises the OX40L binding sites of an antibody of the invention, e.g., an antibody disclosed in the Examples.

[0751] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s in the sequence listing (i.e. Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s in the sequence listing (i.e. Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46).

[0752] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL domains having an amino acid sequence of any one of the VL domains in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48) (optionally comprising also the cognate VH domain as set out in the sequence listing (i.e. Seq ID No:2/16, Seq ID No:34/48, Seq ID No:66/80 or Seq ID No:94/108, in particular Seq ID No:34/48). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR1s in the sequence listing (i.e. Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s in the sequence listing (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s in the sequence listing (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60).

[0753] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34), and one or more VL domains having an amino acid sequence of any one of the VL domains in the sequence listing (i.e. Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48).

[0754] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s in the sequence listing (i.e. Seq ID No: 18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No: 116, in particular Seq ID No:50 or Seq ID No:56). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No: 10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s in the sequence listing (i.e. Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No: 112 or Seq ID No: 118, in particular Seq ID No:52 or Seq ID No:58). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s in the sequence listing (i.e. Seq ID No:4, Seq ID No: 10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42), and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s in the sequence listing (i.e. Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No: 120, in particular Seq ID No:54 or Seq ID No:60).

[0755] As discussed in more detail elsewhere herein, a composition of the invention may be used either alone or in combination with other compounds or compositions. Moreover, the antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionucleotides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

[0756] In some embodiments, provided herein are methods for decreasing or inhibiting binding of hOX40L to an OX40L receptor or cognate ligand (e.g., OX40) in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L). In some embodiments, a hOX40L biological activity, such as secretion of CCL20, IL8 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ or another cytokine disclosed herein, is also decreased in the subject, for example decreased by at least 10, 20, 30, 40, 50 or 60%, or 70%, or 80%, or 90% or 95% or >95%.

[0757] In certain embodiments, provided herein are methods for decreasing or inhibiting a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES or other cytokine, or INF-γ, TNF-α or IL-2, in particular INF-γ in a subject (e.g., a human subject), comprising administering to the subject an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed hOX40L), wherein hOX40L biological activity is decreased by the antibody.

[0758] In other embodiments, provided herein are methods for decreasing or inhibiting binding of hOX40L to an OX40L receptor or cognate ligand (e.g., OX40) in a cell having cell surface-expressed hOX40L, contacting the cell with an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L), such as a hOX40L polypeptide, a hOX40L polypeptide fragment, or a hOX40L epitope. In some embodiments, a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ or other cytokine disclosed herein, is also decreased in the cell.

[0759] In certain embodiments, provided herein are methods for decreasing or inhibiting a hOX40L biological activity, such as secretion of interferon gamma, IL-2, CCL20, IL8 and/or RANTES or other cytokine disclosed herein, in a cell having a cell surface-expressed hOX40L receptor (such as OX40), contacting the cell with an effective amount of an antibody that specifically binds to a hOX40L polypeptide (e.g., a cell surface-expressed or soluble hOX40L) wherein hOX40L biological activity is decreased by the antibody.

[0760] Antibodies of the present invention may be used, for example, to purify, detect, and target hOX40L antigens, in both in vitro and in vivo diagnostic and therapeutic methods. For example, the modified antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of hOX40L in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988).

[0761] The invention also provides methods of preventing, managing, treating and/or ameliorating a hOX40L-mediated disease by administrating to a subject of an effective amount of an antibody, or pharmaceutical composition comprising an antibody of the invention. In one aspect, an antibody is substantially purified (i.e., substantially free from substances that limit its effect or produce undesired side-effects). In preferred embodiments, the antibody is a fully human monoclonal antibody, such as a fully human monoclonal antagonist antibody. The subject administered a therapy is preferably a mammal such as non-primate (e.g., cows, pigs, horses, cats, dogs, rodents, mice or rats) or a primate (e.g., a monkey, such as a rhesus or cynomolgous monkey, or a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely. In another embodiment, the subject is a human with a hOX40L-mediated disease.

[0762] Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (e.g., an antibody of the invention), including, but not limited to:, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering a prophylactic or therapeutic agent (e.g., an antibody of the invention), or pharmaceutical composition include, but are not limited to, parenteral administration (e.g., intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (e.g., intranasal and oral routes). In a specific embodiment, a prophylactic or therapeutic agent (e.g., an antibody of the present invention), or a pharmaceutical composition is administered intranasally, intramuscularly, intravenously, or subcutaneously. The prophylactic or therapeutic agents or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, intranasal mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, e.g., U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903.

[0763] In a specific embodiment, it may be desirable to administer a prophylactic or therapeutic agent, or a pharmaceutical composition of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion, by topical administration (e.g., by intranasal spray), by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering an antibody of the invention, care must be taken to use materials to which the antibody does not absorb.

[0764] In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990, Science 249:1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

[0765] In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:20; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a prophylactic or therapeutic agent (e.g., an antibodies of the invention) or a composition of the invention (see e.g., Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds), Wiley, New York (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 7 1:105); U.S. Pat. No. 5,679,377, U.S. Pat. No. 5,916,597, U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, i.e., the nasal passages or lungs, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention. See, e.g., U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning et al., 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179-189, Song et al., 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek et al., 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int1. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam et al., 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760.

[0766] In a specific embodiment, where the composition of the invention is a nucleic acid encoding a prophylactic or therapeutic agent (e.g., an antibody of the invention), the nucleic acid can be administered in vivo to promote expression of its encoded prophylactic or therapeutic agent, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see, e.g., Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

[0767] In a specific embodiment, a composition of the invention comprises one, two or more antibodies or fragments of the invention. In another embodiment, a composition of the invention comprises one, two or more antibodies or fragments of the invention and a prophylactic or therapeutic agent other than an antibody of the invention. Preferably, the agents are known to be useful for or have been or are currently used for the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease. In addition to prophylactic or therapeutic agents, the compositions of the invention may also comprise a carrier.

[0768] The compositions of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (e.g., compositions that are suitable for administration to a subject or patient) that can be used in the preparation of unit dosage forms. In a preferred embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (e.g., an antibody of the invention or other prophylactic or therapeutic agent), and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical compositions are formulated to be suitable for the route of administration to a subject.

[0769] In a specific embodiment, the term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa. Such compositions will contain a prophylactically or therapeutically effective amount of the antibody, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0770] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anaesthetic such as lignocamne to ease pain at the site of the injection. Such compositions, however, may be administered by a route other than intravenous.

[0771] Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0772] The invention also provides that an antibody of the invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of antibody. In one embodiment, the antibody is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, e.g., with water or saline to the appropriate concentration for administration to a subject. Preferably, the antibody is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 0.1 mg, at least 0.5 mg, at least 1 mg, at least 2 mg, or at least 3 mg, and more preferably at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, or at least 100 mg. The lyophilized antibody can be stored at between 2 and 8° C. in its original container and the antibody can be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, an antibody is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody. Preferably, the liquid form of the antibody is supplied in a hermetically sealed container at least 0.1 mg/ml, at least 0.5 mg/ml, or at least 1 mg/ml, and more preferably at least 5 mg/ml, at least 10 mg/ml, at least 15 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 40 mg/ml, at least 50 mg/ml, at least 60 mg/ml, at least 70 mg/ml, at least 80 mg/ml, at least 90 mg/ml, or at least 100 mg/ml.

[0773] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0774] The amount of a prophylactic or therapeutic agent (e.g., an antibody of the invention), or a composition of the invention that will be effective in the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease can be determined by standard clinical techniques.

[0775] Accordingly, a dosage of an antibody or a composition that results in a serum titer of from about 0.1 μg/ml to about 450 μg/ml, and in some embodiments at least 0.1 μg/ml, at least 0.2 μg/ml, at least 0.4 μg/ml, at least 0.5 μg/ml, at least 0.6 μg/ml, at least 0.8 μg/ml, at least 1 μg/ml, at least 1.5 μg/ml, and preferably at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least 250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the prevention, management, treatment and/or amelioration of a hOX40L-mediated disease. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of a hOX40L-mediated disease, and should be decided according to the judgment of the practitioner and each patient's circumstances.

[0776] Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0777] For the antibodies of the invention, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. In some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 5 mg/kg of the patient's body weight. 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. Further, the dosage and frequency of administration of the antibodies of the invention may be reduced by enhancing uptake and tissue penetration of the antibodies by modifications such as, for example, lipidation.

[0778] In one embodiment, approximately 100 mg/kg or less, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less of an antibody or fragment the invention is administered 5 times, 4 times, 3 times, 2 times or, preferably, 1 time to manage a hOX40L-mediated disease. In some embodiments, an antibody of the invention is administered about 1-12 times, wherein the doses may be administered as necessary, e.g., weekly, biweekly, monthly, bimonthly, trimonthly, etc., as determined by a physician. In some embodiments, a lower dose (e.g., 1-15 mg/kg) can be administered more frequently (e.g., 3-6 times). In other embodiments, a higher dose (e.g., 25-100 mg/kg) can be administered less frequently (e.g., 1-3 times).

However, as will be apparent to those in the art, other dosing amounts and schedules are easily determinable and within the scope of the invention.

[0779] In a specific embodiment, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, approximately 0.1 mg/kg or less of an antibody or fragment the invention in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease. In another specific embodiment, an approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less bolus of an antibody the invention not in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease, and after a certain period of time, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less or an antibody of the invention in a sustained release is administered to said subject (e.g., intranasally or intramuscularly) two, three or four times (preferably one time). In accordance with this embodiment, a certain period of time can be 1 to 5 days, a week, two weeks, or a month.

[0780] In some embodiments, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, twelve times, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty five, or twenty six at bi-weekly (e.g., about 14 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each dose monthly dose may or may not be identical).

[0781] In another embodiment, a single dose of an antibody of the invention is administered to patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve times at about monthly (e.g., about 30 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each dose monthly dose may or may not be identical).

[0782] In one embodiment, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, four, five, or six times at about bi-monthly (e.g., about 60 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each bi-monthly dose may or may not be identical).

[0783] In some embodiments, a single dose of an antibody or fragment of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease two, three, or four times at about tri-monthly (e.g., about 120 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (i.e., each tri-monthly dose may or may not be identical).

[0784] In certain embodiments, the route of administration for a dose of an antibody or fragment of the invention to a patient is intranasal, intramuscular, intravenous, or a combination thereof, but other routes described herein are also acceptable. In certain embodiments, the route of administration is intraocular. Each dose may or may not be administered by an identical route of administration. In some embodiments, an antibody or fragment of the invention may be administered via multiple routes of administration simultaneously or subsequently to other doses of the same or a different antibody or fragment of the invention.

[0785] In certain embodiments, antibodies or fragments of the invention are administered prophylactically or therapeutically to a subject. Antibodies or fragments of the invention can be prophylactically or therapeutically administered to a subject so as to prevent, lessen or ameliorate a hOX40L-mediated disease or symptom thereof.

Gene Therapy

[0786] In a specific embodiment, nucleic acids or nucleotide sequences of the invention are administered to prevent, manage, treat and/or ameliorate a hOX40L-mediated disease by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In an embodiment of the invention, the nucleic acids produce their encoded antibody, and the antibody mediates a prophylactic or therapeutic effect.

[0787] Any of the methods for gene therapy available in the art can be used according to the present invention.

Diagnostic Use of Antibodies

[0788] Although antibodies are mentioned in respect of diagnostic uses, this disclosure is to be read as also applying *mutatis mutandis* to the fragments of the invention.

[0789] Labelled antibodies or of the invention and derivatives and analogues thereof, which specifically bind to a hOX40L antigen can be used for diagnostic purposes to detect, diagnose, or monitor a hOX40L-mediated disease. The invention provides methods for the detection of a hOX40L-mediated disease comprising: (a) assaying the expression of a hOX40L antigen in cells or a tissue sample of a subject using one or more antibodies of the invention that specifically bind to the hOX40L antigen; and (b) comparing the level of the hOX40L antigen with a control level, e.g., levels in normal tissue samples (e.g., from a patient not having a hOX40L-mediated disease, or from the same patient before disease onset), whereby an increase in the assayed level of hOX40L antigen compared to the control level of the hOX40L antigen is indicative of a hOX40L-mediated disease.

[0790] The invention provides a diagnostic assay for diagnosing a hOX40L-mediated disease comprising: (a) assaying for the level of a hOX40L antigen in cells or a tissue sample of an individual using one or more antibodies of the invention that specifically bind to a hOX40L antigen; and (b) comparing the level of the hOX40L antigen with a control level, e.g., levels in normal tissue samples, whereby an increase in the assayed hOX40L antigen level compared to the control level of the hOX40L antigen is indicative of a hOX40L-mediated disease. A more definitive diagnosis of a hOX40L-mediated disease may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the hOX40L-mediated disease.

[0791] Antibodies of the invention can be used to assay hOX40L antigen levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (e.g., see Jalkanen et al., 1985, J. Cell. Biol. 101:976-985; and Jalkanen et al., 1987, J. Cell. Biol. 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). 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 (^{99m}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0792] One aspect of the invention is the detection and diagnosis of a hOX40L-mediated disease in a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labelled antibody that specifically binds to a hOX40L antigen; b) waiting for a time interval following the administering for permitting the labelled antibody to preferentially concentrate at sites in the subject where the hOX40L antigen is expressed (and for unbound labelled molecule to be cleared to background level); c) determining background level; and d) detecting the labelled antibody in the subject, such that detection of labelled antibody above the background level indicates that the subject has a hOX40L-mediated disease. Background level can be determined by various methods including, comparing the amount of labelled molecule detected to a standard value previously determined for a particular system.

[0793] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labelled antibody will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumour imaging is described in S. W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S. W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[0794] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labelled antibody to preferentially concentrate at sites in the subject and for unbound labelled antibody to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0795] In one embodiment, monitoring of a hOX40L-mediated disease is carried out by repeating the method for diagnosing the a hOX40L-mediated disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0796] Presence of the labelled molecule can be detected in the subject using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0797] In a specific embodiment, the molecule is labelled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Pat. No. 5,441,050). In another embodiment, the molecule is labelled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labelled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labelled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Methods of Producing Antibodies

[0798] Antibodies and fragments of the invention that specifically bind to an antigen (OX40L) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. The practice of the invention employs, 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 in the references cited herein and are fully explained in the literature. See, e.g., Maniatis et al. (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook et al. (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook et al. (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Ausubel etal., 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 et al. (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[0799] Polyclonal antibodies that specifically bind to an antigen can be produced by various procedures well-known in the art. For example, a human antigen can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the human antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminium hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0800] 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 et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling 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. Other exemplary methods of producing monoclonal antibodies are discussed elsewhere herein, such as e.g., use of the KM Mouse™. Additional exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

[0801] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with a hOX40L antigen and once an immune response is detected, e.g., antibodies specific for hOX40L 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 ATCC. Hybridomas are selected and cloned by limited dilution.

[0802] Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilptrack et al., 1997 Hybridoma 16:381-9). The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0803] Accordingly, the present invention provides methods of generating antibodies by culturing a hybridoma cell secreting a modified antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with a hOX40L antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind to a hOX40L antigen.

[0804] Antibody fragments which recognize specific hOX40L antigens may be generated by any technique known to those of skill in the art. For example, Fab and F(ab')$_2$ fragments of the invention may 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). F(ab')$_2$ fragments contain the variable region, the Light chain constant region and the CH1 domain of the heavy chain. Further, the antibodies of the present invention can also be generated using various phage display methods known in the art.

[0805] For example, antibodies can also be generated using various phage display methods. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with an 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 VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to a particular antigen can be selected or identified with antigen, e.g., using labelled 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 of the present invention include those disclosed in Brinkman et al., 1995, J. Immunol. Methods 182:41-50; Ames et a/., 1995, J. Immunol. Methods 184:177-186; Kettleborough et al., 1994, Eur. J. Immunol. 24:952-958; Persic et al., 1997, Gene 187:9-18; Burton et al., 1994, Advances in Immunology 57:191-280; PCT Application No. PCT/GB91/01134 (published as WO 1992001047); 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 WO97/13844; and U.S. Pat. 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.

[0806] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, 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 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 et al., 1992, BioTechniques 12(6):864-869; Sawai et al., 1995, AJRI 34:26-34; and Better et al., 1988, Science 240: 1041-1043.

[0807] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, e.g., the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, e.g., human kappa or lambda constant regions. The VH and VL domains may also 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.

[0808] For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies 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. Pat. Nos. 4,444,887 and 4,716,111; 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.

[0809] In preferred embodiments, human antibodies are produced. Human antibodies and/or fully human antibodies can be produced using any method known in the art, including the Examples provided herein. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may 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 may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH 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 a polypeptide of the invention. 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 and Huszar (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., PCT publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Pat. 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. Other methods are detailed in the Examples herein. In addition, companies such as Abgenix, Inc/Amgen. (Thousand Oaks, Calif.) OMT (Paolo Alto, Calif.), Argen-x (Breda, Netherlands), Ablexis (San Francisco, Calif.) or Harbour Antibodies (Cambridge, Mass.) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0810] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. Methods for producing chimeric antibodies are known in the art. See, e.g., Morrison, 1985, Science 229:1202; Oi etal., 1986, BioTechniques 4:214; Gillies etal., 1989, J. Immunol. Methods 125:191-202; and U.S. Pat. Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415.

[0811] A humanized antibody is an antibody or its variant or fragment thereof which 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 a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', F(ab')$_2$, Fabc, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (i.e., donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and IgG4. Usually the

constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG1. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG2 class. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE. Examples of VL and VH constant domains that can be used in certain embodiments of the invention include, but are not limited to, C-kappa and C-gamma-1 (nG1m) described in Johnson et al. (1997) J. Infect. Dis. 176, 1215-1224 and those described in U.S. Pat. No. 5,824,307. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, e.g., the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental FR and CDR sequences, more often 90%, and most preferably greater than 95%. Humanized antibodies can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering 7(6):805-814; and Roguska et al., 1994, PNAS 91:969-973), chain shuffling (U.S. Pat. No. 5,565,332), and techniques disclosed in., e.g., U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, WO 9317105, Tan et al., J. Immunol. 169:1119 25 (2002), Caldas et al., Protein Eng. 13(5):353-60 (2000), Morea et al., Methods 20(3):267 79 (2000), Baca et al., J. Biol. Chem. 272(16):10678-84 (1997), Roguska et al., Protein Eng. 9(10):895 904 (1996), Couto et al., Cancer Res. 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res. 55(8): 1717-22 (1995), Sandhu J S, Gene 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol. 235(3):959-73 (1994). See also U.S. Patent Pub. No. US 2005/0042664 A1 (Feb. 24, 2005). Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modelling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen *et al.*, U.S. Pat. No. 5,585,089; and Reichmann et al., 1988, Nature 332:323).

[0812] Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well-known in the art. See Riechmann et al., 1999, J. Immunol. 231:25-38; Nuttall et al., 2000, Curr. Pharm. Biotechnol. 1(3):253-263; Muylderman, 2001, J. Biotechnol. 74(4):277302; U.S. Pat. No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591, and WO 01/44301.

[0813] Further, the antibodies that specifically bind to a hOX40L 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 & Bona, 1989, FASEB J. 7(5):437-444; and Nissinoff, 1991, J. Immunol., 147(8):2429-2438).

Kits

[0814] The invention also provides a pharmaceutical or diagnostic pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention, such as one or more antibodies or fragments provided herein. 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, e.g., an authorisation number.

[0815] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated hOX40L antigen as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with the hOX40L antigen. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of a modified antibody to a hOX40L antigen (e.g., the antibody may 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 may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized hOX40L antigen. The hOX40L antigen provided in the kit may 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 hOX40L antigen is attached. Such a kit may also include a non-attached reporter-labelled anti-human antibody. In this embodiment, binding of the antibody to the hOX40L antigen can be detected by binding of the said reporter-labelled antibody.

[0816] "Conservative amino acid substitutions" result from replacing one amino acid with another having similar structural and/or chemical properties, such as the replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine. Thus, a "conservative substitution" of a particular amino acid sequence refers to substitution of those amino acids that are not critical for polypeptide activity or substitution of amino acids with other amino acids having similar properties (e.g., acidic, basic, positively or negatively charged, polar or non-polar, etc.) such that the substitution of even critical amino acids does not reduce the activity of the peptide, (i.e. the ability of the peptide to penetrate the blood brain barrier (BBB)). Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, the following six groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W). (See also Creighton, Proteins, W. H. Freeman and Company (1984)). In some embodiments, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids can also be considered "conservative substitutions" if the change does not reduce the activity of the peptide. Insertions or deletions are typically in the range of about 1 to 5 amino acids. The choice of conservative amino acids may be selected based on the location of the amino acid to be substituted in the peptide, for example if the amino acid is on the exterior of the peptide and expose to solvents, or on the interior and not exposed to solvents.

[0817] In alternative embodiments, one can select the amino acid which will substitute an existing amino acid based on the location of the existing amino acid, i.e. its exposure to solvents (i.e. if the amino acid is exposed to solvents or is present on the outer surface of the peptide or polypeptide as compared to internally localized amino acids not exposed to solvents). Selection of such conservative amino acid substitutions are well known in the art, for example as disclosed in Dordo et al, J. Mol Biol, 1999, 217, 721-739 and Taylor etal, J. Theor. Biol. 119(1986);205-218 and S. French and B. Robson, J. Mol. Evol., 19(1983)171. Accordingly, one can select conservative amino acid substitutions suitable for amino acids on the exterior of a protein or peptide (i.e. amino acids exposed to a solvent), for example, but not limited to, the following substitutions can be used: substitution of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P.

[0818] In alternative embodiments, one can also select conservative amino acid substitutions encompassed suitable for amino acids on the interior of a protein or peptide, for example one can use suitable conservative substitutions for amino acids is on the interior of a protein or peptide (i.e. the amino acids are not exposed to a solvent), for example but not limited to, one can use the following conservative substitutions: where Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V. In some embodiments, non-conservative amino acid substitutions are also encompassed within the term of variants.

[0819] As used herein an "antibody" refers to IgG, IgM, IgA, IgD or IgE molecules or antigen-specific antibody fragments thereof (including, but not limited to, a Fab, $F(ab')_2$, Fv, disulphide linked Fv, scFv, single domain antibody, closed conformation multispecific antibody, disulphide-linked scfv, diabody), whether derived from any species that naturally produces an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria. Antibodies can be humanized using routine technology.

[0820] As described herein, an "antigen" is a molecule that is bound by a binding site on an antibody agent. Typically, antigens are bound by antibody ligands and are capable of raising an antibody response *in vivo*. An antigen can be a polypeptide, protein, nucleic acid or other molecule or portion thereof. The term "antigenic determinant" refers to an epitope on the antigen recognized by an antigen-binding molecule, and more particularly, by the antigen-binding site of said molecule.

[0821] As used herein, the term "antibody fragment" refers to a polypeptide that includes at least one immunoglobulin variable domain or immunoglobulin variable domain sequence and which specifically binds a given antigen. An antibody fragment can comprise an antibody or a polypeptide comprising an antigen-binding domain of an antibody. In some embodiments, an antibody fragment can comprise a monoclonal antibody or a polypeptide comprising an antigen-binding domain of a monoclonal antibody. For example, an antibody can include a heavy (H) chain variable region (abbreviated herein as VH), and an OX40L (L) chain variable region (abbreviated herein as VL). In another example, an antibody includes two heavy (H) chain variable regions and two OX40L (L) chain variable regions. The term "antibody fragment" encompasses antigen-binding fragments of antibodies (e.g., single chain antibodies, Fab and sFab fragments, $F(ab')2$, Fd fragments, Fv fragments, scFv, and domain antibodies (dAb) fragments (see, e.g. de Wildt et al., Eur J. Immunol., 1996; 26(3):629-39)) as well as complete antibodies. An antibody can have the structural features of IgA, IgG, IgE, IgD, IgM (as well as subtypes and combinations thereof). Antibodies can be from any source, including mouse, rabbit, pig, rat, and primate (human and non-human primate) and primatized antibodies. Antibodies also include midibodies, humanized antibodies, chimeric antibodies, and the like.

[0822] As used herein, "antibody variable domain" refers to the portions of the OX40L and heavy chains of antibody molecules that include amino acid sequences of Complementarity Determining Regions (CDRs; i.e., CDR1, CDR2, and CDR3), and Framework Regions (FRs). VH refers to the variable domain of the heavy chain. VL refers to the variable domain of the Light chain. According to the methods used in this invention, the amino acid positions assigned to CDRs and FRs may be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)) or according to IMGT nomenclature.

[0823] As used herein, the term "antibody binding site" refers to a polypeptide or domain that comprises one or more CDRs of an antibody and is capable of binding an antigen. For example, the polypeptide comprises a CDR3 (e.g., HCDR3). For example the polypeptide comprises CDRs 1 and 2 (e.g., HCDR1 and 2) or CDRs 1-3 of a variable domain of an antibody (e.g., HCDRs1-3). In an example, the antibody binding site is provided by a single variable domain (e.g., a VH or VL domain). In another example, the binding site comprises a VH/VL pair or two or more of such pairs.

[0824] As used herein, "genotyping" refers to a process of determining the specific allelic composition of a cell and/or subject at one or more position within the genome, e.g. by determining the nucleic acid sequence at that position. Genotyping refers to a nucleic acid analysis and/or analysis at the nucleic acid level. As used herein, "phenotyping" refers a process of determining the identity and/or composition of an expression product of a cell and/or subject, e.g. by determining the polypeptide sequence of an expression product. Phenotyping refers to a protein analysis and/or analysis at the protein level.

[0825] As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). For treatment to be effective a complete cure is not contemplated. The method can in certain aspects include cure as well.

[0826] As used herein, the term "pharmaceutical composition" refers to the active agent in combination with a pharmaceutically acceptable carrier e.g. a carrier commonly used in the pharmaceutical industry. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0827] As used herein, the term "administering," refers to the placement of a compound as disclosed herein into a subject by a method or route which results in at least partial delivery of the agent at a desired site. Pharmaceutical compositions comprising the compounds disclosed herein can be administered by any appropriate route which results in an effective treatment in the subject.

[0828] Multiple compositions can be administered separately or simultaneously. Separate administration refers to the two compositions being administered at different times, e.g. at least 10, 20, 30, or 10-60 minutes apart, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours apart. One can also administer compositions at 24 hours apart, or even longer apart. Alternatively, two or more compositions can be administered simultaneously, e.g. less than 10 or less than 5 minutes apart. Compositions administered simultaneously can, in some aspects, be administered as a mixture, with or without similar or different time release mechanism for each of the components.

[0829] As used herein, "authorization number" or "marketing authorization number" refers to a number issued by a regulatory agency upon that agency determining that a particular medical product and/or composition may be marketed and/or offered for sale in the area under the agency's jurisdiction. As used herein "regulatory agency" refers to one of the agencies responsible for evaluating, e.g., the safety and efficacy of a medical product and/or composition and controlling the sales/marketing of such products and/or compositions in a given area. The Food and Drug Administration (FDA) in the US and the European Medicines Agency (EPA) in Europe are but two examples of such regulatory agencies. Other non-limiting examples can include SDA, MPA, MHPRA, IMA, ANMAT, Hong Kong Department of Health-Drug Office, CDSCO, Medsafe, and KFDA.

[0830] As used herein, "injection device" refers to a device that is designed for carrying out injections, an injection including the steps of temporarily fluidically coupling the injection device to a person's tissue, typically the subcutaneous tissue. An injection further includes administering an amount of liquid drug into the tissue and decoupling or removing the injection device from the tissue. In some embodiments, an injection device can be an intravenous device or IV device, which is a type of injection device used when the target tissue is the blood within the circulatory system, e.g., the blood in a vein. A common, but non-limiting example of an injection device is a needle and syringe.

[0831] As used herein, a "buffer" refers to a chemical agent that is able to absorb a certain quantity of acid or base without undergoing a strong variation in pH.

[0832] As used herein, "packaging" refers to how the components are organized and/or restrained into a unit fit for distribution and/or use. Packaging can include, e.g., boxes, bags, syringes, ampoules, vials, tubes, clamshell packaging, barriers and/or containers to maintain sterility, labeling, etc.

[0833] As used herein, "instructions" refers to a display of written, printed or graphic matter on the immediate container of an article, for example the written material displayed on a vial containing a pharmaceutically active agent, or details on the composition and use of a product of interest included in a kit containing a composition of interest. Instructions set forth the method of the treatment as contemplated to be administered or performed.

[0834] As used herein the term "comprising" or "comprises" is used in reference to antibodies, fragments, uses, compositions, methods, and respective component(s) thereof, that are essential to the method or composition, yet open to the inclusion of unspecified elements, whether essential or not.

[0835] The term "consisting of" refers to antibodies, fragments, uses, compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

[0836] As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

[0837] The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "e.g." is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is synonymous with the term "for example."

[0838] Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 19th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-19-0); Robert S. Porter et al. (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); Benjamin Lewin, Genes X, published by Jones & Bartlett Publishing, 2009 (ISBN-10: 0763766321); Kendrew et al. (eds.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Interscience, Coligan et al., eds.

[0839] Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Sambrook et al., Molecular Cloning: A Laboratory Manual (4 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2012); Davis et al., Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol 152, S. L. Berger and A. R. Kimmel Eds., Academic Press Inc., San Diego, USA (1987); Current Protocols in Protein Science (CPPS) (John E. Coligan, et al., ed., John Wiley and Sons, Inc.), Current Protocols in Cell Biology (CPCB) (Juan S. Bonifacino et al. ed., John Wiley and Sons, Inc.), and Culture of Animal Cells: A Manual of Basic Technique by R. Ian Freshney, Publisher: Wiley-Liss; 5th edition (2005), Animal Cell Culture Methods (Methods in Cell Biology, Vol. 57, Jennie P. Mather and David Barnes editors, Academic Press, 1st edition, 1998).

[0840] The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0841] As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[0842] Any part of this disclosure may be read in combination with any other part of the disclosure, unless otherwise apparent from the context.

EXAMPLES

Example 1

Antigen Preparation, Immunization Procedures, and Hybridoma Generation

[0843] The following example provides a detailed description of the generation and identification of a panel of anti-human OX40L monoclonal antibodies using the KyMouse™ system (see, e.g., WO2011/004192). To this end, genetically engineered mice containing a large number of human immunoglobulin genes were immunized with soluble recombinant human OX40L (commercial or in-house produced) or surface expressed human OX40L displayed on mouse embryonic fibroblast (MEF) cells. Various immunization regimes, including conventional intraperitoneal injections as well as a rapid immunisation at multiple sites regime were set up, boosting animals over several weeks. At the end of each regime, secondary lymphoid tissue such as the spleen, and in some cases, the lymph nodes were removed. Tissues were prepared into a single cell suspension and fused with SP2/0 cells to generate a stable hybridoma cell line.

Materials and Methods

Cloning expression and purification of recombinant Rhesus and human OX40L

[0844] cDNA encoding the extracellular domain of human OX40L was cloned into a pREP4 expression plasmid (Invitrogen) using standard molecular biology techniques. The constructs also contained a FLAG peptide motif to aid purification and an isoleucine zipper motif to aid trimerisation. Constructs were sequenced to ensure their correct sequence composition.

[0845] Rhesus (*Macaca mulatta*) OX40L was created using the human OX40L plasmid created above as a template and using site directed mutagenesis to introduce the amino acid changes.

[0846] Human OX40L well as Rhesus monkey OX40L were expressed transiently to produce recombinant protein using Invitrogen's Freestyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability.

[0847] FLAG-tagged OX40L proteins were purified in a two-step process; firstly the clarified tissue culture supernatants from the CHO-S expression were purified using M2 anti-FLAG affinity chromatography. The eluted fractions containing the OX40L protein were then subjected to size exclusion chromatography and assessed for purity by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280nm.

Cloning expression and purification of recombinant human OX40 receptor

[0848] cDNA encoding the extracellular domain of human OX40 Receptor was cloned into a pREP4 expression plasmid (Invitrogen) using standard restriction enzyme digestion and ligation. The construct contained a human Fc portion to aid purification. Constructs were sequenced to ensure their correct sequence composition.

[0849] Human OX40 Receptor was expressed transiently to produce recombinant protein using Invitrogen's Freestyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process, samples were taken regularly to monitor cell growth and viability.

[0850] The Fc tagged OX40 Receptor protein was purified in a two-step process; firstly the clarified tissue culture supernatants from the CHO-S expression were purified using Protein G affinity chromatography. The eluted fractions containing the OX40 Receptor protein were then subjected to size exclusion chromatography and assessed for purity by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280nm.

Generation of stably transfected MEF and CHO-S cells expressing human OX40L

[0851] The full human OX40L sequences were codon optimized (Seq ID No:173) for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3' and 5' piggyBac specific terminal repeat sequences facilitating stable integration into the cell genome (see: "A hyperactive piggyBac transposase for mammalian applications"; Yusa K, Zhou L, Li MA, Bradley A, Craig NL. Proc Natl Acad Sci USA. 2011 Jan 25). Furthermore, the expression vector contained either a puromycin or neomycin selection cassette to facilitate stable cell line generation. The hOX40L expression plasmid was co-transfected with a plasmid encoding piggyBac transposase into an in-house derived mouse embryonic fibroblast (MEF) cell line (embryos used to generate this line were obtained from a 129S5 crossed to C57BL6 female mouse) and CHO-S cells using the FreeStyle Maxtransfection reagent (Invitrogen) according to manufacturer instructions. 24 hours after transfection, the media was supplemented with G418 or neomycin and grown for at least 2 weeks to select a stable cell line, with media being exchanged every 3-4 days. The expression of hOX40L was assessed by flow cytometry using an anti-human OX40L-PE conjugated antibody (eBioscience). Complete MEF media was made up of Dulbecco's Modified Eagle's Medium (Gibco) supplemented with 10% v/v fetal bovine serum (Gibco). Complete CHO-S media was made up of CD-CHO media supplemented with 8mM glutamax (Gibco).

Generation of HT1080 expressing OX40R and NF-Kappa reporter Gene

[0852] The full human OX40 receptor sequence was codon optimized (Seq ID No:175) for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3' and 5' piggyBac specific terminal repeat sequences facilitating stable integration into the cell genome (see: "A hyperactive piggyBac transposase for mammalian applications"; Yusa K, Zhou L, Li MA, Bradley A, Craig NL. Proc Natl Acad Sci USA. 2011 Jan 25). Furthermore, the expression vector contained either a puromycin selection cassette to facilitate stable cell line generation. The hOX40 receptor expression plasmid was co-transfected with a plasmid encoding piggyBac transposase into HT1080 cells (ATCC® CCL-121) using the FreeStyle Max transfection reagent (Invitrogen) according to manufacturer instructions. 24 hours after transfection, the media was supplemented with puromycin and grown for at least 2 weeks to select a stable cell line with media being exchanged every 3-4 days. The expression of OX40 receptor was assessed by flow cytometry using an anti-human OX40 receptor -PE conjugated antibody (R&D, clone 443318). Following the generation of a stable cell line expressing the OX40 receptor, cells were transfected with the pNiFty-2-SEAP plasmid (invivogen) containing 5 repeated NFkB transcription factor binding sites followed by secreted alkaline phosphatase. Stable cells were selected with the addition to zeocin to the media with fresh media being added every 3-4 days. Complete HT1080 media was made up of MEM supplemented with 10% fetal calf serum.

Preparation of MEF cells for mouse immunizations:

[0853] Cell culture medium was removed and cells washed once with 1×PBS. Cells were treated for 5 minutes with trypsin to loosen cells from tissue culture surface. Cells were collected and trypsin neutralized by the addition of complete media containing 10% v/v fetal bovine serum (FCS). Cells were then centrifuged at 300 ×*g* for 10 minutes and washed with 25 mL of 1×PBS. Cells were counted and resuspended at the appropriate concentration in 1XPBS.

Immunization Procedure:

[0854] Transgenic Kymice were immunized with hOX40L in either soluble recombinant form, expressed by CHO-S cells, or membrane bound form, expressed by stably transfected MEF cells.

[0855] When immunizing with cells, the adjuvant was mixed with cells at a 1:1 v/v ratio and gently mixed by pipetting before injecting intraperitoneally. When immunizing with protein, the adjuvant was mixed with protein at a 1:1 v/v ratio and vortexed repeatedly. All mice were bled before being primed and then boosted every three weeks. At least 3 serial bleeds spaced apart at least 2 weeks were collected and analysed for hOX40L specific IgG titre using an ELISA or flow cytometry based assay

Determination of serum titers by FACS using CHO-S expressed hOX40L

[0856] CHO-S cells expressing hOX40L or untransfected CHO-S cells, diluted in FACS buffer (PBS + 1% w/v BSA + 0.1% w/v NaN_3) were distributed to a 96 well V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Cells were washed with 150 µL of PBS and centrifuged at 300 ×*g* for 3 min. Supernatant was aspirated and 150 µL of PBS added. This wash step was repeated. A titration of mouse serum was prepared, diluting samples in FACS buffer. 50 µL/well of this titration was then added to the cell plate. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1 in 100 in FACS buffer and 50 µL/well added to the cells. A suitable reference antibody (anti-OX40L antibody MAB10541, R&D systems) or mouse IgG1 control antibody (Sigma) were diluted in FACS buffer (between 1-9 µg/mL) and 50 µL added to cells. Cells were incubated at 4 °C for 30 minutes. Cells were washed twice with 150 µL of PBS, centrifuging after each wash step and aspirating supernatant (centrifuged at 300 xg for 3 minutes). To detect antibody binding, APC goat-anti-mouse IgG (Jackson ImmunoResearch) was diluted 1 in 500 in FACS buffer and 50 µL was added to the cells. Cells were incubated 30 minutes at 4 °C in dark. Cells were washed twice with 150 µL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300 xg for 3 minutes). To fix cells 100 µL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4°C, cells were pelleted by centrifugation at 300 ×*g* and the plates resuspended in 50 µL of FACS buffer. APC signal intensity (geomean) was measured by flow cytometry using a BD FACS Array instrument.

Determination of serum titers by DELFIA immunoassay using recombinant hOX40L

[0857] Titers in mouse serum samples were determined using a reverse OX40L ELISA protocol. Anti-mouse IgG capture antibody (Southern Biotech) (4 µg/mL diluted in PBS, 50 µL/well) was adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess IgG was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hr at RT, after which plates were washed as described previously. A titration of mouse serum was prepared, diluting samples in reagent diluent (0.1% w/v BSA/PBS). 50 µL/well of this titration was then added to ELISA plates. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1 in 100 in reagent diluent and 50 µL/well added to the ELISA plate. As a positive control for biotinylated OX40L binding an anti-OX40L antibody (MAB10541, R&D systems) diluted to 1 µg/mL was added to plates at 50 µL. Mouse IgG1 isotype control (Sigma) was included as a negative control and was diluted to 1 µg/mL in reagent diluent and 50 µL/well added to ELISA plate. In some instances serum sample from a mouse immunized with a non-relevant antigen was diluted 1 in 1000 and 50 µL/well was added to the ELISA plate. The plates were incubated at room temperature for at least 1 hour. Following incubation, plates were washed as before to remove unbound proteins. Biotinylated OX40L (100 ng/mL in reagent diluent; 50 µL/well) was then added to the plates and incubated at RT for 1 hour. Unbound biotinylated OX40L was removed by washing with PBS-Tween (0.1% v/v), while the remaining biotinylated OX40L was detected by streptavidin-Europium3+conjugate (DELFIA® detection, PerkinElmer) diluted in DELFIA® assay buffer (Perkin Elmer) or streptavidin-HRP diluted in reagent diluent.

[0858] In the case of streptavidin-HRP, the plates were washed as described before and 50 µL of TMB (Sigma) was added to the plate. Then the reaction was stopped by adding 50 µL of 1M sulfuric acid (Fluka analytical). The OD at 450 nm was measured on an Envision plate reader (PerkinElmer).

[0859] In case of streptavidin-Europium3, the plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 200µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. The time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Fluorescence data was plotted as Europium counts.

Murine tissue isolation and preparation:

[0860] Spleens were excised from immunised mice and washed in 1×PBS and kept on ice until further processing. Tissues were prepared in buffer containing 1×PBS (Invitrogen) and 3% heat-inactivated FBS (Invitrogen). Splenocytes were dispersed by mashing the tissue through a 45 µm strainer (BD Falcon) and rinsing with 30 mL 3%FBS/PBS buffer before centrifugation at 700 g for 10 minutes at 4 °C. To remove red blood cells, the pelleted splenocytes were resuspended in 4 mL of Red Blood Cell Lysis Buffer (Sigma). After 4 minutes of incubation, the lysis reaction was stopped by addition of 3% FBS/1×PBS buffer. Cell clumps were filtered out with a 45 µm strainer. The remaining splenocytes were pelleted for further procedures

Hybridoma Fusion

[0861] For the KM055 experiment, pelleted splenocytes were progressed directly to fusion without any selection or overnight CpG stimulation. For the KM040 experiment, B-cells were subjected to a positive selection method using the MACS® Separation system. Cells were resuspended in 80 µL 3% FBS/PBS buffer per 1×10^7 cells, before adding the anti-mouse IgG1 plus anti-mouse IgG2a+b MicroBeads (Miltenyi Biotec) and incubated for 15 minutes at 4 °C. The cells/MicroBeads mixture was then applied to a pre-wetted LS column placed in a magnetic MACS Separator and washed with 3% FBS/PBS buffer. IgG positive cells were collected in the labelled, column-bound fraction in 3% FBS/PBS buffer.

[0862] For the KM040 experiment, enriched B-cells were treated with CpG overnight (final concentration 25 µM) and the following day washed once in BSA fusion buffer (0.3M D-Sorbitol, 0.11 mM calcium acetate hydrate, 0.5 mM magnesium acetate tetrahydrate and 0.1% BSA (v/w), adjusted to pH7.2). For the KM055 experiment, pelleted splenocytes from red blood cell lysis were washed once in BSA fusion buffer on the same day as tissue preparation. Fusion proceeded in the same way for both experiments after this point. Washed cells were resuspended in 200 µL of BSA fusion buffer and cell count determined. SP2/0 cells were treated in the same way, but washed twice with BSA fusion buffer. B-cells were fused at a ratio of 3:1 with SP2/0 myeloma cells by electrofusion using a BTX ECM 2001 Electro Cell Manipulator (Harvard Apparatus). Each fusion was left overnight in recovery medium (Dulbecco's Modified Eagle's Medium - high glucose (no phenol red, no L-G) containing OPI (Sigma), L-Glutamax (Gibco), 20% FBS (Gibco, batch-tested for hybridoma) and 2-mercaptoethanol). On the final day, cells were pelleted and resuspended in 1 part recovery medium to 9 parts semi-solid medium (ClonaCell-HY Hybridoma Selection Medium D, Stemcell Technologies) and then seeded onto 10 cm petri dishes. Colonies were picked 12 days later into 96-well plates and cultured for another 2-3 days prior to screening.

Example 2

Hybridoma Supernatant Screening

[0863] After generation of hybridoma clones, the hybridoma supernatant was assessed in a sequential primary and secondary screen and appropriate hybridoma clones selected based on criteria of antibody binding to CHO expressed hOX40L and receptor neutralization activity (see details in materials and methods) (Table 1).

[0864] For the primary screen, the inventors devised the following selection criteria: wells containing hybridoma clones were selected if antibodies present in the supernatant could bind to natively displayed hOX40L expressed on the cell surface. This assay was set up by plating CHO-S cells expressing hOX40L on the cell surface, followed by incubation with hybridoma supernatant, followed by a fluorescent detection antibody. The presence of an anti-OX40L antibody in the supernatant was read-out using a plate reader capable of reading the appropriate fluorescence. Furthermore, the inventors assessed hybridoma supernatant for binding to recombinantly expressed human OX40L using an HTRF (Homogeneous Time Resolved Fluorescence) assay. The inventors also determined whether the hybridoma supernatant had the ability to reduce the binding of human recombinant OX40L to human OX40R Fc. Clones meeting certain selection criteria (see further detailed description below), using data from the above mentioned three primary screen assays, were then cherry-picked and moved on to a secondary screen where the ability of each antibody to neutralize hOX40L binding to its receptors, OX40 Receptor (aka CD134), was determined. The inventors decided to assess this using a receptor neutralization HTRF assay and a flow cytometry-based receptor neutralization assay. Lastly, the inventors decided to analyse hybridoma supernatant by SPR to evaluate apparent affinity of the antibodies to recombinant trimeric human OX40L as well as cross-reactivity to Rhesus monkey OX40L.

[0865] Antibodies were defined as a secondary hit when antibodies in hybridoma supernatant bound to hOX40L, with high apparent affinity as well as cross-reacted with recombinant Rhesus monkey OX40L. Additionally, antibodies in the supernatant had to show the ability to neutralize OX40L binding to its receptor, i.e. OX40 Receptor (aka CD134) in either HTRF or flow cytometry based assay.

Materials and Methods

Primary screen - Binding to cell expressed human OX40L

[0866] Supernatants collected from hybridoma cells were tested to assess the ability of secreted antibodies to bind to hOX40L expressed on the surface of CHO-S cells. To determine CHO-S hOX40L binding, cells were plated in clear bottom tissue culture treated 384-well plates (Costar or BRAND) at 2×10^4 cells/well in F12 media (GIBCO) supplemented with 10% v/v FBS (GIBCO) and cultured overnight. Culture media was removed from 384-well assay plates. At least 40 µL of hybridoma supernatant or positive control anti-human OX40L reference antibody (at a final concentration of 1 µg/mL) or isotype IgG1 control antibody (referred to in some instances as Cm7, Sigma M9269, at a final concentration of 1 µg/mL) diluted in hybridoma maintaining media (HMM) were added to each well. Hybridoma maintaining media was made up of, Advanced DMEM (Gibco) supplemented with 1× Glutamax (Gibco), 20% v/v FBS (Gibco), 0.05 mM β-Mercaptoethanol, 1×HT supplement (Gibco), and 1×penicillin/streptomycin (Gibco). Plates were incubated for 1 hour at 4 °C. Culture media was aspirated and 50 µL of goat anti-mouse Alexa Fluor 790 (Jackson ImmunoResearch, 115-655-071) at 1000 ng/mL supplemented with 0.2 µM DRAQ5 (Biostatus) diluted in FACS Buffer (PBS+1% w/v BSA+0.1% v/v NaN_3) were added. Plates were again incubated for 1 hour at 4 °C. Supernatant was aspirated and 25 µL of 4% v/v paraformaldehyde added and plates were incubated 15 minutes at room temperature. Plates were washed twice with 100 µL PBS and then the wash buffer was completely removed. Fluorescence intensity was read by scanning plates using an Odyssey Infrared Imaging System (LI-COR®). Anti-mouse binding (800 nm channel) was normalised to cell number (700 nm channel) according to LI-COR® recommended algorithm. Percent effect was calculated as detailed below (Equation 1). Total binding was defined using reference antibody at a final assay concentration of 1µg/ml. Non specific binding was defined using mouse IgG1 isotype control (Sigma) at a final assay concentration of 1 µg/mL. Wells were defined as hits where percent effect was greater than or equal to 5%.

Equation 1: Calculation of Percentage Effect from Primary Screen (LI-COR) and HTRF (Using 800% Resp values (LI-COR) or 665/620nm ratio (see Equation 2) (HTRF)

$$\frac{\text{sample well} - \text{non specific binding}}{\text{total binding} - \text{non specific binding}} \times 100$$

$$\text{Percent effect} = \frac{}{\text{total binding - non specific binding}}$$

[0867] Non-specific binding = values from wells containing isotype control mouse IgG1 or HMM or buffer

[0868] Total Binding (Binding HTRF and LICOR) = values from wells containing reference antibody Total binding (OX40L/OX40RFc assay) = OX40L and OX40RFc

Primary screen: Binding to recombinant human OX40L:

[0869] In parallel to screening for binding to CHO-S expressed OX40L, supernatants collected from hybridoma wells were also tested to assess the ability of secreted antibodies to bind to hOX40L expressed as a recombinant protein (produced in-house, see details in Example 1). Binding of secreted antibodies to recombinant hOX40L were identified by HTRF® (Homogeneous Time-Resolved Fluorescence, Cisbio) assay format using biotinylated hOX40L. 5 µL of hybridoma supernatant was transferred to a white 384 well low volume non binding surface polystyrene plate (Greiner). Then 5µL of biotinylated hOX40L (working concentration 20 nM) diluted in HTRF buffer (PBS (Sigma) + 0.53 M KF (Sigma) + 0.1% w/v BSA (Sigma) was added. 5 µL of combined detection reagents Streptavidin D2 (Cisbio) diluted 1:100 in HTRF assay buffer for final dilution 1:400 and goat anti-mouse IgG (Southern Biotech) labelled with europium cryptate (Cisbio) diluted 1:100 in HTRF assay buffer for final dilution 1:400 were added. The concentration of goat anti-mouse IgG (Southern Biotech) labelled with europium cryptate was batch dependent and in some cases a dilution of 1:1000 was performed to achieve a final assay concentration of 1:4000. To adjust the total assay volume to 20 µL, 5 µL of HTRF assay buffer was added to all wells. To define non-specific binding, addition of positive control antibody or hybridoma media was replaced with HTRF assay buffer or HMM. The plate was left to incubate in dark for 3 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). More details of the HTRF® assay technology can be found in Mathis (1995) Clinical Chemistry 41(9), 1391-1397. Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 1 respectively.

Equation 2: Calculation of 665/620 ratio

$$\text{665/620 ratio} = \text{(sample 665/620 nm value)} \times 10000$$

[0870] For clones derived from KM040-1 and KM055-1 a selection criteria of greater than or equal to 20 percent effect was applied by the inventors to define a well as a hit from recombinant hOX40L binding as described in Table 1.

Primary screen: human OX40L/human OX40R Fc binding assay:

[0871] In order to determine whether supernatants collected from hybridoma wells inhibited the binding of OX40L to OX40RFc, secreted antibodies were tested in an OX40L/OX40RFc binding HTRF assay. 5 µL of hybridoma supernatant was transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 µL added. OX40RFc was then diluted to working concentration of 4.8 nM and 5 µL added. Non-specific binding was defined by replacing OX40RFc with assay buffer or HMM. Streptavidin cryptate (CISBIO) and anti-human Fc D2 (CISBIO) were diluted in HTRF assay buffer to working concentration of 1:100 and 5nM respectively. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 5 respectively.

[0872] For clones derived from KM040-1 and KM055-1, a selection criteria of less than or equal to 90 percent of the assay signal of OX40 receptor Fc binding to OX40L was applied by the inventors to define a well as a hit as described in Table 1.

Secondary screen: Binding to cell expressed and recombinant human OX40L

[0873] To determine whether wells selected using the primary screen selection criteria had the required characteristics set by the inventors, a number of assays were performed. Hybridoma clones selected as hits from primary screening were cultured for 3 days and the supernatants collected from hybridoma cells were tested to assess whether the secreted antibodies that bind to CHO-S expressed hOX40L, in some case bind to untransfected CHO-S cells and whether they neutralise recombinant OX40R Fc binding to CHO-S hOX40L and ability to neutralise OX40R binding to recombinant biotinylated hOX40L.

Binding to CHO-S expressed hOX40L and receptor neutralisation :

[0874] CHO-S cells expressing hOX40L or untransfected CHO-S cells, diluted in FACS buffer (PBS + 1% w/v BSA + 0.1% w/v NaN_3) were distributed to a 96 well V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Cells were washed with 150 µL of PBS and centrifuged at 300 xg for 3 min. Supernatant was aspirated and 150 µL of PBS added. This wash step was repeated.

[0875] 25 µL of hybridoma supernatant or purified antibody from hybridoma supernatant diluted in FACS buffer was added to the washed cells and incubated for 10-15 minutes. Reference Antibody or mouse IgG1 control antibody (Sigma) were diluted in FACS buffer to 20 µg/mL and 25 µL added to cells. 25 µL of human OX40R Fc (in-house) diluted to 1000 ng/mL in FACS buffer were then added to wells. Cells were incubated at 4 °C for 30 minutes.

[0876] Cells were washed twice with 150 µL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300 xg for 3 minutes).

[0877] To detect antibody and receptor binding, 50 µL of Goat anti-human IgG-PE (Jackson ImmunoResearch) and APC anti-mouse IgG (Jackson ImmunoResearch) diluted 1 in 500 in FACS buffer was added to the cells. Cells were incubated 30 minutes at 4 °C in the dark.

[0878] Cells were washed twice with 150 µL of PBS centrifuging after each wash step and aspirating supernatant (centrifuged at 300 xg for 3 minutes).

[0879] To fix cells 100 µL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4 °C, cells were pelleted by centrifugation 300 xg and the plates and resuspended in 50 µL of FACS buffer. PE and APC signal intensity (geomean) was measured by flow cytometry using a BD FACS Array instrument.

[0880] % of control binding was calculated using geomean fluorescence as described in equation 1 where total binding was defined as reference antibody at 10 µg/mL and non-specific binding as mouse IgG1 antibody at 10 µg/mL. % receptor binding was calculated using Equation 3.

Equation 3: Percentage of receptor binding (FACS)

[0881] Based on geomean fluorescence

$$\%\text{ of Receptor binding} = \frac{\text{sample value - non specific binding}}{\text{total binding - non specific binding}} \times 100$$

[0882] Non-specific binding = No antibody, no receptor
Total binding = receptor (OX40R) only binding (no inhibitor) + isotype control at 10 µg/mL

Secondary Screen - HTRF Ligand/Receptor Neutralisation

[0883] To determine whether antibodies identified from primary screen neutralise OX40L binding to OX40RFc an human OX40L/human OX40R Fc binding assay was performed as described for primary screen.

[0884] Plates were left to incubate in dark for 3 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). More details of the HTRF® assay technology can be found in Mathis (1995) Clinical Chemistry 41(9), 1391-1397. Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5.

Equation 4: Calculation of % DeltaF

$$\%\text{ delta F} = \frac{\text{(sample 665/620 nm ratio value) - (non-specific control 665/620 nm ratio value)}}{\text{(non-specific control 665/620 nm ratio)}} \times 100$$

Equation 5: Percentage of receptor binding (HTRF)

[0885] Based on calculation of % deltaF (Equation 4) or 665/620 ratio (Equation 2)

$$\%\text{ of Receptor binding} = \frac{\text{sample value - non specific binding}}{\text{total binding - non specific binding}} \times 100$$

Non specific binding = HMM or buffer + OX40L (no receptor)

Total binding = receptor (OX40R) and OX40L (no inhibitor)

Hit criteria selection from secondary screening:

[0886] A panel of hits were selected based on binding and neutralisation assays. Hits in CHO-S OX40L binding assay were defined by the inventors as significant binding to CHO-S OX40L cells and no binding to CHO-S cells by FACS. Hits were further defined as having the ability to significantly reduce OX40RFc binding to recombinant OX40L (HTRF) and significantly reduce OX40RFc binding to hOX40L expressed on CHO cells. Data is summarised in Table 1. Apparent affinity measurements by SPR were also considered.

Example 3

Antibody Lead Characterization

[0887] Based on the screening selected wells were expanded and murine/human chimeric antibodies purified using a standard Protein G based affinity chromatography purification (see method below). The antibodies were subjected to various assays to assess their ability to block hOX40L binding to it receptor OX40R, as well as the ability of each antibody to bind to human as well as Rhesus monkey OX40L with high apparent affinity. To decipher which antibodies were the best, selected clones were tested using OX40L/OX40RFc HTRF assay and OX40L induced IL2 release from primary human T-cells.

Table 1: mAb Lead Summary

Antibody	FACS Binding	HTRF Receptor Neutralisation ICso nM (+/- SEM)	Primary T-cell Assay ICso nM (+/- SEM)	Apparent Affinity hOX40L (nM)	Apparent Affinity RhsOX40L (nM)
10A07 (hybridoma)	YES	+++	+++	CNROR	CNROR
10A07 (human)	ND	+++ 1.2nM (+/-0.17)	+++ 0.83nM (+/- 1.2)	CNROR	CNROR
2D10 (hybridoma)	YES	+++	ND	CNROR	CNROR
2D10 (human)	ND	+++ 0.75nM (+/-0.04)	+++ 0.81nM (+/- 0.06)	CNROR	CNROR
9H04 (hybridoma)	YES	+	ND	5.3	ND
19H01 (hybridoma)	YES	++	ND	2.2	ND

CNROR= Cannot resolve off-rate
ICso data represents arithmetic mean +/- standard error of mean (SEM) for three independent experiments or donors.

Materials and Methods:

Purification of antibodies from hybridoma supernatant:

[0888] Antibodies were purified using Protein G affinity chromatography. Antibodies were eluted from the Protein G media using IgG Elute reagent (Pierce) and the eluted antibodies were buffer swapped into PBS prior to use. Antibody purity was assessed by SDS-PAGE analysis and quantified by spectrophotometer reading at OD280 nm.

[0889] Binding of antibodies purified from hybridoma supernatant was carried out as described herein.

HTRF Ligand/Receptor Neutralisation:

[0890] The following methods were carried out with a titration of inhibitor in order to establish the clone potency as measured by IC_{50} values in the assay. Antibody purified from hybridoma was titrated by diluting in HTRF assay buffer and 5 µL of this titration transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 µL added. OX40RFc was then diluted to working concentration of 4.8 nM and 5 µL added. Non-specific binding was defined by replacing OX40RFc with assay buffer or HMM. Streptavidin cryptate (CISBIO) and anti-human Fc D2 (CISBIO) were diluted in HTRF assay buffer to working concentration of 1:100 and 5 nM respectively. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5 or in some cases Equation 6. IC_{50} values were determined using GraphPad Prism software by curve fitting

using a four-parameter logistic equation (Equation 7).

Equation 6: Percentage of receptor binding (HTRF)

Based on calculation of % DeltaF (Equation 8)

$$\%\ \text{of Receptor binding} = \frac{\text{sample value}}{\text{total binding}} \times 100$$

[0891] Total binding = receptor (OX40R) and OX40L (no inhibitor)

Equation 7: Four Parameter logistic calculation

Y= Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope))

X = logarithm of concentration.

Y = specific binding (equation 6)

Top and Bottom = Plateus in same units as Y (specific binding)

Log IC so in same units as X. Y starts at Bottom and goes to Top with a sigmoid shape. Specific binding decreases as X increases.

Profiling of fully human recombinant anti-OX40L antibodies in HTRF Ligand/Receptor Neutralisation assay

[0892] In order to determine whether recombinantly expressed fully human purified IgG inhibit human OX40L binding to OX40RFc the following method was carried out. Fully human purified IgG or other inhibitor were tested in order to establish the clone potency as measured by IC_{50} values in the assay. Antibodies recombinantly expressed and purified were titrated by diluting in HTRF assay buffer and 5 µL of this titration transferred to a white 384 well low volume non-binding surface polystyrene plate (Greiner). Biotinylated OX40L was diluted in HTRF assay buffer to a working concentration of 2.4 nM and 5 µL added. OX40RFc directly labelled with AF647 was then diluted to working concentration of 10 nM and 5 µL added. Non-specific binding was defined by replacing OX40RFc-AF647 with assay buffer or HMM. Streptavidin cryptate (CISBIO) was diluted in HTRF assay buffer to working concentration of 1:100 and 5 µL added to all wells of the plate. Plates were covered, protected from light and incubated at room temperature for 3 hrs prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). Data were analysed by calculating delta F as described in Equation 4 and percentage of receptor for each sample according to Equation 5 or in some cases Equation 6. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 7) (Figure 1).

Determining effect of anti-OX40L antibodies on recombinant OX40L induced IL2 release from primary isolated T-cells

[0893] Recombinant human OX40L (in house) was diluted in culture media to a concentration of 400 ng/mL and 50 µL added to a tissue culture treated 96 well plate (Costar). Anti-OX40L antibodies or appropriate species isotype control (Sigma or in house) were titrated in culture media in a 96 well plate (greiner) and then 50 µL of titration transferred to the 96 well plate containing 50 µL OX40L. The antibody titration was incubated for 30 minutes at room temperature with the recombinant OX40L before CD3 positive T-cells were added.

[0894] PBMCs were isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) by density gradient centrifugation. CD3 positive cells (T-cells) were isolated from human PBMC by negative selection using magnetic microbeads (Miltenyi Biotech) according to manufacturer's recommendations. The isolated cells were centrifuged at 300 xg/5 min, resuspended in culture media (culture media was defined as either RPMI (Gibco) + 10% v/v FBS or RPMI +5% v/v human AB serum) and 50 µL of the cell suspension added to the 96 well plate containing the recombinant OX40L and antibody titration to a achieve final concentration of 2×10^5 cells/well.

[0895] Then 50 µL of PHA at 8 µg/mL was added to all wells to achieve a final assay concentration of 2 µg/mL. The cells were incubated at 37 °C for 3 days before supernatant were harvested and analysed for IL-2 concentration. Maximal IL-2 release was defined by OX40L stimulation in the absence of inhibitor. Minimal IL-2 release was defined by culture media only (no OX40L).

[0896] IL-2 levels in supernatants were determined using human IL-2 Duoset ELISA kit (R &D) Systems) according to manufacturer's recommendations. IL-2 capture antibody (4 µg/mL diluted in PBS, 50 µL/well) was adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess IgG was removed by washing with PBS-Tween and the wells were blocked with 1% bovine serum albumin (BSA) in PBS for 1 hour at room temperature, after which plates were washed as described previously. 50 µL/well of conditioned culture media was then added IL-2 standards (from 2000 pg/mL, 1:2 dilution) were also added to ELISA plates as an ELISA control and the plates were incubated at room temperature for at least 1 hour.

[0897] Following incubation, plates were washed as before to remove unbound proteins. Biotinylated IL-2 detection Ab (200 ng/mL in reagent diluent (0.1% BSA/PBS), 50 µL/well) was then added to the plates and incubated at RT for 1 h. Unbound detection antibody was removed by washing with PBS-Tween (0.1% v/v), while the remaining biotinylated antibody was detected by streptavidin-Europium3+conjugate (DELFIA® detection, PerkinElmer). Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Fluorescence data was plotted as Europium counts or concentration of IL-2 release calculated from standard curve by linear regression according to manufacturer's recommendations. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 7).

Surface Plasmon Resonance Analysis:

[0898] SPR analysis was carried out using the ProteOn™ XPR36 Array System (BioRad). Anti-mouse IgG (GE Healthcare BR-1008-38) was immobilised on a GLM biosensor surface using amine coupling, the surface was then blocked using 1 M ethanolamine. Test antibodies were captured on this surface and recombinant hOX40L (human and rhesus) were used at a single concentration of 256 nM, binding sensorgrams were double referenced using a buffer injection (i.e. 0 nM) to remove baseline drift and injection artefacts. Apparent affinities for the OX40L-antibody interaction were determined using the 1:1 model inherent to the ProteOn XPR36 analysis software. The assay was run using HBS-EP (Teknova) as running buffer and carried out at 25 °C.

Example 4

Sequence Recovery of Lead Antibody Candidates

[0899] After the selection and characterization of lead candidates, their fully human variable domains were recovered using RT-PCR using a mixture of forward and reverse primers. Antibodies were reformatted into a human IgG4 backbone (IgG4-PE) and expressed using a transient expression system in CHO-S cells. A summary of all sequences is displayed in the Sequence Listing.

RNA isolation from hybridoma cells:

[0900] Total RNA was extracted from hybridoma cells using TRIzol™ Reagent (Invitrogen). The quantity and quality of the isolated RNA was analysed spectrophotometrically.

Antibody variable domain recovery by RT-PCR:

[0901] Selected clones were used for preparing total RNA, which was used in an RT-PCR reaction to recover the heavy chain V-regions. IgG specific reverse primers and Ig leader sequence specific forward primer sets or alternatively IgG specific reverse primers and Ig 5' untranslated region (UTR) sequence specific forward primer sets were used for the heavy chains. Kappa constant region specific reverse primers and kappa leader sequence specific forward primer sets or alternatively Kappa constant region specific reverse primers and kappa 5'UTR sequence specific forward primer sets were used for the kappa OX40L chains. The RT-PCR products were separated by agarose gel electrophoresis with the DNA of the predicted size being sequenced in the forward and reverse directions. Alternatively, the RT-PCR products were subcloned into a cloning vector and DNA of individual colonies submitted for sequencing.

Cloning of recombinant antibodies

[0902] DNA encoding the heavy chain variable region of mAb 10A7 was cloned into a pREP4 expression plasmid (Invitrogen) in frame with the Human IgG1 constant region and DNA encoding the light chain variable region of mAb 10A7 was cloned into a pREP4 expression plasmid in frame with the Human Kappa constant region using standard restriction enzyme digestion and ligation.

[0903] The heavy chain variable region coding sequences of mAbs 10A7 and 2D10 in frame with the Human IgG4-PE constant region were codon optimized for mammalian expression and cloned into a pXC-18.4 expression plasmid (Lonza) and the light chain coding sequences of mAbs 10A7 and 2D10 in frame with the Human Kappa constant region were codon optimized for mammalian expression and cloned into a pXC-17.4 expression plasmid (Lonza) using standard restriction enzyme digestion and ligation. For the simultaneous expression of the heavy and light chains the vectors a pXC-17.4 and a pXC-18.4 were fused into one single vector using standard restriction enzyme digestion and ligation.

[0904] All constructs were sequenced to ensure their correct sequence composition.

Transient Expression of OX40L Antibodies

[0905] Antibodies were expressed transiently to produce recombinant protein using Invitrogen's Freestyle™ CHO-S suspension adapted cell line. Plasmids were transfected into the cells using PEI (polyethylenimine MW 40000) and left to overgrow for a period of 13 days before harvesting the supernatant for purification. Cells were fed during the overgrow process with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability.

Generation of Stable Lonza Pools

[0906] In order to produce the gram amounts required for toxicology studies, 10A7 and 2D10 OX40L antibodies were transferred to the Lonza GS Xceed system for stable expression. The HC and LC for each antibody was first codon optimised for expression in CHO cells by Genewiz. The HC cassette (containing the optimised IgG4PE constant region) was then cloned into Lonza's pXC18.4 vector and LC cassette (containing the optimised kappa constant region) cloned into Lonza's pXC17.4 vector using standard restriction enzyme digestion and ligation. A double gene vector (DGV) encoding both the HC and LC sequences was then created by restriction enzyme digestion and ligation and sequence confirmed before expression.

[0907] Prior to stable pool creation; the single gene vectors encoding the HC and LC's separately as well as the DGV containing both, were expressed in the Lonza CHOK1SVKO cell line transiently using PEI (polyethylenimine MW 40000). Cells were left to overgrow for a period of 13 days before harvesting the supernatant for purification. During this period cells were fed with ActiCHO™ Feeds A and B from GE Healthcare to help boost productivity and promote longevity of the cells. During the overgrow process samples were taken regularly to monitor cell growth and viability. Once transient expression was confirmed and purified material analysed the antibodies were expressed as stable pools.

[0908] Stable pools were generated using Lonza's proprietary methods and media. 4 pools were created per antibody and left to recover over a period of 10-15 days. After the cells had recovered, pre-seed stocks (PSS) of cells were frozen down for later recovery and creation of MCB. Small scale (50 mL) shake flask fed batch overgrows were then set up using Lonza's proprietary media. Cells were left to overgrow for a period of 14 days. During this period cells were monitored for growth, viability and glucose levels. Cells were supplemented accordingly with Lonza's proprietary feed and 400g/L glucose. Samples were also taken throughout the process for crude sample quantification. At the end of the overgrow process the supernatant was harvested for purification.

[0909] Stable pools were generated using Lonza's proprietary methods and media. 4 pools were created per antibody and left to recover over a period of 10-15 days. After the cells had recovered, pre-seed stocks (PSS) of cells were frozen down for later recovery and creation of MCB. Small scale (50 mL) shake flask fed batch overgrows were then set up using Lonza's proprietary media. Cells were left to overgrow for a period of 14 days. During this period cells were monitored for growth, viability and glucose levels. Cells were supplemented accordingly with Lonza's proprietary feed and 400 g/L glucose. Samples were also taken throughout the process for crude sample quantification. At the end of the overgrow process the supernatant was harvested for purification.

[0910] Whilst the 2D10 and 10A07 were similar in sequence, there expression profiles in the stable Lonza pools were different, 10A07 expressed to very low titres, whereas 2D10 expressed at much greater titres (see Table 2) under optimal conditions when using shake flasks in 4 separate generated stable pools.

Table 2 (Concentration in mg/L)

Stable pool	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
2D10-1	261	492	681	993	1157	1590	1530	1575
2D10-2	245	461	665	983	1127	1485	2025	1995
2D10-3	317	528	731	1163	1367	1785	1905	1860
2D10-4	372	677	785	1286	1350	1935	1965	1800
Control Antibody 1	92	129	167	229	297	357	416	N/A
Control Antibody 1	68	95	127	161	209	238	266	N/A
Control Antibody 1	68	102	132	192	266	324	314	N/A
Control Antibody 1	88	129	165	245	328	410	385	N/A

[0911] After expression, the antibody to be used in the Rhesus Macaque GvHD model was purified using a two-step purification process. The antibodies were first purified using MabSelect SuRe (GE Healthcare) affinity chromatography. Antibodies were eluted from the MabSelect SuRe media using IgG Elute reagent (Pierce) and the eluted antibodies were dialysed in sodium acetate (pH 5.5) buffer prior to the second purification step. Antibodies were then purified by cation exchange and eluted with sodium chloride in sodium acetate buffer. Eluted antibodies were dialysed in PBS. Antibodies were quantified by spectrophotometer reading at OD280nm and adjusted to the desired concentration (10mg/ml). Antibody purity was assessed by SDS-PAGE analysis and size exclusion chromatography. Endotoxin concentration was measured with Endosafe PTS and LAL Test Cartridges (Charles River Laboratories).

Example 5

Determining effect of anti-OX40L antibodies in allogeneic PBMC Mixed Lymphocyte Reaction

[0912] PBMCs are isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) density gradient centrifugation. PBMC are pre-incubated with mitomycin C (Sigma) at 10 µg/mL in PBS for one hour at 37 °C. Cells are then washed 3 times in PBS centrifuging at 300 xg for 3 minutes, aspirating the supernatant after each wash. Allogeneic PBMC (not treated with mitomycin C) are added to a 96-well plate in RPMI supplemented with 10% v/v FBS at a concentration of 2×10^5/ml, 50 µL/well. Anti-OX40L antibodies are diluted in culture media and added to 96 well plate containing PBMC (not mitomycin C treated) at 50 µL/well. Mitomycin C treated PBMC are then added to allogeneic PBMC (not treated with mitomycin C) in 96-well plate at a final cell ratio in range of 1:1 to 4:1 mitomycin C treated to non mitomycin C based on number of cells/well. The cells are incubated for five days at 37 °C/5% CO_2. After five days TNF-α, IFN-γ, and IL-2 are measured by duoset ELISA (R&D Systems) according to manufacturer's recommendations. Proliferation is measured by CFSE dilution according to manufacturer's recommendations.

[0913] PBMCs were isolated from leukoreduction system chambers (NHSBT) using Ficoll-Paque plus (GE Healthcare) density gradient centrifugation. PBMC were pre-incubated with mitomycin C (Sigma) at 10 µg/mL in PBS for one hour at 37 °C. Cells were then washed 3 times in PBS centrifuging at 300 xgfor 3 minutes, aspirating the supernatant after each wash. T-lymphocytes (T-cells) in some cases CD3 positive and in other cases CD4 and CD8 positive were isolated from allogeneic PBMC by negative selection using magnetic microbeads (Miltenyi Biotech) according to manufacturer's recommendations. In some cases, non-mytomycin C treated PBMC were used instead of T-cells. The isolated cells were centrifuged at 300 xg/5 min, resuspended in culture media (culture media was defined as either RPMI (Gibco) +10% v/v FBS or RPMI +5% v/v human AB serum) and 50 µL of the cell suspension added to the 96 well plate containing the recombinant OX40L and antibody titration to a achieve final concentration of 2×10^5 cells/well. Anti-OX40L antibodies were diluted in culture media to a final assay concentration 100nM or in some cases a titration of antibody was used. The antibodies were added to 96 well plate containing T-cells or non-mytomycin C treated PBMC at 50 µL/well. Mitomycin C treated PBMC were then added to Tcells or non mytomycin C treated PBMC in 96-well plate at a final cell ratio in range of 1:1 to 4:1 mitomycin C treated PBMC to T-cells (or PBMC) based on number of cells/well. The cells were incubated for five days at 37 °C/5% CO_2. After five days, IFN-γ was measured by duoset ELISA (R&D Systems) according to manufacturer's recommendations.

[0914] Anti-OX40L antibodies were defined as inhibitors in allogeneic PBMC/T cell MLR or PBMC/PBMCI MLR when >20% inhibition (see Equation 8) of factor release (IFN-γ_1) or were observed relative to control wells in the absence of antibody. From four experiments performed, one experiment was a technical failure, defined as no MLR response (IFN-γ release) detected between allogeneic donors. Of the three remaining experiments, all three showed inhibition (>20% inhibition of factor release (IFN-γ_1) observed relative to control wells in the absence of antibody) with 2D10, 10A07 and positive control 1, however in one of three experiments, significant inhibition was also observed with the isotype control antibody (Figure 2). For PBMC/PBMC MLR, three experiments were performed. Of three experiments, two were regarded as technical failure as there was no or low IFN-γ release. However, in another experiment 10A07 inhibited IFN-γ release when compared to the isotype control.

Equation 8: Percentage inhibition (MLR)

[0915] Based on values from IFN-γ or IL2 release (pg/mL) determined as described

$$\%\ \text{inhibition} = 100 - \frac{\text{sample value} - \text{no stimulus}}{\text{No IgG} - \text{no stimulus}} \times 100$$

No Stimulus = wells where only T-cells or non-mytomycin C treated PBMC are added (no mitomycin C treated PBMC)

No IgG = wells where T-cells or in some cases non-mytomycin C treated PBMC along with mytomycin C treated PBMC are added but no IgG

Example 6

Determining effect of anti-OX40L antibodies on CD3 primed primary human T lymphocytes

[0916] In order to determine whether anti-OX40L had the ability to induce T-cell responses in the absence of OX40L, the assay below was performed using method adapted from Wang et al., Hybridoma (Larchmt)., 2009 Aug; 28(4):269-76, in which an agonist anti-OX40L antibody was described.

[0917] A mouse anti-human CD3 antibody (Becton Dickinson) was diluted to 0.5 µg/mL in sterile PBS and 50 µL/well added to a 96 well high binding sterile plate and incubated overnight at 4 °C.

[0918] Following overnight incubation, the plate was washed three times with 100 µL of sterile PBS.

[0919] T-cells (CD3 positive) were isolated from PBMC derived from leukoreduction system chambers (NHSBT) as described in Example 3. Following isolation, the cells were added to wells in 100 µL to achieve a final concentration of 1×10^5 cells/well.

[0920] Test antibodies were diluted in RPMI+ 10% FBS and 50 µL or 100 µL/well added to cell plate to achieve a final assay concentration of 10 µg/mL. In some cases, a mouse anti-human CD28 antibody (Becton Dickinson) was also added to wells at a final concentration of 1 µg/ml

[0921] The assay was incubated for 5 days. After 5 days, harvest supernatants and IFN-γ levels in supernatant were determined as described in Example 5.

[0922] The assay was performed in four independent donors and no effect of adding 10A07 or 2D10 in IgG4PE format was observed (IFN-γ release) over that observed with human IgG4PE isotype control.

Example 7

Rhesus Macaque Graft versus Host Disease (GvHD) Model

[0923] The effectiveness of antibody 2D10 IgG4PE as a monotherapy prophylactic for the prevention of GvHD was examined in a Rhesus Macaque model of haploidentical hematopoietic stem cell transplantation (HSCT). It had been previously described that monkeys undergoing HSCT in this model had a survival time of 6-8 days (Miller, Weston P, et al. "GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ Teells as a reservoir of breakthrough T cell proliferation during costimulation blockade and sirolimus-based immunosuppression." Blood, 116, 24(2010):5403-5418.)

[0924] All transplants were between half-sibling pairs that are mismatched at one MHC haplotype ("haploidentical-HCTs"). Recipient animals had irradiation based pre-myeloablative pre-transplant conditioning using a linear accelerator. Dose rate: 7cGy/min. Dose 1020 cGy given in 4 fractions. The leukapheresis donor animal underwent GCSF mobilisation and underwent leukapheresis using a Spectra Optia apheresis machine. The table below gives the dose per kg of total nucleated cells (TNC) dose of CD3+ cells, and CD34+ cells for the four successful experiments.

Table 3

Recipient ID#	Animal No.	Recipient Bodyweight (kg)	TNC (10^8/kg)	CD3+T-cells 10^6/kg	CD34+ cells 10^6/kg
A14079	#2	9.75	11.13	149.76	0.51
A14081	#4	7.02	2.99	389.08	4.79
A14082	#5	7.6	2.24	312.95	2.69
A14087	#6	5.75	3.44	385.66	9.99

[0925] 2D10 IgG4PE was dosed at 10 mg/kg i.v. according to a planned dosing schedule to take place on Day -2, Day +5, Day +12, Day +19, Day +26, Day +33, Day +40, Day +47 post-transplant. No serious adverse dosing side effects were seen with any of the animals as a result of administering 2D10 IgG4PE.

[0926] Samples were taken during the course of the study to monitor donor chimerism (Table 4) and white blood cell counts. The primary end point was based on survival, with a survival to 15 days deemed to be a sign of successful prophylactic therapy (and compared to the documented survival of 6-8 days with no prophylaxis; Miller et al 2010, *supra*). Though full pathology and histology with GvHD grading scores, markers of T-cell proliferation and activation (such as Ki-67 and granzyme B) and gene array analysis are planned, they were not available for inclusion at the time of drafting.

[0927] Methods for these studies are essentially as described in Miller WP et al., (2010) "GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ T cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression", Blood 116:5403-5418.

Clinical staging of GvHD

[0928] Scoring of clinical symptoms was based on observational assessments and clinical chemistry, classified according to the criteria set out in Table 5.

Histopathology

[0929] Tissues, including lung, liver, skin and gastrointestinal tract were collected at necropsy and fixed in formalin and paraffin-embedded. Sections were cut, slide-mounted and stained with haematoxylin/eosin or with T cell markers for visualisation of tissue infiltration by lymphocytes. Prepared slides are read by a histopathologist with specific expertise in GvHD using a semiquantitative scoring system.

Flow cytometry

[0930] Longitudinal peripheral blood samples were collected before and after haematopoietic stem cell transplant and at necropsy for flow cytometric analysis of lymphocyte subsets. Lung, liver, colon spleen and lymph node (axillary and inguinal) tissues were collected at necropsy and dissociated or enzymatically digested as appropriate for subsequent analysis of lymphocyte infiltrates by flow cytometry. Samples were analysed by multicolour flow cytometry using a LSRFortessa cell analyser (BD Biosciences) using the following T lymphocyte marker probes: CD3 (APC-Cy7 label; clone SP34-2, BD Biosciences), CD4 (BV786 label; clone L200, BD Biosciences), CD8 (BUV395 label; clone RPA-T8, BD Biosciences), CD28 (PE-Cy7 label; clone CD28.2, eBioscience), CD95 (BV605 label; clone DX2, Biolegend). Proliferating cell populations were identified using Ki-67 (FITC label, Dako). CD4+ or CD8+ T cell subcompartments were labelled as follows: naive T-cells (CD28+/CD95-), central memory T-cells (CD28+/CD95+), effector memory T-cells (CD28-/CD95+).

[0931] Blood was collected into tubes with Sodium EDTA, and then red blood cells were lysed with lysis buffer containing ammonium chloride. Remaining leukocytes were washed with FACS buffer (PBS with 2% FBS) and stained with antibody cocktail (Table 7) for 30 minutes at 4 °C. After staining, cells were washed and fixed in 1x BD Stabilizing Fixative. Acquisition of flow data was performed on BD LSR Fortessa cytometer. Data were analyzed using FloJo. T-cells were defined as CD3+CD14/CD20-lymphocytes.

Table 7. List of used antibodies for T cell immunophenotyping by flow cytometry

Antibody	Fluorochrome	Clone	Company
CD3	APC-Cy7	SP34-2	BD Biosciences
CD4	BV786	L200	BD Biosciences
CD8	BUV395	RPA-T8	BD Biosciences
CD14	PerCP-Cy5.5	M5E2	BD Biosciences
CD20	PerCP-Cy5.5	2H7	eBioscience
CD28	PE-Cy7	CD28.2	eBioscience
CD45RA	APC	2H4LDH11LDB9	Beckman Coulter
CD95	BV605	DX2	Biolegend
CCR7 (CD197)	BV421	G043H7	Biolegend
OX40 (CD134)	PE	L106	BD Biosciences

Results:

1: Expansion of memory stem T-cells after transplantation

[0932] In a non-human primate model of acute Graft-versus-Host disease (GVHD), allogeneic hematopoietic cell transplantation (HCT) results in early expansion of both CD4 and CD8 memory stem T-cells (Tscm: CD45RA+CCR7+CD95+) at the expense of reconstitution of bona fide naive T-cells (Tn: CD45RA+CCR7+CD95-) (Fig 3). These Tscm cells circulate in the blood, and also reside in both lymphoid (lymph nodes, spleen) and non-lymphoid organs (lung, liver and colon).

2: 2D10 IgG4PE limits expansion of Tscm

[0933] Treatment with the blocking anti-OX40L antibody, 2D10 IgG4PE, results in prolonged survival of animals after allogeneic HCT and reduces clinical symptoms of acute GVHD. This delay in GVHD progression was associated with limited CD4+Tscm expansion and preservation of CD4+Tn cells (Fig 4).

3: CD4 Tscm cells express OX40 on their surface

[0934] As shown in Figure 5, CD4+Tscm express OX40 on their surface, but naive T-cells do not. Moreover, the level of OX40 expression was comparable between CD4+Tscm and central memory cells (Tcm). Importantly, OX40 expression was detected on CD4+Tscm cells broadly. They are detected in naive monkeys before transplantation (both in the blood and lymphoid organs), as well as in leukopheresis products. This expression is also seen in allogeneic HCT recipients longitudinally after transplantation.

4: Comparative Analysis of Tscm in 02D10 Ig4PE treated animals compared to standard GvHD therapies

[0935] The proportion of post-HCT Tscm cells evident in the peripheral blood of rhesus monkeys that received 02D10 IgG4PE were compared with Tscm from separate groups of animals administered either sirolimus (rapamycin) or a combination of tacrolimus plus methotrexate (Tac/MTX). The results for CD4+ Tscm cells are shown in Figure 6a, and the results for CD8+ Tscm cells are shown in Figure 6b. Data indicate that treatment with anti-OX40L antibody 02D10 IgG4PE results in a sustained inhibition of the proportion of Tscm cells compared with the sirolimus and Tac/MTX treatment.

Conclusions:

[0936] An OX40-expressing subset of Tscm might be sensitive to 2D10 IgG4PE-mediated OX40L-blockade. This blockade may control Tscm expansion and therefore limit the progression of acute GVHD. The OX40 pathway is a potentially novel mechanism of Tscm regulation, which can be used in clinical practice to treat immune-mediated diseases or improve the outcome of adoptive immunotherapy.

Chimerism

[0937] Peripheral blood or T cell (CD3+/CD20-) chimerism was determined using divergent donor- and recipient-specific MHC-linked microsatellite markers, by comparing peak heights of the donor- and recipient-specific amplicons (Penedo MC et al., (2005) "Microsatellite typing of the rhesus macaque MHC region", Immunogenetics 57:198-209).

Table 5

Stage	Skin	Liver (Billirubin)	GI
0	No GVHD rash	< 4-fold increase over baseline	No diarrhea
1	Rash <25% of surface area	4- to 8-fold increase	"Mild" diarrhea
2	Rash 25-50% of surface area	8- to 20-fold increase	"Moderate" diarrhea
3	Rash >50% of surface area	20- to 50-fold increase	"Severe" diarrhea
4	Generalized erythroderma with bullous formation	> 50-fold increase	"Very severe" diarrhea

[0938] A total of six animals were selected to receive HSCT. Of these 6 animals, two of the experiments were deemed a technical failure, one animal experienced viral reactivation which may have hampered engraftment and it was seen that donor chimerism initially climbed but then dropped, indicating that second reconstitution was autologous repopulation. A single high cytomegalovirus (CMV) and *Rhesus macaque* Lymphocryptovirus (rhLCV) reading was seen at the same time as the drop in chimerism and autologous repopulation. The second technical failure was the result of failure of the apheresis machine to produce a suitable product for transplantation. Since the recipient animal had already been irradiated, it had to be sacrificed. The four other animals all survived to the primary endpoint of 15 days, exhibiting extended survival compared to both historical and contemporaneous no-prophylaxis controls. Table 6 below outlines the summary of each animal in this study.

Example 8

Pharmacokinetics

[0939] Rhesus macaques were dosed with 10 mg/kg of 2D10 or appropriate non-functional isotype control antibody on Day 0. Samples were taken, after +15 minutes, +1 hour, +8 hours, +24-36 hours, +72 hours, +96 hours, +Day 8, +Day 11, +Day 15, +Day 18, +Day 22, +Day 25. On Day 29, animals were dosed with 3 mg/kg of 2D10 or appropriate non-functional isotype control antibody. Samples were taken on Day 29 after +15 minutes, +1 hour, +8 hours and then 24-36 hours after Day 29. Samples continued to be taken on +Day 32, +Day 33, +Day 36, +Day 39, +Day 43, +Day 46, +Day 50, +Day 53, +Day 57, +Day 60, +Day 64, +Day 67 and +Day 71.

[0940] To determine the PK, anti-human IgG is diluted to 8 μg/mL in PBS and is adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4 °C. Excess IgG is removed by washing with PBS-Tween and wells are blocked with 5% w/v non-fat dried milk (blocking buffer) for 1 hour at room temperature. Following incubation period, plates are washed. Plasma samples are diluted in blocking buffer (multiple dilutions). A standard curve is also generated using a titration of positive control anti-OX40L antibody diluted in blocking buffer from 10 μg/mL (1 in 3 dilution). Either titration or diluted plasma sample are added to plate and incubated for 1 hr at room temperature. Plates are then washed and biotinylated human OX40L is diluted to 500 ng/mL in blocking buffer added for 1 hour at room temperature. Plates are then washed and streptavidin-Europium3+conjugate (DELFIA® detection, PerkinElmer) diluted in DELFIA® assay buffer (Perkin Elmer) is added. Plates are then washed 3 times in Tris Buffered Saline +0.1% tween. Then, DELFIA Enhancement solution (Perkin Elmer) is added to the plate and time-resolved fluorescence is measured at 615 nm on an Envision plate reader (PerkinElmer). The concentration of anti-OX40L antibody in the plasma is calculated by extrapolating fluorescence values from sample wells to those obtained from the standard curve generated from the titration of the positive control anti-OX40L antibody using a four parameter logistics curve fitting algorithm.

Example 9

Rhesus Macaque (GvHD) Model: effect of combined prophylaxis with 2D10 IgG4PE plus rapamycin

[0941] A further rhesus macaque GvHD study was conducted to determine the effect of combined post-HSCT prophylaxis with 2D10 IgG4PE and rapamycin. The study was performed as described in Example 7, with dosing as follows: 2D10 IgG4PE was administered i.v. at 10mg/kg on Day -2, Day +5, Day +12, Day +19, Day +26, Day +33, Day +40, Day +47 and Day +56 post-transplant. Rapamycin was administered at a loading dose of 0.1 mg/kg i.m. on Day -14, followed by daily i.m. maintenance doses of 0.025 mg/kg until the scheduled termination of the study at Day +100. Rapamycin dosing was adjusted to maintain serum trough levels within the range 5-15ng/mL.

Results:

[0942] Post-HSCT administration of 2D10 IgG4PE together with rapamycin resulted in extended GvHD-free and absolute survival (median survival time, MST > 82 days; n=3) compared to historical control animals that did not receive post-HSCT experimental treatment (MST=8 days; n=4; Furlan et al, Science Translational Medicine, Vol 7 (315); 315ra1910). The effect of combined 2D10 IgG4PE plus rapamycin dosing appeared also to be greater than the additive effect of each molecule when administered alone (Figure 7: MST for post-HSCT 2D10 IgG4PE and rapamycin were 19 and 17 days, respectively; both n-4). It is also noted that Furlan et al discloses a MST for combined prohylaxis with tacrolimus plus methotrexate of 49 days. It is expected that a combination of tacrolimus plus methotrexate and an anti-OX40L antibody (such as 2D10), or indeed a combination of tacrolimus and an anti-OX40L antibody (such as 2D10), would also provide the synergistic results as seen in this Example.

Table 4

Animal No.	Animal ID	Survival Duration (days)	Whole Blood Chimerism (%)																
			Day 0	Day 1	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 12	Day 14	Day 15	Day 16	Day 18	Day 20	Day 21	Day 23	Day 26
(#1)	(13188)	(24)	0		6.6			27.5		90.4		91.8			19.7		0		
#2	14079	16	0	5.7		31.7			86.3		82.3		88.2	79.8					
(#3)	(14076)	(0)																	
#4	14081	26		22.9		68.2			82.9		92.1		97.5			98.4		98.8	98.7
#5	14082	22				91.4			98.4		98.8		99.1			99.2		98.6	
#6	14087	16		16.6		66.3			97.4		99.5		99.4						

[0943] Data in brackets indicates experimental failure due to infection (animal 1) or technical failure (animal 3).

Table 6

2D10 IgG4PE Rhesus GvHD Study	
Animal	**Details**
#1	Survival to day 24. Received 4 doses of 2D10 IgG4PE. Biphasic hematopoietic reconstitution, peripheral blood chimerism data indicated initial donor engraftment followed by autologous repopulation concurrent with evidence of CMV and rhLCV infection. Viral infection considered possible cause of graft failure. Recorded as Technical Failure.
#2	Survival to Day 16. Received 3 doses of 2D10 IgG4PE. Peak peripheral blood donor chimerism of 88% at Day 15. No evidence of CMV or rhLCV infection. Study terminated on veterinary advice due to wound at catheter site (not deemed to be treatment or GvHD related). GvHD staging at necropsy: skin 1 (rash < 25%); liver 0 (no bilirubin elevation); GI 0 (no diarrhoea).
#3	Recorded as Technical Failure. Apheresis equipment failure resulted in drastically suboptimal donor blood product.
#4	Survival to Day 26. Received 4 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 99% by Day 23. No evidence of CMV or rhLCV infection. Study terminated on veterinary advice due to scrotal oedema. GvHD staging at necropsy: skin 2 (rash 25-50 %); liver 0 (no bilirubin elevation); GI 0 (no diarrhoea). Gross necropsy confirmed no overt visceral GvHD.
#5	Survival to Day 22. Received 4 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 99% by Day 12. No evidence of CMV or rhLCV infection. Study terminated due to persistent low platelet count with high bleeding risk and developing signs of acute systemic GVHD. GvHD staging at necropsy: skin 3 (rash >50 %); liver 1 (4-8 x bilirubin elevation); GI 3 (severe diarrhoea).
#6	Survival to Day 16. Received 3 doses of 2D10 IgG4PE. Clear hematopoietic reconstitution with peak peripheral blood donor chimerism of 100% on Day 12. No evidence of CMV or rhLCV infection. GvHD staging at necropsy: skin 2 (rash 25-50 %); liver 1 (4-8 x bilirubin elevation); GI 2 (moderate diarrhoea).

SEQUENCE LISTING

SEQ ID NO:				
1	10A07		VH Nucleotide Sequence	GAGGTGCAACTGGTGGAGTCTGGGGGAGTCTTGGTACAGCCGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGTTATATTATGACTT GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGTATTAGTGG TAGTGGTGCTGGTACATACTACGCAGACTCCATGAAGGGCCGGTTCACCATCT CCAGAGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGAGAGTC GAGGACACGGCCGTATATTACTGTGCGAAAGATCGGTTAGGTCCGATTACTTT GGTTCGGGGGGGCTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACG GTCACCGTCTCCTCA
2			VH Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYIMTWVRQAPGKGLEWVSGISGS GGGTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDRLGPITLVR GGYYYGMDVWGQGTTVTVSS
3			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACCTTTAGCAGTTATATT
4			HCDR1 Amino Acid Sequence (IMGT)	GFTFSSYI
5			HCDR2 Nucleotide Sequence (IMGT)	ATTAGTGGTAGTGGTGGTGGTACA
6			HCDR2 Amino Acid Sequence (IMGT)	ISGSGGGT
7			HCDR3 Nucleotide Sequence (IMGT)	GCGAAAGATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTACGG TATGGACGTC
8			HCDR3 Amino Acid Sequence (IMGT)	AKDRLGPITLVRGGYYYGMDV
9			HCDR1 Nucleotide Sequence (KABAT)	AGTTATATTATGACT
10			HCDR1 Amino Acid Sequence (KABAT)	SYIMT
11			HCDR2 Nucleotide Sequence (KABAT)	GGTATTAGTGGTAGTGGTGGTGGTACATACTACGCAGACTCCATGAAGGGC
12			HCDR2 Amino Acid Sequence (KABAT)	GISGSGGGTYYADSMKG
13			HCDR3 Nucleotide Sequence (KABAT)	GATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTACGGTATGGA CGTC
14			HCDR3 Amino Acid Sequence (KABAT)	DRLGPITLVRGGYYYGMDV
15			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTATGCTGCATCCAGT TTGCAAAGTGGAGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTT CACTCTCACCGTCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCA
				ACAGAGTTACAGTACCCCTCGGACGTTCGGCCAAGGGACCAGGGTGGAAATCA AA
16			VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKFLIYAASSLQ SGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQSYSTPRTFGQGTKVEIK
17			LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCAGCTATTAT
18			LCDR1 Amino Acid Sequence (IMGT)	QSISDY
19			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
20			LCDR2 Amino Acid Sequence (IMGT)	AAS
21			LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGTTACAGTACCCCTCGGACG
22			LCDR3 Amino Acid Sequence (IMGT)	QQSYSTPRT

SEQ ID NO:				
23			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCGACTATTTAAAT
24			LCDR1 Amino Acid Sequence (KABAT)	RASQSISDYLN
25			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
26			LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
27			LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTTACAGTACCCCTCGGACG
28			LCDR3 Amino Acid Sequence (KABAT)	QQSYSTPRT
29			Heavy Chain Nucleotide Sequence	GAGGTCCAGCTCGTGGAAAGCGGAGGAGTGCTCGTGCAGCCTGGAGGCAGCC TCAGGCTGTCCTGTGCCGCCTCCGGCTTCAGCTTCAGCAGCTACATCATGAGC TGGGTGAGGCAGGCTCCCGGAAAGGCCTGGAGTGGGTGTCGGCATCTCCG GATCCGGAGGAGGCACATACTACGCCGACAGCATGAAGGGCCGGTTCACCATC AGCCTGGGACAATAGCAAGAATACCCTCTACCTGCAAATGAACAGCCTGCGGGT GGAGGATACCGCCGTGTACTACTGCGCCAAAGATAGGCTGGGCCCCATTACCC TCGTGAGGGGAGGCTATTACTACGGCATGGATGTGTGGGGCCAGGGCACCAC CGTGACAGTGTCCAGCGCCAGCACCAAGGGCCCTTCCGTGTTCCCGCTGGCCC CTGCAGCAGAGCACCTCCGAATCCACAGCTGCCCTGGGCTGTCTGGTGAAG GACTACTTTCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCTCTGACATC CGGGGTCCACACCTTTCCTGCCGTCCTGCAGTCCTCGGACTCTACTCCCTGT CCTCCGTGGTGACCGTGCCTAGCTCTCTCCCTCGGCACCAAGACCTACACCTGT AACGTGGACCACAAACCCTCCAACACCAAGGTGGACAAGAGGGTCGAGAGCAA GTACGGCCCTCCCTGCCCTCCTGTCCTGCCCCGAGTTCGAAGGCGGACCCA GCGTGTTCCTGTTCCCTCCTAAGCCCAAGGACACCCTCATGATCAGCCGGACA CCCGAGGTGACCTGCGTGGTGGTGGATGTGAGCCAGGAGGACCCTGAGGTCC AGTTCAACTGGTATGTGGATGGCGTGGAGGTGCACAACGCCAAGACCAAGCCC CGGGAGGAGCAGTTCAACTCCACCTACAGGGTGGTCAGCGTGCTGACCGTGCT GCATCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCAGCAATAAG
				GGACTGCCCAGCAGCATCGAGAAGACCATCTCCAAGGCTAAAGGCCAGCCCCG CGAACCTCAGGTGTACACCCTGCCTCCCAGCCAGGAGGAGATGACCAAGAACC AGGTGAGCCTGACCTGCCTGGTGAAGGGATTCTACCCTTCGGACATCGCCGTG GAGTGGGAGTCCAACGGCCAGCCGGAGAACAATTATAAGACCACCCCTCCCGT CCTGGACAGCGACGGATCCTTCTTTCTGTACTCCAGGCTGACCGTGGATAAGT CCAGGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCT GCACAATCACTACACCCAGAAGTCCCTGAGCCTGTCCCTGGGAAAG
30			Heavy Chain Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYTMTWVRQAPGKGLEWVSGISGS GGSTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDRLGPITLVR GGYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKP SNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK
31			Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGTCCGCCTCCGTGGGAGACAG GGTGACCATCACCTGCCGGGCCAGCCAGTCGATCAGCAGCTACCTGAACTGGT ATCAGCAGAAGCCCGGCAAGGCCCCTAAGTTCCTGATCTACGCCGCTTCCTCC CTGCAGTCCGGAGTGCCCAGCAGGTTTTCCGGCTCCGGATCCGGCACCGACTT CACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCC AGCAGAGCTACAGCACCCCCAGAGACATTTGGCCAGGGCACCCGGGTGGAGAT CAAGAGGACCGTGCCTGCCCCCTCCGTGTTTATCTTCCCCCCAGCGACGAGC AGCTGAAATCCGGCACCGCCTCCGTGGTCTGCCTGCTGAATAACTTCTACCCT CGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGAAACT CCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACTCCACCTACAGCCTGTCC TCCACCCTGACACTGTCCAAGGCCGATTACGAGAAGCACAAGGTGTACGCCTG CGAGGTGACCCACCAGGGCCTGTCCTCCCCCGTGACCAAGTCCTTCAACCGGG GCGAGTGC
32			Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPRTFGQGTNVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
33	02D10		VH Nucleotide Sequence	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTCACTTTAGCAACTATGCCATGAACT GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGGGG AAGTGGTGGTGCCACAAGGTATTCCAGACTCCGTGAAGGGCCGATTCACCATAT
				CCAGAGACAATTCCAAGGAACACGGTGTATCTGCAAATGAACAGCCTGAGAGTC GAGGACACGGCCGTTTTTACTGTACGAAAGATCGGCTCATTATTGGCTACGGT TCGGGGACCCTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCA
34			VH Amino Acid Sequence	EVQLVESGGLVQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLEWVSTISGS GGATRYADSVKGRFTISRDNSRNTVYLQMNSLRVEDTAVFYCTKDRLIMATVRS PYYYGMDVWGQGTTVTVSS
35			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTTAGCAACTATGCC
36			HCDR1 Amino Acid Sequence (IMGT)	GFTFSNYA
37			HCDR2 Nucleotide Sequence (IMGT)	ATTAGCGGAAGTGGTGGTGCCACA
38			HCDR2 Amino Acid Sequence (IMGT)	ISGSGGAT
39			HCDR3 Nucleotide Sequence (IMGT)	ACGAAAGATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTAT GGACGTC
40			HCDR3 Amino Acid Sequence (IMGT)	TKDRLIMATVRGPYYYGMDV
41			HCDR1 Nucleotide Sequence (KABAT)	AACTATGCCATGAAC
42			HCDR1 Amino Acid Sequence (KABAT)	NYAMN
43			HCDR2 Nucleotide Sequence (KABAT)	ACTATTAGCGGAAGTGGTGGTGCCACAAGGTATGCAGACTCCGTGAAGGGC
44			HCDR2 Amino Acid Sequence (KABAT)	TISGSGGATRYADSVKG
45			HCDR3 Nucleotide Sequence (KABAT)	GATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTATGGACGT C
46			HCDR3 Amino Acid Sequence (KABAT)	DRLIMATVRGPYYYGMDV
47			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAACCTCCTGATCTATGCTGCATCCAGT TTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTT CACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCA ACAGAGTCACAGTGTCTCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCA AA
48			VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGTKVDIK
49			LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCAGCTAT
50			LCDR1 Amino Acid Sequence (IMGT)	QSISSY
51			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
52			LCDR2 Amino Acid Sequence (IMGT)	AAS
53			LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGTCACAGTGTCTCATTCACT
54			LCDR3 Amino Acid Sequence (IMGT)	QQSHSVSFT
55			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCAGCTATTTAAAT
56			LCDR1 Amino Acid Sequence (KABAT)	RASQSISSYLN
57			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
58			LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
59			LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTCACAGTGTCTCATTCACT
60			LCDR3 Amino Acid Sequence (KABAT)	QQSHSVSFT
61			Heavy Chain Nucleotide Sequence	GAAGTGCAACTGGTGGAGTCCGGAGGAGGCCTGGTGCAGCCTGGAGGAAGCC TGAGGCTGAGCTGTGCCGCCAAGGGCTTCACCTTCAGCAACTACGCCATGAAC TGGGTGAGGCAGGCCCTGGCAAGGGACTGGAGTGGGTCTCCACCATCAGCG GCTCCGGAGGTGCCTACAGGATACAGATGGCCGTGAAGGGCCGGTTTACCAT TTCCCGGGACAACTCCCGGAACACCGTGTACCTCCAGATGAACAGCCTGAGGG TGGAGGATACCGCCGTGTTCTACTGCACCAAGGACAGGCTGATTATTGGCCACC GTGAGGGGACCTTACTACTATGGTATGGATGTGTGGGGCCAGGGGACACCG TCACCGTGTCCTCCGCCTCCACCAAGGGACCTAGCGTGTTCCCTCTGGCCCCC TGTTCCAGGTCCACAAGCGGACTCACCGCCTGCCCTCGGCTGTCTGGTGAAGGA CTACTTTCCCGAGCCCGTGACCGTCTCCTGGAATAGCGGAGCCCTGACCTCCG GCGTGCACACATTTCCCGCCGTCCTGCAGAGCAGCGGACTGTATAGCCTGAGC AGCGTGGTGACCGTCCCCAGCTCCAGCCTCGGCACCAAAACCTACACCTGCAA CGTGGACCACAAGCCCTCCAACACCAAGGTGGACAAGCGGGTGGAGAGCAAG TACGGCCCCCCTTGCCCTCCTTGTCCTGCCCCTGAGTTCGAGGGAGGACCCTC CGTGTTCCTGTTCCCCCCAAACCCAAGGACACCCTGATGATCTCCCGGACCCC CGAGGTGACCTGTGTGGTCGTGGACGTCAGCCAGGAGGACCCCGAGGTGCAG TTCAACTGGTATGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCAAG GGAGGAGCAGTTCAATTCCACCTACAGGGTGGTGAGCGTGCTGACCGTCCTGC ATCAGGATTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGG ACTGCCCAGCTCCATCGAGAAGACCATCTCCAAGGCTAAGGGCCAGCCCAGGG AGCCCCAGGTGTATACCCTGCCTCCTAGCCAGGAGGAGATGACCAAGAACCAA GTGTCCCTGACCTGCCTGGTGAAGGGATTCTACCCTTCCGACATCGCCGTGGA GTGGGAGAGCAATGGCCAGCCCGAGAACAACTACAAGACCACCCCTCCCGTGC TCGATAGCGACGGCAGCTTCTTCCTCTACAGCAAGCTGACCGTGGACAAGAGC AGGTGGCAGCAGGGCAACGTGTTCTCCTGTTCCGTGATGCACGAGGCCCTGC ACAATCACTACACCCAGAAGAGCCTCTCCCTGTCCCTGGGCAAG
62			Heavy Chain Amino Acid Sequence	EVQLVESGGGLVQPGGSLRLSCAAGFTFSNYAMNWVRQAPGKGLEWVSTISGS GGATRYADSVKGRFTISRDNSRNTVYLQMNSLRVEDTAVFYCTKDRLIMATVRS PYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSN TKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK
63			Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGAGCGCTAGCGTGGGAGATAG GGTGACCATCACCTGCAGGGGCTCCCAAAGCATCTCGTCTCTCCCTGAACTGGT ACCAGCAGAAACCGGGCAAGGCCCCCAAGCTGCTGATCTACGCTGCTCCTCC CTCCAGTCCGGCGTGCCTAGCAGGTTTAGCGGCTCCGGAAGCGAGACCGACTT CACCCTGACCATCTCCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA

SEQ ID NO:				
				GCAATCCCACAGCGTGTCCTTCACCTTCGGCCCCGGCACCAAGGTGGACATCA AGAGGACCGTGGCCGCCCCCTCCGTGTTCATCTTTCCCCCCTCCGATGAACAG CTGAAGAGCGGCACCGCTAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAG GGAGGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGTCCGGCAACAGC CAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCCTC CACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGTGTACGCCTGCG AAGTGACCCATCAGGGCCTGAGCTCCCCCGTGACCAAGTCCTTTAACAGGGGC GAGTGC
64			Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAASSLQ SGVPSRFSGSGSETDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGTKVDIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
65	09H04		VH Nucleotide Sequence	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCC TGAGACTCTCCTGTGCAGCCTCTCGATTCACCCTCAGTGACTACTACATGACCT GGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAG TAGTGGTAATACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCT CCAGGGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCCGTGTATTACTGTGCGAGAGATCTGAGTGGGAGCTACTGGG ACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC TCA
66			VH Amino Acid Sequence	QVQLVESGGGLVKPGGSLRLSCAASRFTLSDYYMTWIRQAPGKGLEWVSYISSS GNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLSGSYWDYY YGMDVWGQGTTVTVSS
67			HCDR1 Nucleotide Sequence (IMGT)	CGATTCACCCTCAGTGACTACTAC
68			HCDR1 Amino Acid Sequence (IMGT)	RFTLSDYY
69			HCDR2 Nucleotide Sequence (IMGT)	ATTAGTAGTAGTGGTAATACCATA
70			HCDR2 Amino Acid Sequence (IMGT)	ISSSGNTI
71			HCDR3 Nucleotide Sequence (IMGT)	GCGAGAGATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTC
72			HCDR3 Amino Acid Sequence (IMGT)	ARDLSGSYWDYYYGMDV
73			HCDR1 Nucleotide Sequence (KABAT)	GACTACTACATGACC
74			HCDR1 Amino Acid Sequence (KABAT)	DYYMT
75			HCDR2 Nucleotide Sequence (KABAT)	TACATTAGTAGTAGTGGTAATACCATATACTACGCAGACTCTGTGAAGGGC
76			HCDR2 Amino Acid Sequence (KABAT)	YISSSGNTIYYADSVKG
77			HCDR3 Nucleotide Sequence (KABAT)	GATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTC
78			HCDR3 Amino Acid Sequence (KABAT)	DLSGSYWDYYYGMDV
79			VL Nucleotide Sequence	GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTACATCTGTAGGAGACAG AGTCACCATCGCTTGCCGGGCAAGTCAGGGCATTAACAATGCTTTAGCCTGGT ATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCTGATCTATGATGCCTCCAGT TTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATT TCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTC AACAGTTTAATAGTTACCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATC AAA
80			VL Amino Acid Sequence	AIQLTQSPSSLSTSVGDRVTIACRASQGINNALAWYQQKPGKAPKLLIYDASSLES GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPRTFGQGTKVEIK
81			LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAACAATGCT
82			LCDR1 Amino Acid Sequence (IMGT)	QGINNA
83			LCDR2 Nucleotide Sequence (IMGT)	GATGCCTCC
84			LCDR2 Amino Acid Sequence (IMGT)	DAS
85			LCDR3 Nucleotide Sequence (IMGT)	CAACAGTTTAATAGTTACCCTCGGACG
86			LCDR3 Amino Acid Sequence (IMGT)	QQFNSYPRT
87			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGGGCATTAACAATGCTTTAGCC
88			LCDR1 Amino Acid Sequence (KABAT)	RASQGINNALA
89			LCDR2 Nucleotide Sequence (KABAT)	GATGCCTCCAGTTTGGAAAGT
90			LCDR2 Amino Acid Sequence (KABAT)	DASSLES
91			LCDR3 Nucleotide Sequence (KABAT)	CAACAGTTTAATAGTTACCCTCGGACG
92			LCDR3 Amino Acid Sequence (KABAT)	QQFNSYPRT
93	19H01		VH Nucleotide Sequence	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGGGTCCC TTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACGCCTGGATGAGC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTGGCCGTATTAAAA GCAAAACTGAAGGTGGGACAACAGACTACGCTGCACCCGTGAAAGGCAGATTC ACCATCTCAAGAGATGATTCAAAAAACACGCTGTATCTGCAAATGAACAGCCTG AAAACCGAGGACACAGCCGTGTATTACTGTACCACAGATTTTCTATGGTTCGG GGAGTTCCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
94			VH Amino Acid Sequence	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKS KTEGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTDFLWFGE FPFDYWGQGTLVTVSS
95			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTCAGTAACGCCTGG
96			HCDR1 Amino Acid Sequence (IMGT)	GFTFSNAW
97			HCDR2 Nucleotide Sequence (IMGT)	ATTAAAAGCAAAACTGAAGGTGGGACAACA
98			HCDR2 Amino Acid Sequence (IMGT)	IKSKTEGGTT
99			HCDR3 Nucleotide Sequence (IMGT)	ACCACAGATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTAC
100			HCDR3 Amino Acid Sequence (IMGT)	TTDFLWFGEFPFDY
101			HCDR1 Nucleotide Sequence (KABAT)	AACGCCTGGATGAGC
102			HCDR1 Amino Acid Sequence (KABAT)	NAWMS
103			HCDR2 Nucleotide Sequence (KABAT)	CGTATTAAAAGCAAAACTGAAGGTGGGACAACAGACTACGCTGCACCCGTGAA AGGC
104			HCDR2 Amino Acid Sequence (KABAT)	RIKSKTEGGTTDYAAPVKG
105			HCDR3 Nucleotide Sequence (KABAT)	GATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTAC
106			HCDR3 Amino Acid Sequence (KABAT)	DFLWFGEFPFDY
107			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCGAGTCAGGGCATTAGCAATTATTTAGCCTGGT ATCAGCAGAAACCAGGGAAAATTCCTAAGCTCCTGATCTATGCTGCATCCACTT TGCAATCAGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTC ACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAA AAGTATAACAGTGCCCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAA A DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKIPKLLIYAASTLQS GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPRTFGQGTKVEIK
108			VL Amino Acid Sequence	. DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKIPKLLIYAASTLQS GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPRTFGQGTKVEIK
109			LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAGCAATTAT
110			LCDR1 Amino Acid Sequence (IMGT)	QGISNY
111			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
112			LCDR2 Amino Acid Sequence (IMGT)	AAS
113			LCDR3 Nucleotide Sequence (IMGT)	CAAAAGTATAACAGTGCCCCTCGGACG
114			LCDR3 Amino Acid Sequence (IMGT)	QKYNSAPRT
115			LCDR1 Nucleotide Sequence (KABAT)	CGGGCGAGTCAGGGCATTAGCAATTATTTAGCC
116			LCDR1 Amino Acid Sequence (KABAT)	RASQGISNYLA
117			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCACTTTGCAATCA
118			LCDR2 Amino Acid Sequence (KABAT)	AASTLQS
119			LCDR3 Nucleotide Sequence (KABAT)	CAAAAGTATAACAGTGCCCCTCGGACG
120			LCDR3 Amino Acid Sequence (KABAT)	QKYNSAPRT
121	Human IgG4 heavy chain constant region #1	IGHG *01	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagcc gccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagagagttgagtccaaatatggtcccccatgcccatcatgcccagcacctgagtt cctggggggaccatcagtcttcctgttccccccaaaacccaaggacactctcatgatctcccggacccct gaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtgg atggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctcc aacaaaggcctcccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccac aggtgtacaccctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtc aaaggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactac aagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaggctaaccgtggacaag agcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac acagaagagcctctccctgtctctgggtaaa
122			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
123	Human IgG4 heavy chain constant region #2	IGHG *02	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagcc gccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaac
				accaaggtggacaagagagttgagtccaaatatggtcccccgtgcccatcatgcccagcacctgagtt cctggggggaccatcagtcttcctgttccccccaaaacccaaggacactctcatgatctcccggacccct

SEQ ID NO:				
				gaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtgg atggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctcc aacaaaggcctcccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccac aggtgtacaccctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtc aaaggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactac aagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaggctaaccgtggacaag agcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac gcagaagagcctctccctgtctctgggtaaa
124			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
125	Human IgG4 heavy chain constant region #3	IGHG *03	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagcc gccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagagagttgagtccaaatatggtcccccatgcccatcatgcccagcacctgagtt cctggggggaccatcagtcttcctgttccccccaaaacccaaggacactctcatgatctcccggacccct gaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtgg atggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctcc aacaaaggcctcccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccac aggtgtacaccctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtc aaaggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactac aagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaag agcaggtggcaggaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac gcagaagagcctctccctgtctctgggtaaa
126			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ
				PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
127	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version A	gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacggc cgccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctgaatt tgaggggggaccatcagtcttcctgttccccccaaaacccaaggacactctcatgatctcccggacccct gaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtgg atggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctcc aacaaaggcctcccgtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagcca caggtgtacaccctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggt caaaggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaacta caagaccacgcctcccgtgctggactccgacggatccttcttcctctacagcaggctaaccgtggacaa gagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactaca cacagaagagcctctccctgtctctgggtaaa
128	IgG4 heavy chain constant region -IgG4-PE		Heavy Chain Constant Region Amino Acid Sequence - Encoded by Synthetic Version A, B & C	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
129	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version B	Gcctccaccaagggacctagcgtgttccctctcgccccctgttccaggtccacaagcgagtccaccgct gccctcggctgtctggtgaaagactactttcccgagcccgtgaccgtctcctggaatagcggagccctg acctccggcgtgcacacatttcccgccgtgctgcagagcagcggactgtatagcctgagcagcgtggt gaccgtgcccagctccagcctcggcaccaaaacctacacctgcaacgtggaccacaagccctccaaca ccaaggtggacaagcgggtggagagcaagtacggccccccttgccctccttgtcctgcccctgagttcg agggaggaccctccgtgttcctgtttccccccaaacccaaggacaccctgatgatctcccggacaccccg aggtgacctgtgtggtcgtggacgtcagccaggaggaccccgaggtgcagttcaactggtatgtggac ggcgtggaggtgcacaatgccaaaaccaagcccagggaggagcagttcaattccacctacagggtg gtgagcgtgctgaccgtcctgcatcaggattggctgaacggcaaggagtacaagtgcaaggtgtcca acaagggactgcccagctccatcgagaagaccatcagcaaggctaagggccagccgagggagccc caggtgtataccctgcctcctagccaggaagagatgaccaagaaccaagtgtccctgacctgcctggt gaagggattctacccctccgacatcgccgtggagtgggagagcaatggccagcccgagaacaactac
				aaaacaacccctcccgtgctcgatagcgacggcagcttctttctctacagccggctgacagtggacaag agcaggtggcaggagggcaacgtgttctcctgttccgtgatgcacgaggccctgcacaatcactacac ccagaagagcctctccctgtccctgggcaag
130	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version C	gccagcaccaagggcccttccgtgttccccctggccccttgcagcaggagcacctccgaatccacagct gccctgggctgtctggtgaaggactacttccccgagcccgtgaccgtgagctggaacagcggcgctct gacatccggcgtccacacctttcctgccgtcctgcagtcctccggcctctactccctgtcctccgtggtgac cgtgcctagctcctccctcggcaccaagacctacacctgtaacgtggaccataaaccctccaacacca aggtggacaaacgggtcgagagcaagtacggccctccctgccctccttgtcctgcccccgagttcgaag gcggacccagcgtgttcctgttccctcctaagcccaaggacaccctcatgatcagccggacacccgag gtgacctgcgtggtggtggatgtgagccaggaggaccctgaggtccagttcaactggtatgtggatgg cgtggaggtgcacaacgccaagacaaagccccgggaagagcagttcaactccacctacagggtggt cagcgtgctgaccgtgctgcatcaggactggctgaacggcaaggagtacaagtgcaaggtcagcaat aagggactgcccagcagcatcgagaagaccatctccaaggctaaaggccagccccgggaacctcag gtgtacaccctgcctcccagccaggaggagatgaccaagaaccaggtgagcctgacctgcctggtga agggattctacccttccgacatcgccgtggagtgggagtccaacggccagcccgagaacaattataag accacccctcccgtcctcgacagcgacggatccttcttcctgtactccaggctgaccgtggataagtcca ggtggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaatcactacacccag aagtccctgagcctgtccctgggaaag
131	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version D	gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacggc cgccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctccagt tgcggggggaccatcagtcttcctgttccccccaaaacccaaggacactctcatgatctcccggacccct gaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtgg atggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctcc aacaaaggcctcccgtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagcca caggtgtacaccctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggt caaaggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaacta caagaccacgcctcccgtgctggactccgacggatccttcttcctctacagcaggctaaccgtggacaa gagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactaca cacagaagagcctctccctgtctctgggtaaa
132			Heavy Chain Constant Region Amino Acid Sequence - encoded by Synthetic Version D	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP PVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
133	Human IgG1 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcg gccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccct gaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaaca ccaaggtggacaagaaagtggagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagc acctgaactcgcggggggcaccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcc cggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaact ggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagc acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtg caaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccc cgagaaccacaggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctga cctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccgga gaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcacc gtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaa ccactacacgcagaagagcctctccctgtctccgggtaaa
134			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
135	Human CK constant region	IGKC *01	Cκ Light Chain Constant Region Nucleotide Sequence	cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgctt ctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtggacaacgcc ctgcagtccggcaactcccaggaatccgtgaccgagcaggactccaaggacagcacctactccctgtc ctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccacc agggcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
136			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
137	Human CK constant region	IGKC *02	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctct gttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctc caatcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagcacctacagcctcagc agcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccat cagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
138			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQESKDSTYSLSSTLTLSKADYEKHKVYAGEVTHQGLSSPVTKSFNRGEC
139	Human CK constant region	IGKC *03	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctct gttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagcggaaggtggataacgccctc caatcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagcacctacagcctcagc agcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatc agggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt

SEQ ID NO:				
140			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQRKVDNALQSGNSQES VTEQESKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
141	Human Cκ constant region	IGKC *04	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctct gttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctc caatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagc agcaccctgacgctgagcaaagcagactacgagaaacacaaactctacgcctgcgaagtcacccatc agggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
142			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKLYACEVTHQGLSSPVTKSFNRGEC
143	Human Cκ constant region	IGKC *05	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctct gttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctc caatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagc aacaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatc agggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgc
144			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSNTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
145	Human Cλ constant region	IGCλ 1*01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggccaaccccacggtcactctgttcccgccctcctctgaggagctccaagccaacaaggccac actagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcttggaaggcagatggcagccc cgtcaaggcgggagtggagacgaccaaaccctccaaacagagcaacaacaagtacgcggccagca gctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatga agggagcaccgtggagaagacagtggcccctacagaatgttca
146			Cλ Light Chain Constant Region Amino Acid Sequence	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTK PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
147	Human Cλ constant region	IGCλ 1*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagccaacaag gccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatgg cagccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaacaagtacgcgg ccagcagctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcac gcatgaagggagcaccgtggagaagacagtggcccctacagaatgttca
148			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVET TKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
149	Human Cλ constant region	IGCλ 2*01	Cλ Light Chain Constant Region Nucleotide Sequence - Version A	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagccaacaag gccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatgg cagccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaacaagtacgcgg ccagcagctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcac gcatgaagggagcaccgtggagaagacagtggcccctacagaatgttca
150			Cλ Light Chain Constant Region Nucleotide Sequence - Version B	ggccagcctaaggccgctccttctgtgaccctgttccccccatcctccgaggaactgcaggctaacaag gccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggctgatagc tcccctgtgaaggccggcgtggaaaccaccaccccttccaagcagtccaacaacaaatacgccgcctc ctcctacctgtccctgacccctgagcagtggaagtcccaccggtcctacagctgccaagtgacccacga gggctccaccgtggaaaagaccgtggctcctaccgagtgctcc
151			Cλ Light Chain Constant Region Nucleotide Sequence - Version C	ggccagcctaaagctgcccccagcgtcaccctgtttcctccctccagcgaggagctccaggccaacaa ggccaccctcgtgtgcctgatctccgacttctacccgggcgctgtgaccgtggcttggaaagccgactcc agccctgtcaaagccggcgtggagaccaccacaccctccaagcagtccaacaacaagtacgccgcct ccagctatctctccctgacccctgagcagtggaagtcccaccggtcctactcctgtcaggtgacccacga gggctccaccgtggaaaagaccgtcgcccccaccgagtgctcc
152			Cλ Light Chain Constant Region Amino Acid Sequence - Encoded by Version A, B &C	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVET TKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
153	Human Cλ constant region	IGCλ 2*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaag gccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatag cagccccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggc cagcagctatctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacg catgaagggagcaccgtggagaagacagtggcccctacagaatgttca
154			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVET TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
155	Human Cλ constant region	IGCλ 3*01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggccaca ctggtgtgtctcataagtgacttctacccgggagccgtgacagttgcctggaaggcagatagcagcccc gtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagcag
				ctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagttgcccctacggaatgttca
156			Cλ Light Chain Constant Region Amino Acid Sequence	PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTP SKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
157	Human Cλ constant region	IGCλ 3*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaag gccacactggtgtgtctcataagtgacttctacccggggccagtgacagttgcctggaaggcagatagc agccccgtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggcc agcagctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgc atgaagggagcaccgtggagaagacagtggcccctacggaatgttca
158			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGPVTVAWKADSSPVKAGVET TTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
159	Human Cλ constant region	IGCλ 3*03	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaag gccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatag cagccccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggc cagcagctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacg catgaagggagcaccgtggagaagacagtggcccctacagaatgttca
160			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVET TTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
161	Human Cλ constant region	IGCλ 3*04	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaag gccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatag cagccccgtcaaggcgggagtggagaccaccacactctccaaacaaagcaacaacaagtacgcggc cagcagctacctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacg catgaagggagcaccgtggagaagacagtggcccctacagaatgttca
162			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVET TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
163	Human Cλ constant region	IGCλ 6*01	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccgccctcctctgaggagcttcaagccaacaag gccacactggtgtgcctgatcagtgacttctacccgggagctgtgaaagtggcctggaaggcagatgg cagccccgtcaacacgggagtggagaccaccacaccctccaaacagagcaacaacaagtacgcggc cagcagctacctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacg catgaagggagcaccgtggagaagacagtggcccctgcagaatgttca
164			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVET TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
165	Human Cλ constant region	IGCλ 7*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccaccctcctctgaggagcttcaagccaacaag gccacactggtgtgtctcgtaagtgacttctacccgggagccgtgacagtggcctggaaggcagatgg cagccccgtcaaggtgggagtggagaccaccaaaccctccaaacaaagcaacaacaagtatgcggc
				cagcagctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccgggtcacg catgaagggagcaccgtggagaagacagtggcccctgcagaatgctct
166			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTVAWKADGSPVKVGVET TKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
167	Recombinant Human OX40L (Leader sequence, Isoleucine Zipper and FLAG Sequence Included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCA CAGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGAAGATAAAA TTGAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAAATTGCGCGTATC AAAAAGCTGATTGGCGAACGTGGCGGTGGCAGCGGTGGCGGTAGCGGCGGTG GCAGCCAGGTGTCCCACCGATACCCCAGGATCCAGTCCATCAAGGTCCAGTTC ACCGAGTACAAAAAGGAGAAGGGATTCATCCTGACCTCCCAAAAGGAGGACGA GATCATGAAGGTGCAAAACAACTCCGTGATCATCAACTGCGACGGCTTCTACC TGATCTCCCTGAAGGGCTACTTCTCCCAGGAGGTGAACATCTCCCTGCACTAC CAGAAGGACGAGGAGCCCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATT CCCTGATGGTGGCCAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACC ACCGACAACACCAGCCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCT GATCCATCAGAACCCCGGCGAGTTTTGCGTCCTG
168			Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIARIKKLI GERGGGSGGGSGGGSQVSHRYPRIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQ NNSVIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTY KDKVYLNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL

SEQ ID NO:				
169	Recombinant Rhesus OX40L (Leader Seq uence, FLAG and Isoleucine zipper included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCA CAGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGAAGATAAAA TTGAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAAATTGCGCGTATC AAAAAGCTGATTGGCGAACGTGGCGGTGGCAGCGGTGGCGGTAGCGGCGGTG GCAGCCAGGTGTCCCACCAATACCCCAGGATCCAGTCCATCAAGGTCCAGTTC ACCGAGTACAAAAAGGAGGAGGGATTCATCCTGACCTCCCAAAAGGAGGACGA GATCATGAAGGTGCAAAACAACTCCGTGATCATCAACTGCGACGGCTTCTACC TGATCTCCCTGAAGGGCTACTTCTCCCAGGAGGTGAACATCTCCCTGCACTAC CAGAAGGACGAGGAGCCCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATT CCCTGATGGTGGCCAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACC ACCGACAACACCAGCCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCT GATCCATCAGAACCCCGGCGAGTTTTGCGTCCTG
170			Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIARIKKLI GERGGGSGGGSGGGSQVSHQYPRIQSIKVQFTEYKKEEGFILTSQKEDEIMKVQ
				NNSVIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTY KDKVYLNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
171	Recombinant Human OX40R (Leader Sequence and Human Fc Sequence included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCA CAGCCTGCATTGCGTGGGCGACACCTATCCCTCCAACGACAGGTGCTGCCACG AGTGCAGGCCTGGAAACGGCATGGTGAGCAGGTGCAGCCGGTCCCAGAATAC CGTGTGTAGGCCCTGCGGCCCCGGCTTTTACAACGACGTGGTGTCCTCCAAGC CCTGCAAGCCCTGCACATGGTGCAACCTGCGGTCCGGCAGCGAGAGGAAGCA GCTCTGCACAGCCACCCAGGACACCGTCTGTAGGTGTAGGGCTGGCACCCAGC CTCTGGACTCCTACAAGCCCGGCGTGGATTGTGCTCCTTGCCCTCCCGGCCAT TTCTCCCCTGGCGACAACCAGGCTTGCAAGCCCTGGACCAACTGTACCCTGGC CGGCAAGCATACACTGCAGCCTGCTTCCAACTCCTCCGACGCTATCTGCGAGG ATAGGGACCCCCCTGCCACACAACCCCAGGAGACACAGGGCCCTCCTGCTAGG CCCATCACAGTCCAACCCACCGAAGCCTGGCCCAGGACATCCCAAGGCCCTTC CACCAGGCCTGTGGAAGTGCCTGGAGGAAGGGCTGTGGCCATTGAAGGTCGT ATGGATGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGC CCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGG ACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGT GCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGG TGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTAC AAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTC CAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCA GGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTC TACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAA CTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACA GCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTG CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCC TGAGCCCCTGA
172			Amino Acid Sequence	MGWSCIILFLVATATGVHSLHCVGDTYPSNDRCCHECRPGNGMVSRCSRSQNTV CRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCRAGTQPLD SYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQPASNSSDAICEDRDP PATQPQETQGPPARPITVQPTEAWPRTSQGPSTRPVEVPGGRAVAIEGRMDEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
				NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSP
173	Cell Expressed OX40L (CHO/MEF) (Leader sequence included)		Nucleotide Sequence	ATGGAGAGGGTGCAGCCCCTCGAGGAGAACGTGGGAAACGCCGCCAGGCCTA GGTTCGAGAGGAACAAGCTGCTGCTGGTGGCTTCCGTGATCCAAGGACTCGG CCTGCTGCTCTGCTTCACCTACATCTGCCTCCACTTCAGCGCCCTGCAGGTGTC CCACCGATACCCCAGGATCCAGTCCATCAAGGTCCAGTTCACCGAGTACAAAA AGGAGAAGGGATTCATCCTGACCTCCCAAAAGGAGGACGAGATCATGAAGGTG CAAAACAACTCCGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCCTGAAG GGCTACTTCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACGAGGA GCCCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATTCCCTGATGGTGGCCA GCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACCACCGACAACACCAGC CTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCTGATCCATCAGAACCC CGGCGAGTTTTGCGTCCTGTAA
174			Amino Acid Sequence	MERVQPLEENVGNAARPRFERNKLLLVASVIQGLGLLLCFTYICLHFSALQVSHRY PRIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQNNSVIINCDGFYLISLKGYFSQEV NISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLNVTTDNTSLDDFHVNGG ELILIHQNPGEFC
175	Cell Expressed OX40 receptor (HT1080)		Nucleotide Sequence	ATGTGCGTGGGGGCTCGGCGGCTGGGCCGCGGGCCGTGTGCGGCTCTGCTCC TCCTGGGCCTGGGGCTGAGCACCGTGACGGGGCTCCACTGTGTCGGGGACAC CTACCCCAGCAACGACCGGTGCTGCCACGAGTGCAGGCCAGGCAACGGGATG GTGAGCCGCTGCAGCCGCTCCCAGAACACGGTGTGCCGTCCGTGCGGGCCGG GCTTCTACAACGACGTGGTCAGCTCCAAGCCGTGCAAGCCCTGCACGTGGTGT AACCTCAGAAGTGGGAGTGAGCGGAAGCAGCTGTGCACGGCCACACAGGACA CAGTCTGCCGCTGCCGGGCGGGCACCCAGCCCCTGGACAGCTACAAGCCTGG AGTTGACTGTGCCCCCTGCCCTCCAGGGCACTTCTCCCCAGGCGACAACCAGG CCTGCAAGCCCTGGACCAACTGCACCTTGGCTGGGAAGCACACCCTGCAGCCG GCCAGCAATAGCTCGGACGCAATCTGTGAGGACAGGGACCCCCCAGCCACGCA GCCCCAGGAGACCCAGGGCCCCCCGGCCAGGCCCATCACTGTCCAGCCCACTG AAGCCTGGCCCAGAACCTCACAGGGACCCTCCACCCGGCCCGTGGAGGTCCCC GGGGGCCGTGCGGTTGCCGCCATCCTGGGCCTGGGCCTGGTGCTGGGGCTGC TGGGCCCCCTGGCCATCCTGCTGGCCCTGTACCTGCTCCGGAGGGACCAGAG GCTGCCCCCCGATGCCCACAAGCCCCCTGGGGGAGGCAGTTTCCGGACCCCCA TCCAAGAGGAGCAGGCCGACGCCCACTCCACCCTGGCCAAGATCTGA
176			Amino Acid Sequence	MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDRCCHECRPGNGMVS RCSRSQNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCR CRAGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQPASNS SDAICEDRDPPATQPQETQGPPARPITVQPTEAWPRTSQGPSTRPVEVPGGRAV AAILGLGLVLGLLGPLAILLALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAH STLAKI
177	OX40L15B07		Amino Acid Sequence of OX40L15B07 (Seq ID No 179 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELVATITGG SSINYGDFVKGRFTISIDNAKNTVYLQMNNLKPEDTAVYYCNFNKYVTSRDTWG QGTQVTVSS
178	OX40L01B11		Amino Acid Sequence of OX40L01B11 (Seq ID No 180 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCVASGRSFSTYIMGWFRQAPGKEREFVATISRSG ITIRSADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAGPYVEQTLGLYQ TLG PWDYWGQGTQVTVSS
179	OX40L01E07		Amino Acid Sequence of OX40L01E07 (Seq ID No 181 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFVAAISRS GRSTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAVGGATTVTAS EWDYWGLGTQVTVSS
180	OX40L01E10		Amino Acid Sequence of OX40L01E10 (Seq ID No 182 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGDSLRLSCAASGLTFSSFAMGWFRQAPGKEREFVAAISRS GYGTSEADSVRDRFIISRDNAKNTVTLHLSRLKPEDTAVYYCAAEHTLGRPSRSQI NYLYWGQGTQVTVSS
181	OX40L18E09		Amino Acid Sequence of OX40L18E09 (Seq ID No 183 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASRNILSLNTMGWYRHAPGKPRELVARISSNS KTDYADSVKGRFTISRDNAKNTVLLQMNSLKPEDTGVYYCNLNVWRTSSDYWG QGTQVTVSS
182	OX40L19A07		Amino Acid Sequence of OX40L19A07 (Seq ID No 184 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSRIKISN GRTTYAGSVKGRFTISSDNAKNTVYLQMNSLNAEDTAVYYCAADRSSLLFGSNW DRKARYDYWGQGTQVTVSS
183	OX40L19D08		Amino Acid Sequence of OX40L19D08 (Seq ID No 185 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGASLRLSCAASGRRFISNYAMGWFRQAPGQERAFVAAISR SGSITYYTDSVKGRFSISRDYAKSTVYLQMDNLKPEDTAVYYCAADGGAVRDLTT NLPDYWGRGTQVTVSS
184	OX40L075		Amino Acid Sequence of OX40L075 (Seq ID No 199 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRSFSTYIMGWFRQAPGKEREFVATISRSG ITTRSADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAGPYVEQTLG LYQTLGPWDYWGQGTLVTVSS
185	OX40L024		Amino Acid Sequence of OX40L024 (Seq ID No 200 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
186	OX40L025		Amino Acid Sequence of OX40L025 (Seq ID No 201 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
187	OX40L026		Amino Acid Sequence of OX40L026 (Seq ID No 202 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
188	OX40L027		Amino Acid Sequence of OX40L027 (Seq ID No 203 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
189	OX40L028		Amino Acid Sequence of OX40L028 (Seq ID No 204 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KEREFV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
190	OX40L039		Amino Acid Sequence of OX40L039 (Seq ID No 205 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
191	OX40L030		Amino Acid Sequence of OX40L030 (Seq ID No 206 in WO2011/073180, Table A-2)	DVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISID NAKNTVYLQM N N LKPEDTAVYYCN FN KYVTSRDTWGQGTQVTVSS

SEQ ID NO:				
192	OX40L040		Amino Acid Sequence of OX40L040 (Seq ID No 207 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
193	OX40L041		Amino Acid Sequence of OX40L041 (Seq ID No 208 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHATGEPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
194	OX40L042		Amino Acid Sequence of OX40L042 (Seq ID No 209 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
195	OX40L043		Amino Acid Sequence of OX40L043 (Seq ID No 210 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGKPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
196	OX40L044		Amino Acid Sequence of OX40L044 (Seq ID No 211 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGEPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
197	OX40L045		Amino Acid Sequence of OX40L045 (Seq ID No 212 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASRSIG RLD RMGWYRHATG KPRE LV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
198	OX40L046		Amino Acid Sequence of OX40L046 (Seq ID No 213 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
199	OX40L047		Amino Acid Sequence of OX40L047 (Seq ID No 214 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGKPRELV ATTGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
200	OX40L048		Amino Acid Sequence of OX40L048 (Seq ID No 215 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYADFWG RFTSRD NSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
201	OX40L049		Amino Acid Sequence of OX40L049 (Seq ID No 216 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYG DSVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
202	OX40L050		Amino Acid Sequence of OX40L050 (Seq ID No 217 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYADSWG RFTSRD NSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
203	OX40L053		Amino Acid Sequence of OX40L053 (Seq ID No 218 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYGDFVKGRFTISIDNSKNTVYLQM NSLRPEDTAVYYCN FNK YVTS RDTWGQGTLVTVSS
204	OX40L054		Amino Acid Sequence of OX40L054 (Seq ID No 219 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYG D FVKG RFTISRDNAKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
205	OX40L055		Amino Acid Sequence of OX40L055 (Seq ID No 220 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATTGGSSINYGDFVKGRFTISRDNSKNTVYLQM NN LRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
206	OX40L056		Amino Acid Sequence of OX40L056 (Seq ID No 221 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYADSWG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
207	OX40L069		Amino Acid Sequence of OX40L069 (Seq ID No 222 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYADSWG RFTSIDNSKNTVYLQM NSLRPE DTAVYYCN FN K YVTS RDTWGQGTLVTVSS
208	OX40L070		Amino Acid Sequence of OX40L070 (Seq ID No 223 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYADSWG RFTSRD NSKNTVYLQM N N LRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
209	OX40L071		Amino Acid Sequence of OX40L071 (Seq ID No 224 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYADSWG RFTISI DNSKNTVYLQM N N LRPEDTAVYYCN FN KVVTSRDTWGQGTLVTVSS
210	OX40L082		Amino Acid Sequence of OX40L082 (Seq ID No 225 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELVA TITGGSSINYGDSVKGRFTISIDNSKNTVYLQM NSLRPEDTAVYYCNFNKY VTS RDTWGQGTLVTVSS
211	OX40L083		Amino Acid Sequence of OX40L083 (Seq ID No 226 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATTGGSSINYGDSVKGRFTISIDNSKNTVYLQMNSLRPEDTAVYYCN FNK YVTS RDTWGQGTLVTVSS
212	OX40L benchmark antibody heavy chain		Amino acid sequence of OX40L benchmark antibody heavy chain (Seq ID No:177 in WO2011/073180, Table A-5)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEW VSISGSGG FTYYADSVKG RFTISRDNSRTTLYLQM NSLRAEDTAVYYCA KDWLVAPGTDYWGQGALVTVSSASTKG PSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLF P PKPKDTLM IS RTPEVTCVVVDVSH E D P EVKFNWYVDGVEVH NAKTKP REEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSN KALPAPI EKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPE N N YKTTPPVLDSDGSFFLYSKLTVD KSRWQQG NVFSCSVM H EALH N HYTQ KSLSLSPGK
213	OX40L benchmark antibody light chain		Amino acid sequence of OX40L benchmark antibody light chain (Seq ID No:178 in WO2011/073180, Table A-5)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNSYPYTFG QGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLN N FYPREAKVQWK VDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTH QGLSSPVTKSFNRGEC
214	κ light chain variable region of LC.001		Amino acid sequence of kappa light chain variable region of LC.001 (Seq ID No: 1 in WO2006/029879)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK
215	γ heavy chain variable region of LC.001		Amino acid sequence of γ heavy chain variable region of LC.001 (Seq ID No: 2 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEWVSLISGS GGFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYCAKDRLVAPGTFDY WGQGALVTVSS
216	κ light chain variable region of LC.005		Amino acid sequence of kappa light chain variable region of LC.005 (Seq ID No: 3 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPITFGPGTKVDIK
217	γ heavy chain variable region of LC.005		Amino acid sequence of γ heavy chain variable region of LC.005 (Seq ID No: 4 in WO2006/029879)	QVQLVESGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWY DGSKDKYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYF DYWGQGTLVTVSS
218	κ light chain variable region of LC.010		Amino acid sequence of kappa light chain variable region of LC.010 (Seq ID No: 5 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPITFGPGTKVDIK
219	γ heavy chain variable region of LC.010		Amino acid sequence of γ heavy chain variable region of LC.010 (Seq ID No: 6 in WO2006/029879)	QVQLVESGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWY DGHDKYYAYYVDSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYF DYWGQGTLVTVSS
220	κ light chain variable region of LC.029		Amino acid sequence of kappa light chain variable region of LC.029 (Seq ID No: 7 in WO2006/029879)	QMQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAAIWY DGHDKTSFYVDSVRGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARDSSSWYRYF DYWGQGTLVTVSS
221	γ heavy chain variable region of LC.029		Amino acid sequence of γ heavy chain variable region of LC.029 (Seq ID No: 8 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVAVIWY DGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDNWSFDFW GQGTLVTVSS
222	κ light chain variable region of LC.019		Amino acid sequence of kappa light chain variable region of LC.019 (Seq ID No: 9 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQSVSRYLAWYQQKPGQAPRLLIYDASNRA TGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWYTFGQGTKLEI
223	γ heavy chain variable region of LC.019		Amino acid sequence of γ heavy chain variable region of LC.019 (Seq ID No: 10 in WO2006/029879)	QMQLVEFGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIWN DGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPRGYYYYG MDVWGQGTTVTVSS
224	κ light chain variable region of LC.033		Amino acid sequence of kappa light chain variable region of LC.033 (Seq ID No: 11 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWYTFGQGTKVEI

SEQ ID NO:				
225	γ heavy chain variable region of LC.033		Amino acid sequence of γ heavy chain variable region of LC.033 (Seq ID No: 12 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEWVSIISGS GGFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYCAKDRLVAPGTFDY WGQGALVTVSS
226	mutant κ light chain variable region of LC.033		Amino acid sequence of mutant kappa light chain variable region of LC.033 (Seq ID No: 16 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTKVDIK
227	γ heavy chain variable region of LC.059		Amino acid sequence of γ heavy chain variable region of LC.059 (Seq ID No: 17 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGS GGFTYYADSVKGRFTISRDNSKNTLYLQMNRLRAEDTAIYFCAKDDIPAAGTFDP WGQGTLVTVSS
228	κ light chain variable region of LC.060		Amino acid sequence of kappa light chain variable region of LC.060 (Seq ID No: 18 in WO2006/029879)	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDVSSLES GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYWTFGQGTKVEIK
229	γ heavy chain variable region of LC.060		Amino acid sequence of γ heavy chain variable region of LC.060 (Seq ID No: 19 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSLISGS GGLTKYADSVKGRFTISRDNSKRTLYLQMNSLRAEDTAVYYCAKDILVTGALDYW GQGTLVTVSS
230	γ heavy chain variable region of LC.063		Amino acid sequence of γ heavy chain variable region of LC.063 (Seq ID No: 20 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGS GGFTYYADSVKGRFTISRDNSKKTLYLQMSRLRAEDTAIYFCAKDDIPAAGTFDP WGQGTLVTVSS
231	8E12 light chain variable region		Amino acid sequence of 8E12 light chain variable region (Seq ID No: 13 in US7,812,133)	DILMTQTPLSLPVSLGDQASISCRSSQSIVHGNGNTYLEWHLQKPGQSPKLLIYR VSNRFSGVPDRFSGSGSGTDFTLKINRVEAEDLGVYYCFQGSHVPYTFGGGTKVE IKR
232	8E12 heavy chain variable region		Amino acid sequence of 8E12 heavy chain variable region (Seq ID No: 14 in US7,812,133)	DIVMTQTPLSLPVSLGDQASMYCRSSQSPVHSNGNTYLHWYLQKPGQSPKLLIY KVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHIPWTFGGGTKV EIKR
233	13G5 light chain variable region		Amino acid sequence of 13G5 light chain variable region (Seq ID No: 15 in US7,812,133)	QVQLQQPGAELVRPGASVKLSCKASGYTFTSYWLNWVKQRPGQGLEWIVMIDP SDSETHYNQVFKDKATLTVDKSSSTAYMQLSSLTSEDSAVYYCIRGRGNFYGGS HAMEYWGQGTLLTVSS
234	13G5 heavy chain variable region		Amino acid sequence of 13G5 heavy chain variable region (Seq ID No: 16 in US7,812,133)	QVQLQQPGAELVKPGTSVKLSCKASGYSFTSYWMHGVRQRPGQGLEWIGEIDPS NGRTNYNEKFKSKATLTVDKSSSTAYIQLSSLTSEDSAVYYCTRERSPRYFDVWG AGTTLTVSS
IMGT indicates that CDR is determined using IMGT nomenclature; KABAT indicates that CDR is determined using Kabat nomenclature. The numbering in the sequence correlation table takes precedence over any inconsistent numbering elsewhere in this text.				

REFERENCES CITED IN THE DESCRIPTION

Cited references

Patent documents cited in the description

- WO2006029879B [0009]
- US7812133B [0154] [0409] [0410] [0411] [0943] [0943] [0943] [0943]
- EP1731269A [0184]
- WO2014142225A [0395]
- WO2013055555A [0395]
- WO2013130102A [0395]
- WO2013119202A [0395]
- WO2013088131A [0395]
- WO2013025281A [0395]
- WO2013008171A [0395]
- WO2012027326A [0395]
- WO2010086418A [0395]
- WO2009079336A [0395]
- WO2008106115A [0395]
- WO2007062245A [0395]
- WO03106493A [0395]
- WO9942585A [0395]
- WO9521251A [0395]
- WO9521915A [0395]
- WO9512673A [0395]
- WO2011073081A [0409] [0410] [0411] [0943]
- WO2006029879A [0409] [0410] [0411] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943] [0943]
- WO05103021A [0571]
- US6245759B [0667]
- US6399633B [0667]
- US6383790B [0667]
- US6335155B [0667]
- US6271242B [0667]
- US6242196B [0667]
- US6218410B [0667]
- US6218372B [0667]
- US6057300A [0667]
- US6034053A [0667]
- US5985877A [0667]
- US5958769A [0667]
- US5925376A [0667]
- US5922844A [0667]
- US5911995A [0667]
- US5872223A [0667]
- US5863904A [0667]
- US5840745A [0667]
- US5728868A [0667]
- US5648239A [0667]
- US5587459A [0667]
- US6458335B [0667]
- US6451512B [0667]
- US6440974B [0667]
- US6436955B [0667]
- US6432953B [0667]
- US6420367B [0667]
- US6414145B [0667]
- US6410561B [0667]
- US6410333B [0667]
- US6403581B [0667]
- US6399615B [0667]
- US6387905B [0667]
- US6372747B [0667]
- US6369034B [0667]
- US6362188B [0667]
- US6342765B [0667]
- US6342487B [0667]
- US6300501B [0667]
- US6268363B [0667]
- US6265422B [0667]
- US6248755B [0667]
- US6239140B [0667]
- US6232338B [0667]
- US6228865B [0667]
- US6221335B [0667]
- US6204095B [0667]
- US6211193B [0667]
- US6177695B [0667]
- US6169096B [0667]
- US6159984A [0667]
- US6143766A [0667]
- US6133303A [0667]
- US6127366A [0667]
- US6124465A [0667]
- US6124345A [0667]
- US6103723A [0667]
- US6093737A [0667]
- US6090948A [0667]
- US6080870A [0667]
- US6077853A [0667]
- US6071935A [0667]

- US6066733A [0667]
- US6002930A [0667]
- US6054466A [0667]
- US6051582A [0667]
- US6051574A [0667]
- US6040305A [0667]
- US6277832B [0667]
- US5998596A [0667]
- US5985534A [0667]
- US5734023A [0667]
- US5615759A [0667]
- WO9733966A [0668]
- WO0734311A [0668]
- WO9923105A [0668]
- US5399063A [0673]
- US5622323A [0673]
- US5559045A [0673]
- US5340053A [0673]
- US5447851A [0673]
- US5723125A [0673]
- US5783181A [0673]
- US5808626A [0673]
- US5840095A [0673]
- US6112346A [0673]
- EP307434A [0673]
- EP367166A [0673]
- EP394827A [0673]
- WO0106570A [0673]
- WO9804366A [0673]
- WO0622024A [0673]
- WO9734631A [0673]
- WO0504812A [0673]
- US5605722A [0674]
- US5811238A [0674]
- US5830721A [0674]
- US5834252A [0674]
- US5837458A [0674]
- US4579990A [0675]
- US4486045A [0680]
- US4544546A [0680]
- US6013556A [0680]
- US3773919A [0688]
- US4328245A [0715]
- US4409239A [0715]
- US4410545A [0715]
- USRE28819E [0716]
- US4358603A [0716]
- US3710795A [0718]
- US4044126A [0730]
- US4414209A [0730]
- US4364923A [0733]
- US6267983B [0737]
- US6261595B [0737]
- US6256533B [0737]
- US6197331A [0737]
- US6024975A [0737]
- US6010715A [0737]
- US5985317A [0737]
- US5993134A [0737]
- US5948433A [0737]
- US5990957A [0737]
- US6316652B [0740]
- US6274552B [0740]
- US6271359B [0740]
- US6253872B [0740]
- US6139865A [0740]
- US6131570A [0740]
- US6120751A [0740]
- US6071495A [0740]
- US6060082A [0740]
- US6048736A [0740]
- US6039975A [0740]
- US6004534A [0740]
- US5985307A [0740]
- US5972366A [0740]
- US5900252A [0740]
- US5840674A [0740]
- US5759542A [0740]
- US5709874A [0740]
- US4522811A [0741]
- WO9202455A [0755]
- WO9114438A [0755]
- WO8912624A [0755]
- US5314995A [0755]
- EP396387A [0755]
- US6019968A [0762]
- US5985320A [0762]
- US5985309A [0762]
- US5934272A [0762]
- US5874064A [0762]
- US5855913A [0762]
- US5290540A [0762]
- US4880078A [0762]
- WO9219244A [0762]
- WO9732572A [0762]
- WO9744013A [0762]
- WO9831346A [0762]
- WO9966903A [0762]
- US5679377A [0765]
- US5916597A [0765]
- US5912015A [0765]
- US5989463A [0765]
- US5128326A [0765]
- WO9915154A [0765]
- WO9920253A [0765]
- US4526938A [0765]
- WO0105548A [0765]
- WO9620698A [0765]
- US4980286A [0766]
- US5441050A [0767]
- GB9101134W [0805]
- WO1992001047A [0805]
- WO0028909A [0805]
- WO0110737A [0805]
- WO9201047A [0805]
- WO0218612A [0805]
- WO9211255A [0805]
- WO0515922A [0805]
- WO9620401A [0805]
- WO9713844A [0805]
- US5698426A [0805]
- US6223409A [0805]
- US5403484A [0805]
- US5580717A [0805]
- US5427908A [0805], [0805]
- US5750753A [0805]
- US5821047A [0805]
- US5571698A [0805]
- US5516637A [0805]
- US5780225A [0805]
- US5658727A [0805]
- US5733743A [0805]
- US5969108A [0805]
- WO9222324A [0805]
- US4444887A [0808]
- US4716111A [0805]
- WO0546645A [0808]
- WO9850433A [0808]
- WO0624823A [0808], [0809]
- WO9816654A [0808]
- WO9634096A [0808], [0809]
- WO9633735A [0808], [0809]
- WO9110741A [0808]
- US5413923A [0809]
- US5625126A [0809]
- US5633425A [0809]

- US5563825A [0300]
- US5601016A [0308]
- US5545806A [0300]
- US5814318A [0308]
- US5939598A [0300]
- US5807715A [0310]
- US4816567A [0310]
- US4816397A [0310]
- US6331415B [0310]
- US5821337A [0310]
- EP239400A [0311]
- WO9109967A [0311]
- US5225539A [0311]
- US5530101A [0311]
- US5585089A [0311] [0311]
- EP592106A [0311]
- EP519596A [0311]
- US5565332A [0311]
- US6407213B [0311]
- US5766886A [0311]
- WO9317105A [0311]
- US20050042664A1 [0311]
- US6005079A [0312]
- WO9404678A [0312]
- WO9425591A [0312]
- WO0144301A [0312]
- WO2010004192A [0412]

Non-patent literature cited in the description

- **HILL-FERRARA**Blood, 2000, vol. 95, 92754-275 [0006]
- **REDDY-FERRARA**Blood, 2003, vol. 17, 4 [0006]
- **MCCORMICK et al.**J Immuno, 1999, vol. 163, 105693-5699 [0007]
- **SARANTOPOULOS et al.**Clin Cancer Res, 2007, vol. 13, 6107- [0007]
- **SVEGLIATI et al.**Blood, 2007, vol. 110, 1237-241 [0007]
- **MORANTE et al.**Clinical and Experimental Immunology, vol. 145, 36-43 [0008]
- **KOTANI et al.**Blood, 2001, vol. 98, 103162-3164 [0008]
- **TSUKADA et al.**Blood, 2000, vol. 95, 7 [0008]
- **BLAZAR et al.**Blood, 2003, vol. 101, 93741-3748 [0008]
- **TOTSUKA et al.**AJP - GI, 2003, vol. 284, 4G595-G603 [0008]
- **PAKALA et al.**European Journal of Immunology, 2004, vol. 34, 113039-3046 [0008]
- **LAMB, L.S.ABHYANKAR, S.A.HAZLETT, L.O'NEAL, W.FOLK, R.S.VOGT, S.PARRISH, R.S.BRIDGES, K.HENSLEE-DOWNEY, P.J.GEE, A. P.**Expression of CD134 (0X-40) on T-cells during the first 100 days following allogeneic bone marrow transplantation as a marker for lymphocyte activation and therapy-resistant graft-versus-host diseaseCytometry, 1999, vol. 38, 238-243 [0009]
- **XUPENG GEJULIA BROWNMEGAN SYKESVASSILIKI A. BOUSSIOTIS**CD134-Allodepletion Allows Selective Elimination of Alloreactive Human T-cells without Loss of Virus-Specific and Leukemia-Specific EffectorsBiology of Blood and Marrow Transplantation, 2008, vol. 14, 5518-530 [0009]
- OX40-OX40 Ligand Interaction in T-Cell-Mediated Immunity and Immunopathology**NAOTO ISHIITAKESHI TAKAHASHIPEJMAN SOROOSHKAZUO SUGAMURA**Advances in ImmunologyAcademic Press20100000vol. 105, 63-98 [0009]
- **CROFT, M.SO, T.DUAN, W.SOROOSH, P.**The significance of OX40 and OX40L to T-cell biology and immune diseaseImmunological Reviews, 2009, vol. 229, 173-191 [0009]
- **FURLAN et al.**Science Translational Medicine, 2015, vol. 7, 315 [0021]
- **KASER A**Increased expression of CCL20 in human inflammatory bowel diseaseJ. Clin. Immunol., 2004, vol. 24, 174-85 [0029]
- **PFEIFFER IA**Leukoreduction system chambers are an efficient, valid, and economic source of functional monocyte-derived dendritic cells and lymphocytesImmunobiology, 2013, vol. 8, 111392-401 [0030]
- **DEURING et al.**The cell biology of the intestinal epithelium and its relation to inflammatory bowel diseaseThe International Journal of Biochemistry & Cell Biology, 2013, vol. 45, 798-806 [0033]
- **HISAMATSU et al.**Immune aspects of the pathogenesis of inflammatory bowel diseasePharmacology & Therapeutics, 2013, vol. 137, 283-297 [0033]
- **MUZES et al.**Changes of the cytokine profile in inflammatory bowel DiseasedWorld J Gastroenterol, 2012, vol. 18, 411007-93275848-5861 [0035]
- **ITO et al.**Clinical and Experimental Immunology, 2006, vol. 146, 330-338 [0038]
- **GALES D**The Chemokine CXCL8 in Carcinogenesis and Drug ResponseISRN Oncol., 2013, vol. 2013, 859154- [0040]
- **SINGH S**CXCL8 and its cognate receptors in melanoma progression and metastasisFuture Oncol., 2010, vol. 6, 1111-6 [0040]
- **KEAN, LS et al.**Induction of chimerism in rhesus macaques through stem cell transplant and costimulation blockade-based immunosuppressionAm J Transplant., 2007, vol. 7, 2320-35 [0258]
- **LEVINE et al.**A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre studyLancet Haematol, 2015, vol. 2, e21-29 [0265] [0673]
- **MILLER, WESTON P. et al.**GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+T cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression.Blood, 2010, vol. 116, 245403-5418 [0266]
- **GATTINONIRESTIFO**Inside Blood, 2013, vol. 121, 4567-568 [0292]
- **BAUMGARTHROEDERER**Journal of Immunological Methods, 2000, vol. 243, 77-97 [0292]
- **PRZEPIORKA et al.**1994 Consensus Conference on Acute GvHD Grading Bone Marrow Transplant 1995, 1995, 15825-828 [0353]
- **LAZAR et al.**Proc. Natl. Acad. Sci. U.S.A., 2006, vol. 103, 114005-10 [0390]
- **NATSUME et al.**Drug Des Devel Ther., 2009, vol. 3, 7-16 [0390]
- **SHIELDS et al.**J Biol Chem., 2001, vol. 276, 96591-604 [0390]
- **IDUSOGIE et al.**J. Immunol., 2001, vol. 166, 2571-2575 [0391]
- **NATSUME et al.**Cancer Res., 2008, vol. 68, 3863-3872 [0391]
- **WEINBERG, A.D. et al.**J. Immunother., 2006, vol. 29, 575-585 [0395]
- **MATSUMURA et al.**J Immunol., 1999, vol. 163, 3007- [0400]
- **TUTT**J. Immunol., 1991, vol. 147, 60-69 [0572]
- **KARLINALTSCHUL**Proc. Natl. Acad. Sci. U.S.A., 1990, vol. 87, 2264-2268 [0587]
- **KARLINALTSCHUL**Proc. Natl. Acad. Sci. U.S.A., 1993, vol. 90, 5873-5877 [0587]
- **ALTSCHUL et al.**J. Mol. Biol., 1990, vol. 215, 403- [0587]
- **ALTSCHUL et al.**Nucleic Acids Res., 1997, vol. 25, 3389-3402 [0587]
- **MYERSMILLER**CABIOS, 1988, vol. 4, 11-17 [0587]
- Fundamental ImmunologyRaven Press19890000332-336 [0590]
- Remington's Pharmaceutical SciencesMack Publishing Co.19900000 [0597] [0679] [0627] [0755] [0762]
- **KABAT et al.**Sequences of Proteins of Immunological InterestU.S. Department of Health and Human Services19910000 [0598] [0610] [0619]
- **TAYLOR, L. D. et al.**Nucl. Acids Res., 1992, vol. 20, 6287-6295 [0600]
- **KABAT, E. A. et al.**Sequences of Proteins of Immunological InterestU.S. Department of Health and Human Services19910000 [0600]
- **KABAT et al.**Ann. NY Acad. Sci., 1971, vol. 190, 382-391 [0610]
- **KOHLER et al.**Nature, 1975, vol. 256, 495- [0611]
- Short Protocols in Molecular BiologyJohn Wiley and Sons20020000 [0611] [0634]
- **THOMSON et al.**Nat. Rev. Immunol., 2009, vol. 9, 5324-337 [0636]
- **SCHEFFERTRAZA**J. Thorac. Dis., 2014, vol. 6, 81039-1053 [0636]
- **KABAT et al.**Sequences of proteins of immunological interestU.S. Department of Health and Human Services19910000 [0643]
- **PLUCKTHUN**The Pharmacology of Monoclonal AntibodiesSpringer-Verlag19940000vol. 113, 269-315 [0644]
- **JAKOBOVITS et al.**Proc. Natl. Acad. Sci., 1993, vol. 90, 2551- [0656]
- **JAKOBOVITS et al.**Nature, 1993, vol. 362, 255-258 [0656]
- **BRUGGERMANN et al.**Year in Immunol., 1993, vol. 7, 33- [0656]
- **HOOGENBOOM et al.**J. Mol. Biol., 1991, vol. 227, 381- [0657]
- **MARKS et al.**J. Mol. Biol., 1991, vol. 222, 581- [0657]
- **CHOTHIA et al.**J. Mol. Biol., 1998, vol. 278, 457-479 [0659]
- **WOYKE et al.**Antimicrob. Agents Chemother., 2002, vol. 46, 3802-8 [0667]
- **WOYKE et al.**Antimicrob. Agents Chemother., 2001, vol. 45, 3580-4 [0667]
- **MOHAMMAD et al.**Anticancer Drugs, 2001, vol. 12, 735-40 [0667]
- **WALL et al.**Biochem. Biophys. Res. Commun, 1999, vol. 266, 76-80 [0667]
- **MOHAMMAD et al.**Int. J. Oncol., 1999, vol. 15, 367-72 [0667]
- **KANTARJIAN et al.**Clin Cancer Res., 2002, vol. 8, 72167-76 [0667]
- **TAKAHASHI et al.**J. Immunol., 1994, vol. 6, 1567-1574 [0668]
- **DENARDO et al.**Clin Cancer Res., 1998, vol. 4, 102483-90 [0671]
- **PETERSON et al.**Bioconjug. Chem., 1999, vol. 10, 4553-7 [0671]
- **ZIMMERMAN et al.**Nucl. Med. Biol., 1999, vol. 26, 8943-50 [0671]
- **GENTZ et al.**Proc. Natl. Acad. Sci. USA, 1989, vol. 86, 821-824 [0672]
- **WILSON et al.**Cell, 1984, vol. 37, 767- [0672]
- Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy**ARNON et al.**Monoclonal Antibodies And Cancer TherapyAlan R. Liss, Inc.19850000243-56 [0673]
- Antibodies For Drug Delivery**HELLSTROM et al.**Controlled Drug DeliveryMarcel Dekker, Inc.19870000623-53 [0673]
- Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review**THORPE et al.**Monoclonal Antibodies 84: Biological And Clinical Applications19850000475-506 [0673]
- Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer TherapyMonoclonal Antibodies For Cancer Detection And TherapyAcademic Press19850000303-16 [0673]
- **THORPE et al.**Immunol. Rev., 1982, vol. 62, 119-58 [0673]
- **ASHKENAZI et al.**Proc. Natl. Acad. Sci. USA, 1991, vol. 88, 10535-10539 [0673]
- **TRAUNECKER et al.**Nature, 1988, vol. 331, 84-86 [0673]
- **ZHENG et al.**J. Immunol., 1995, vol. 154, 5590-5600 [0673]
- **VIL et al.**Proc. Natl. Acad. Sci. USA, 1992, vol. 89, 11337-11341 [0673]
- **PATTEN et al.**Curr. Opinion Biotechnol., 1997, vol. 8, 724-33 [0674]
- **HARAYAMA**Trends Biotechnol., 1998, vol. 16, 276-82 [0674]
- **HANSSON et al.**J. Mol. Biol., 1999, vol. 287, 265-76 [0674]
- **LORENZOBLASCO**Biotechniques, 1998, vol. 24, 2308-313 [0674]
- **EPSTEIN et al.**Proc. Natl. Acad. Sci. USA, 1985, vol. 82, 3688- [0680]
- **HWANG et al.**Proc. Natl. Acad. Sci. USA, 1980, vol. 77, 4030- [0680]
- **MARTIN et al.**J. Biol. Chem., 1982, vol. 257, 286-288 [0681]
- **GABIZON et al.**J. National Cancer Inst., 1989, vol. 81, 191484- [0681]
- **ANSEL**Introduction to Pharmaceutical Dosage Forms19850000126- [0693]
- **HARLOW et al.**Antibodies: A Laboratory ManualCold Spring Harbor Laboratory Press19880000 [0760] [0800]
- **WUWU**J. Biol. Chem., 1987, vol. 262, 4429-4432 [0762]
- **LANGER**Science, 1990, vol. 249, 1527-1533 [0764] [0765]
- **TREAT et al.**Liposomes in the Therapy of Infectious Disease and CancerLiss19890000353-365 [0764]
- **LOPEZ-BERESTEIN**LIPOSOMES IN THE THERAPY OF INFECTIOUS DISEASE AND CANCERLiss317-327 [0764]
- **SEFTON**CRC Crit. Ref. Biomed. Eng., 1987, vol. 14, 20- [0765]
- **BUCHWALD et al.**Surgery, 1980, vol. 88, 507- [0765]
- **SAUDEK et al.**N. Engl. J. Med., 1989, vol. 321, 574- [0765]
- Medical Applications of Controlled ReleaseCRC Pres.19740000 [0765]
- Controlled Drug Bioavailability, Drug Product Design and PerformanceWiley19840000 [0765]
- **RANGERPEPPAS**J., Macromol. Sci. Rev. Macromol. Chem., 1983, vol. 23, 61- [0765]
- **LEVY et al.**Science, 1985, vol. 228, 190- [0765]
- **DURING et al.**Ann. Neurol., 1989, vol. 25, 351- [0765]
- **HOWARD et al.**J. Neurosurg., 1989, vol. 7 1, 105- [0765]
- **GOODSON**Medical Applications of Controlled Release, 1984, vol. 2, 115-138 [0765]
- **NING et al.**Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release GelRadiotherapy & Oncology, 1996, vol. 39, 179-189 [0765]
- **SONG et al.**Antibody Mediated Lung Targeting of Long-Circulating EmulsionsPDA Journal of Pharmaceutical Science & Technology, 1995, vol. 50, 372-397 [0765]
- **CLEEK et al.**Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular ApplicationPro. Int'l. Symp. Control. Rel. Bioact. Mater., 1997, vol. 24, 853-854 [0765]
- **LAM et al.**Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local DeliveryProc. Int'l. Symp. Control Rel. Bioact. Mater., 1997, vol. 24, 759-760 [0765]
- **JOLIOT et al.**Proc. Natl. Acad. Sci. USA, 1991, vol. 88, 1864-1868 [0766]

- **JALKANEN et al.**J. Cell. Biol., 1985, vol. 101, 976-985 [0231]
- **JALKANEN et al.**J. Cell. Biol., 1987, vol. 105, 3087-3096 [0231]
- Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments.**S. W. BURCHIEL et al.**Tumor Imaging: The Radiochemical Detection of CancerMasson Publishing Inc.19820000 [0231]
- **MANIATIS et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press19820000 [0232]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press19890000 [0232]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press20010000 [0232]
- **AUSUBEL et al.**Current Protocols in Molecular BiologyJohn Wiley & Sons19870000 [0232]
- Current Protocols in ImmunologyJohn Wiley & Sons19870000 [0232]
- Oligonucleotide Synthesis: A Practical ApproachIRL Press19840000 [0232]
- Oligonucleotides and Analogues: A Practical ApproachIRL Press19910000 [0232]
- Genome Analysis: A Laboratory ManualCold Spring Harbor Laboratory Press19990000 [0232]
- **HAMMERLING et al.**Monoclonal Antibodies and T-Cell HybridomasElsevier19810000563-681 [0232]
- **KILPTRACK et al.**Hybridoma, 1997, vol. 16, 381-9 [0232]
- **BRINKMAN et al.**J. Immunol. Methods, 1995, vol. 182, 41-50 [0232]
- **AMES**J. Immunol. Methods, 1995, vol. 184, 177-186 [0232]
- **KETTLEBOROUGH et al.**Eur. J. Immunol., 1994, vol. 24, 952-958 [0232]
- **PERSIC et al.**Gene, 1997, vol. 187, 9-18 [0232]
- **BURTON et al.**Advances in Immunology, 1994, vol. 57, 191-208 [0232]
- **MULLINAX et al.**BioTechniques, 1992, vol. 12, 6864-869 [0232]
- **SAWAI et al.**AJRI, 1995, vol. 34, 26-34 [0232]
- **BETTER et al.**Science, 1988, vol. 240, 1041-1043 [0232]
- **LONBERGHUSZAR**Int. Rev. Immunol., 1995, vol. 13, 65-93 [0232]
- **MORRISON**Science, 1985, vol. 229, 1202- [0232]
- **Oi et al.**BioTechniques, 1986, vol. 4, 214- [0232]
- **GILLIES et al.**J. Immunol. Methods, 1989, vol. 125, 191-202 [0232]
- **JOHNSON et al.**J. Infect. Dis., 1997, vol. 176, 1215-1224 [0232]
- **PADLAN**Molecular Immunology, 1991, vol. 28, 4-5489-498 [0232]
- **STUDNICKA et al.**Protein Engineering, 1994, vol. 7, 6805-814 [0232]
- **ROGUSKA et al.**PNAS, 1994, vol. 91, 969-973 [0232]
- **TAN et al.**J. Immunol., 2002, vol. 169, 1119-25 [0232]
- **CALDAS et al.**Protein Eng., 2000, vol. 13, 5353-60 [0232]
- **MOREA et al.**Methods, 2000, vol. 20, 3267-79 [0232]
- **BACA et al.**J. Biol. Chem., 1997, vol. 272, 1610678-84 [0232]
- **ROGUSKA et al.**Protein Eng., 1996, vol. 9, 10895-904 [0232]
- **COUTO et al.**Cancer Res., 1995, vol. 55, 23597s-5977s [0232]
- **COUTO et al.**Cancer Res., 1995, vol. 55, 81717-22 [0232]
- **SANDHU J S**Gene, 1994, vol. 150, 2409-10 [0232]
- **PEDERSEN et al.**J. Mol. Biol., 1994, vol. 235, 3959-73 [0232]
- **REICHMANN et al.**Nature, 1988, vol. 332, 323- [0232]
- **RIECHMANN et al.**J. Immunol., 1999, vol. 231, 25-38 [0232]
- **NUTTALL et al.**Curr. Pharm. Biotechnol., 2000, vol. 1, 3253-263 [0232]
- **MUYLDERMAN**J. Biotechnol., 2001, vol. 74, 4277302- [0232]
- **GREENSPANBONA**FASEB J., 1989, vol. 7, 5437-444 [0232]
- **NISSINOFF**J. Immunol., 1991, vol. 147, 82429-2438 [0232]
- **CREIGHTON**ProteinsW. H. Freeman and Company19840000 [0232]
- **DORDO et al.**J. Mol Biol, 1999, vol. 217, 721-739 [0232]
- **TAYLOR et al.**J. Theor. Biol., 1986, vol. 119, 205-218 [0232]
- **S. FRENCHB. ROBSON**J. Mol. Evol., 1983, vol. 19, 171- [0232]
- **DE WILDT et al.**Eur J. Immunol., 1996, vol. 26, 3629-39 [0232]
- **KABAT**Sequences of Proteins of Immunological InterestNational Institutes of Health19870000 [0232]
- The Merck Manual of Diagnosis and TherapyMerck Research Laboratories20060000 [0232]
- The Encyclopedia of Molecular BiologyBlackwell Science Ltd.19940000 [0232]
- **BENJAMIN LEWIN**Genes.Jones & Bartlett Publishing20090000vol. X, 65391
- Molecular Biology and Biotechnology: a Comprehensive Desk ReferenceVCH Publishers, Inc.19950000 [0232]
- Current Protocols in Protein SciencesWiley Interscience20090000 [0232]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press20120000 [0232]
- **DAVIS et al.**Basic Methods in Molecular BiologyElsevier Science Publishing, Inc.19950000 [0232]
- Methods in Enzymology: Guide to Molecular Cloning TechniquesAcademic Press Inc.19870000vol. 152, [0232]
- Current Protocols in Protein Science (CPPS)John Wiley and Sons, Inc. [0232]
- Current Protocols in Cell Biology (CPCB)John Wiley and Sons, Inc. [0232]
- **R. IAN FRESHNEY**Culture of Animal Cells: A Manual of Basic TechniqueWiley-Liss20050000 [0232]
- **1998**Animal Cell Culture Methods (Methods in Cell BiologyAcademic Pressvol. 57, [0232]
- **YUSA KZHOU LLI MABRADLEY ACRAIG NL**A hyperactive piggyBac transposase for mammalian applicationsProc Natl Acad Sci USA., 2011, [0232] [0232]
- **MATHIS**Clinical Chemistry, 1995, vol. 41, 91391-1397 [0232] [0232]
- **WANG et al.**Hybridoma (Larchmt), 2009, vol. 28, 4269-76 [0232]
- **MILLER, WESTON P. et al.**GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ Teells as a reservoir of breakthrough T cell proliferation during costimulation blockade and sirolimus-based immunosuppression.Blood, 2010, vol. 116, 245403-5418 [0232]
- **MILLER WP et al.**GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ T cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppressionBlood, 2010, vol. 116, 5403-5418 [0232]
- **PENEDO MC et al.**Microsatellite typing of the rhesus macaque MHC regionImunogenetics, 2005, vol. 57, 198-209 [0232]
- **FURLAN et al.**Science Translational Medicine, vol. 7, 315315-1910 [0232]

Patentkrav

1. Kombination, som omfatter et antistof eller et fragment deraf, der binder specifikt til hOX40L, hvor antistoffet eller fragmentet omfatter et V_H-domæne, der omfatter en aminosyresekvens ifølge SEQ ID NO: 34; og et V_L-domæne, der omfatter en aminosyresekvens ifølge SEQ ID NO:48, hvor antistoffet er et IgG4-antistof,
og et yderligere terapeutisk middel, der er valgt uafhængigt fra gruppen, der består af rapamycin (sirolimus), tacrolimus, ciclosporin, kortikosteroider (f.eks. methylprednisolon), basilixumab og daclizumab.

2. Kombination ifølge krav 1, hvor antistoffet eller fragmentet omfatter første og anden kopier af V_H-domænet, og/eller hvor antistoffet eller fragmentet omfatter første og anden kopier af V_L-domænet.

3. Kombination ifølge krav 1 eller 2, hvor
(a) antistoffet eller fragmentet omfatter en kappa-let kæde; og/eller
(b) den lette kæde omfatter en konstant region fra gnaver, rotte, mus, menneske, kanin, kylling, kamel, får, okse, ikke-human primat eller haj; og/eller
(c) antistoffet eller fragmentet yderligere omfatter humane eller humaniserede konstante regioner af let kæde, f.eks. human CL; og/eller
(d) antistoffet eller fragmentet omfatter en kappa-let kæde, der omfatter en konstant region valgt fra gruppen, der består af aminosyresekvenserne for konstant region af kappa-let kæde ifølge SEQ ID NO: 136, 138, 140, 142 og 144; og/eller
(e) antistoffet er et fuldstændigt humant antistof; og/eller
(f) antistoffet omfatter en human gamma 4-konstant region, eventuelt en konstant region af tung kæde ifølge SEQ ID NO: 128.

4. Kombination ifølge et hvilket som helst af ovennævnte krav, hvor antistoffet eller fragmentet omfatter en tung kæde, der omfatter en aminosyresekvens, der består af sekvensen ifølge SEQ

ID No: 62, og en let kæde, der omfatter en aminosyresekvens, der består af sekvensen ifølge SEQ ID NO: 64.

5. Kombination ifølge et hvilket som helst af ovennævnte krav, der er formuleret til parenteral administration valgt blandt intravenøs eller subkutan administration.

6. Kit, som omfatter:
(i) et antistof eller et fragment deraf ifølge et hvilket som helst af ovennævnte krav; og
(ii) et yderligere terapeutisk middel, der er valgt uafhængigt fra gruppen, der består af rapamycin (sirolimus), tacrolimus, ciclosporin, kortikosteroider (f.eks. methylprednisolon), basilixumab og daclizumab.

7. Kit ifølge krav 6, hvor kittet omfatter en etiket eller en vejledning, hvor etiketten eller vejledningen er til anvendelse til behandling og/eller forbyggelse af en hOX40L-medieret tilstand eller sygdom valgt blandt en autoimmunsygdom eller -tilstand, en systemisk inflammatorionssygdom eller -tilstand eller transplantatafstødning; for eksempel inflammatorisk tarmsygdom (IBD), Crohns sygdom, rheumatoid arthritis, allogen transplantatafstødning, *graft-versus-host*-sygdom (GvHD), ulcerativ colitis, systemisk lupus erythematosus (SLE), diabetes, uveitis, ankyloserende spondylitis, kontaktoverfølsomhed, multipel sklerose og aterosklerose, især GvHD, eventuelt
hvor etiketten eller vejledningen omfatter et markedsføringstilladelsesnummer (f.eks. et FDA- eller EMA-tilladelsesnummer).

8. Kit ifølge et hvilket som helst af kravene 6 eller 7, som omfatter en i.v.- eller injektionsanordning, der omfatter antistoffet eller fragmentet deraf.

9. Kombination ifølge et hvilket som helst af kravene 1 til 5 til anvendelse til behandling og/eller forebyggelse af en hOX40L-medieret sygdom valgt blandt en autoimmunsygdom, en

systemisk inflammationssygdom eller transplantatafstødning.

10. Antistof eller fragment deraf ifølge et hvilket som helst af kravene 1 til 5 til anvendelse til behandling eller forebyggelse af en hOX40L-medieret sygdom valgt blandt en autoimmunsygdom, en systemisk inflammationssygdom eller transplantatafstødning hos et individ,
hvor individet også får administreret et yderligere terapeutisk middel, der er valgt uafhængigt fra gruppen, der består af rapamycin (sirolimus), tacrolimus, ciclosporin, kortikosteroider (f.eks. methylprednisolon), basilixumab og daclizumab.

11. Kombination til anvendelse ifølge krav 9 eller antistof eller fragment til anvendelse ifølge krav 10, hvor den hOX40L-medierede sygdom er valgt blandt inflammatorisk tarmsygdom (IBD), Crohns sygdom, rheumatoid arthritis, allogen transplantatafstødning, *graft-versus-host*-sygdom (GvHD), ulcerativ colitis, systemisk lupus erythematosus (SLE), diabetes, uveitis, ankyloserende spondylitis, kontaktoverfølsomhed, multipel sklerose og aterosklerose.

12. Kombination til anvendelse ifølge krav 9 eller antistof eller fragment til anvendelse ifølge krav 10, hvor den hOX40L-medierede sygdom er dermatitis.

13. Kombination til anvendelse ifølge et hvilket som helst af kravene 9, 11 og 12 eller antistof eller fragment til anvendelse ifølge et hvilket som helst af kravene 10 til 12, hvor antistoffet eller fragmentet administreres parenteralt, for eksempel ved intravenøs eller subkutan administration.

14. Kombination ifølge et hvilket som helst af kravene 1 til 5 til anvendelse til terapi.

DRAWINGS

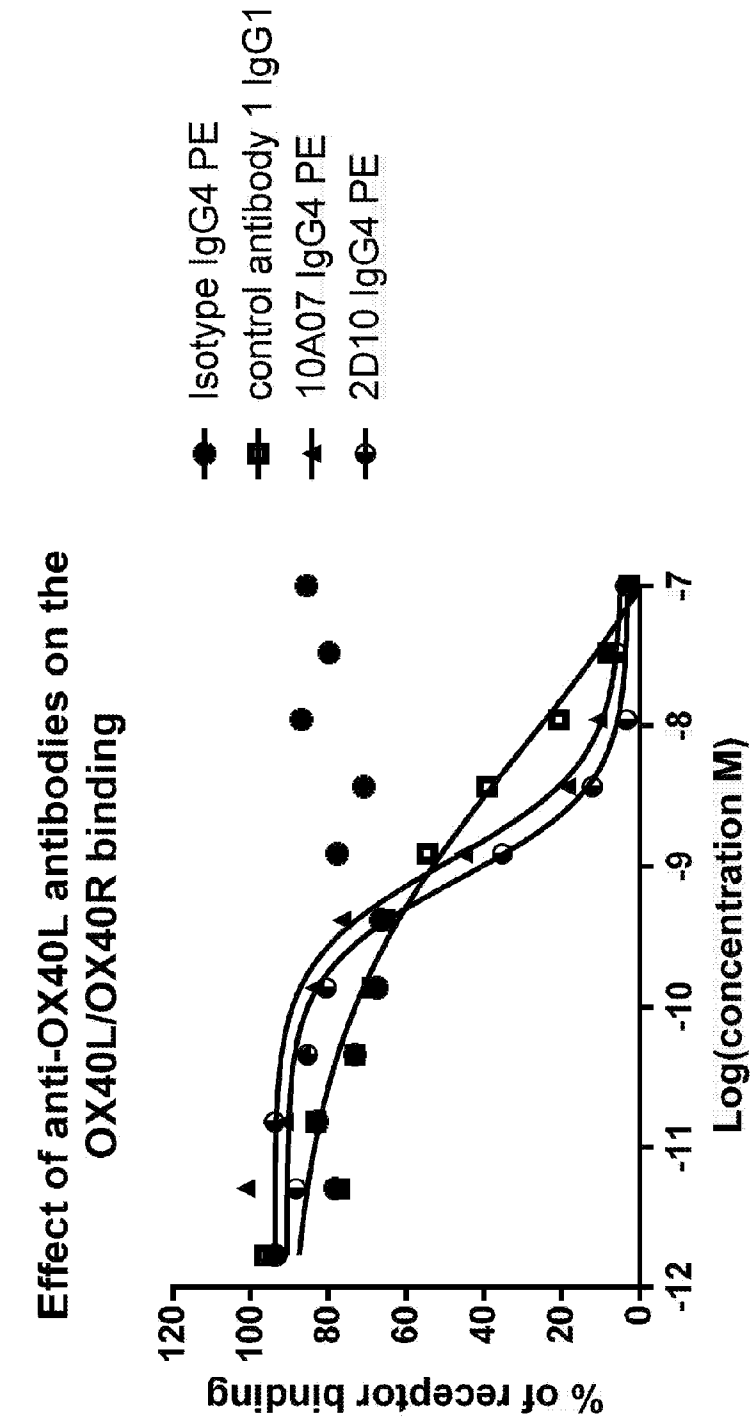
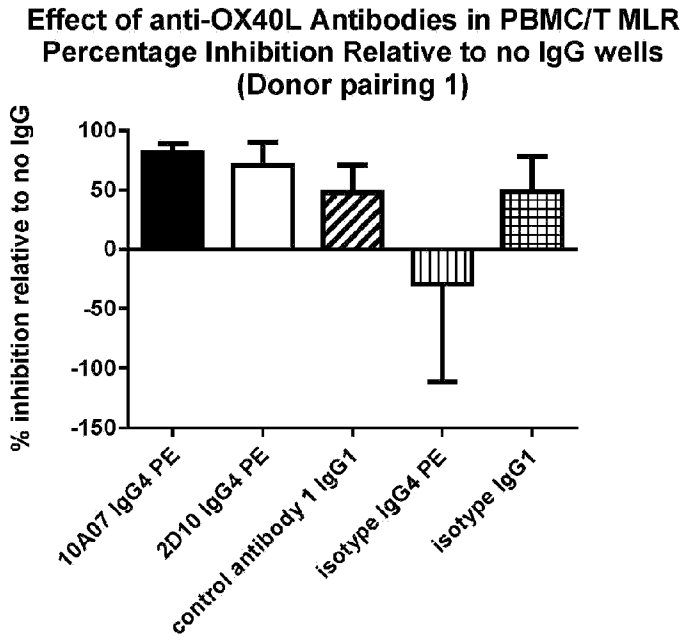


Figure 1

Figure 2


Effect of anti-OX40L Antibodies in PBMC/T MLR
Percentage Inhibition Relative to no IgG wells
(Donor pairing 1)
% inhibition relative to no IgG
100
50
0
-50
-100
-150
10A07 IgG4 PE
2D10 IgG4 PE
control antibody 1 IgG1
isotype IgG4 PE
isotype IgG1

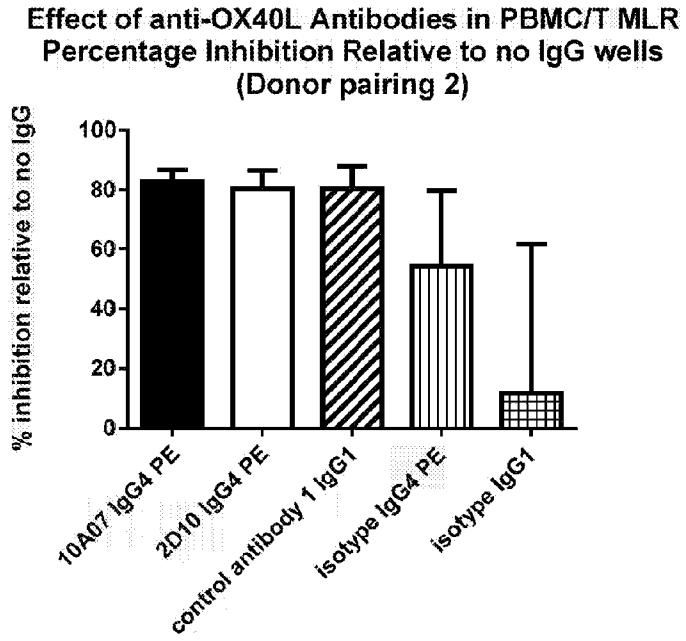
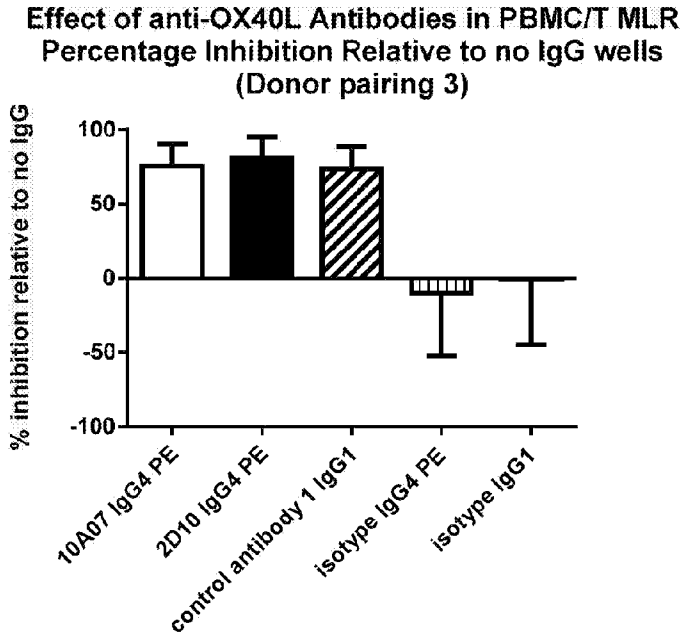

Effect of anti-OX40L Antibodies in PBMC/T MLR
Percentage Inhibition Relative to no IgG wells
(Donor pairing 2)
% inhibition relative to no IgG
100
80
60
40
20
0
10A07 IgG4 PE
2D10 IgG4 PE
control antibody 1 IgG1
isotype IgG4 PE
isotype IgG1

Figure 2 continued



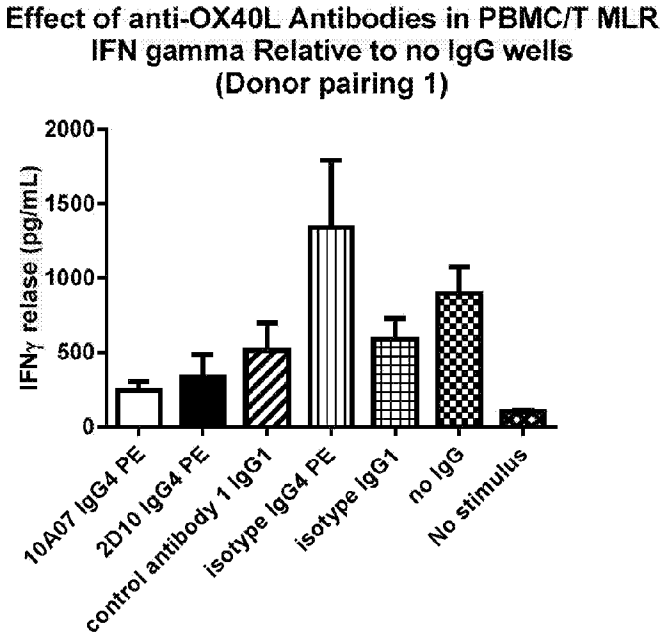
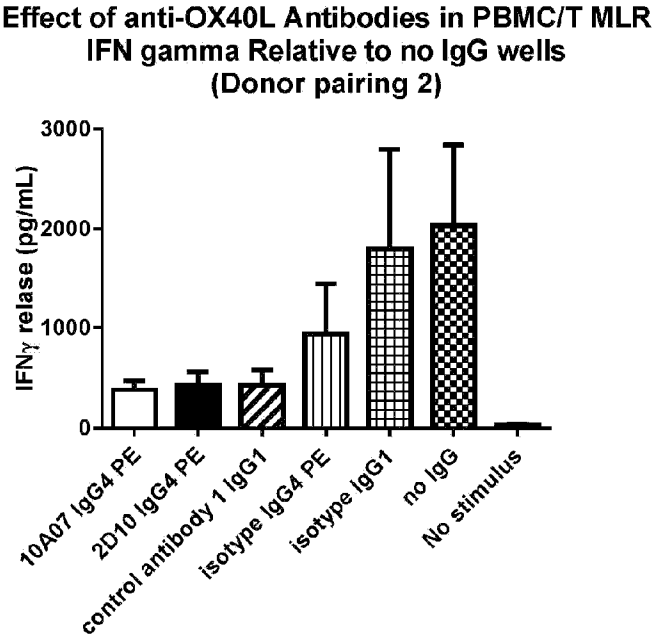


Figure 2 continued



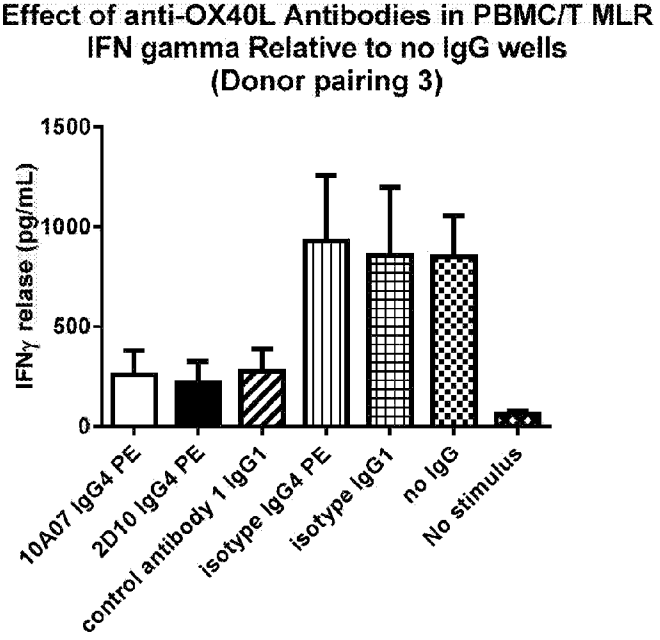


Figure 3

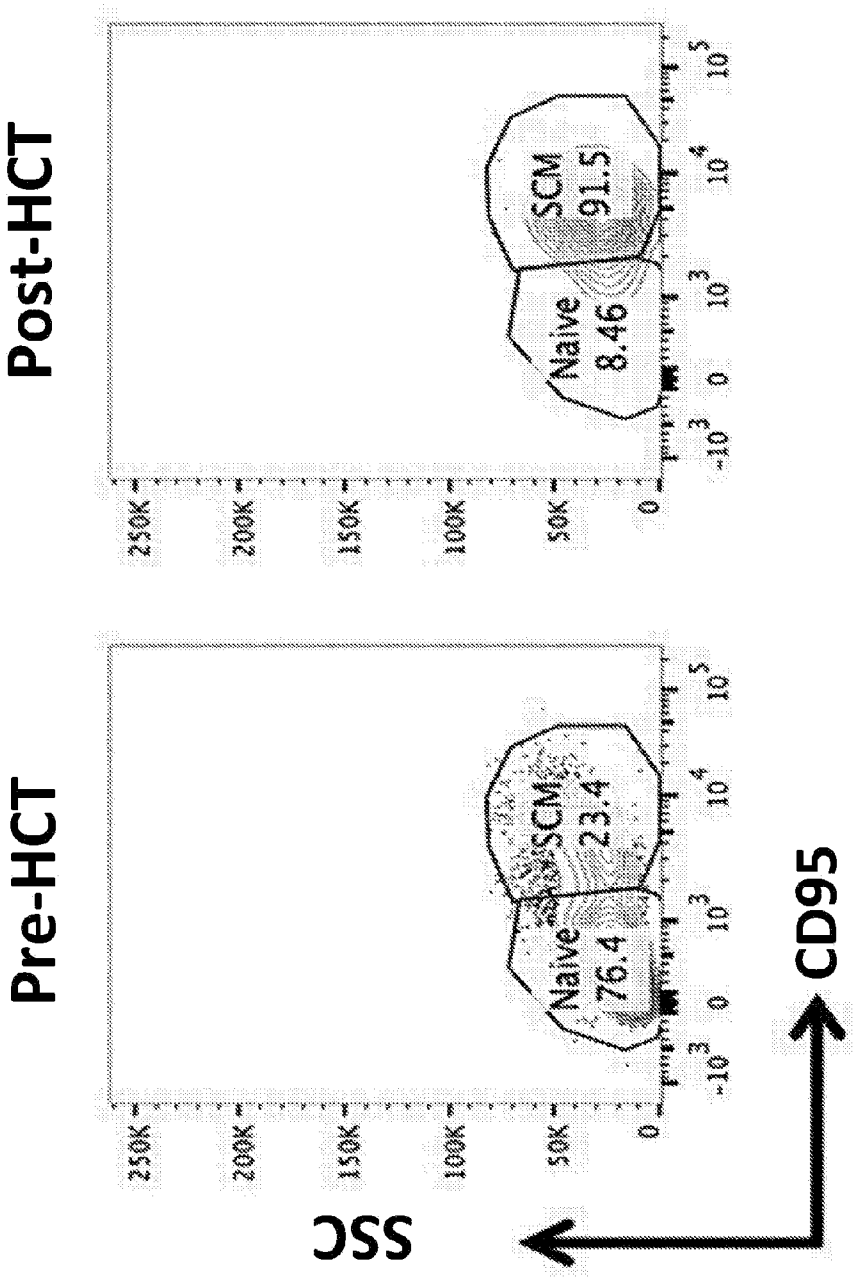

Post-HCT
Pre-HCT
SSC
CD95
SCM
91.5
Naive
8.46
SCM
23.4
Naive
76.4
250K
200K
150K
100K
50K
0
-10^3
0
10^3
10^4
10^5

Figure 4

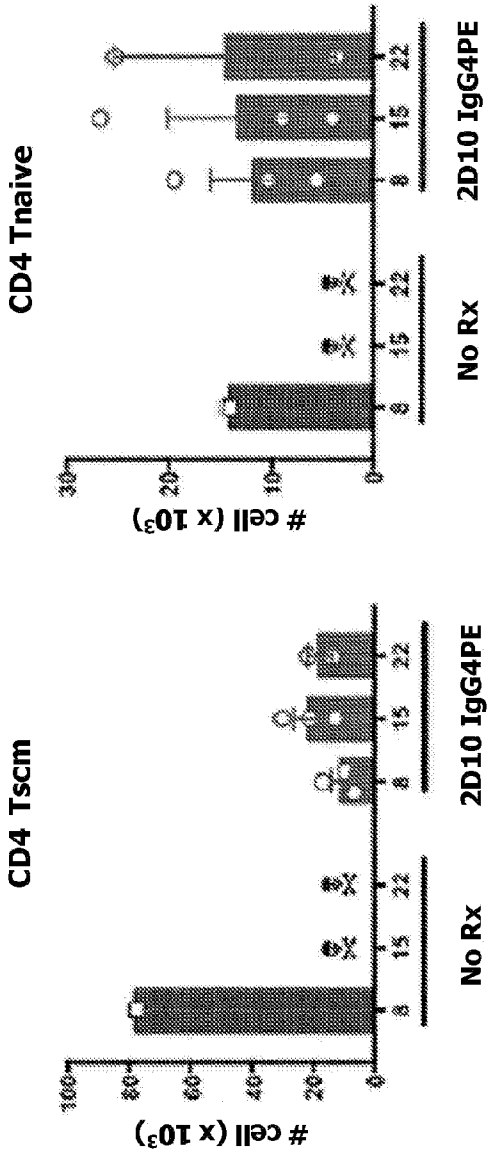

CD4 Tnaive
cell (x 10³)
30
20
10
0
8
15
22
No Rx
2D10 IgG4PE
CD4 Tscm
cell (x 10³)
100
80
60
40
20
0
8
15
22
No Rx
2D10 IgG4PE

Figure 5

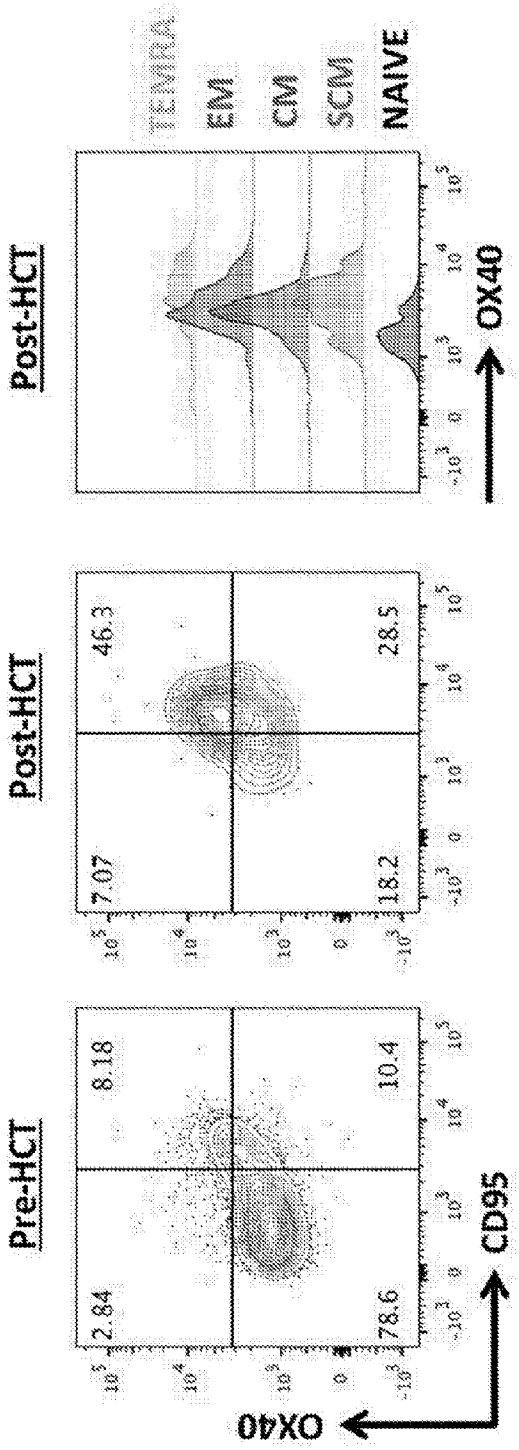

Pre-HCT
Post-HCT
Post-HCT
TEMRA
EM
CM
SCM
NAIVE
2.84
8.18
78.6
10.4
7.07
46.3
18.2
28.5
OX40
CD95
OX40

Figure 6a

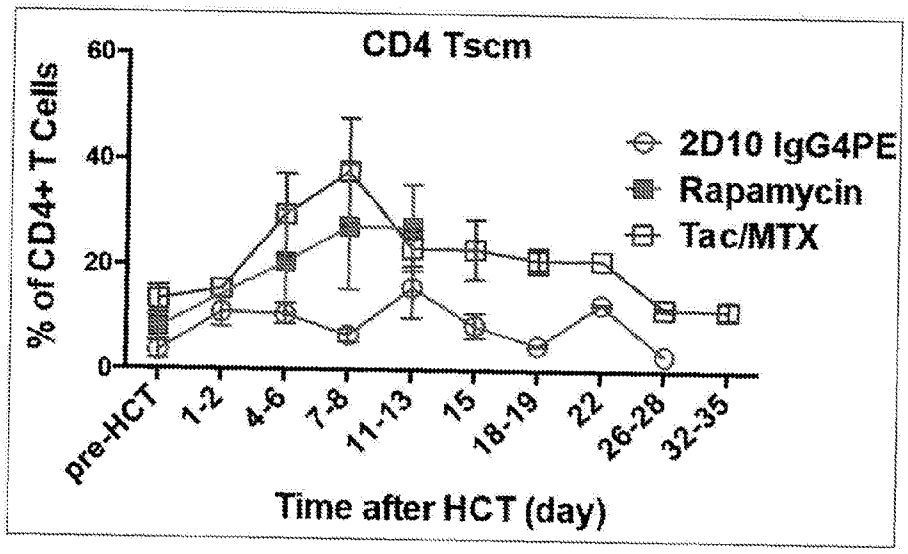


Figure 6b

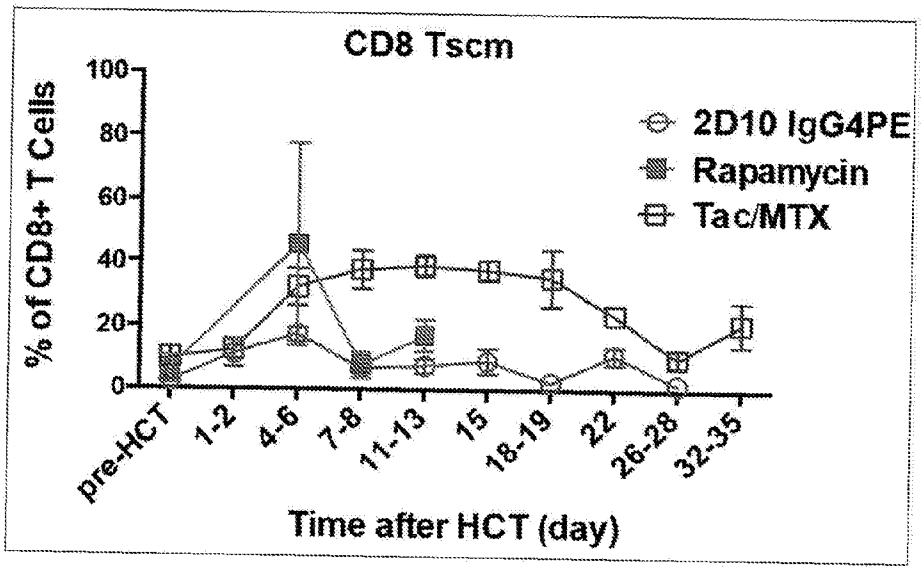
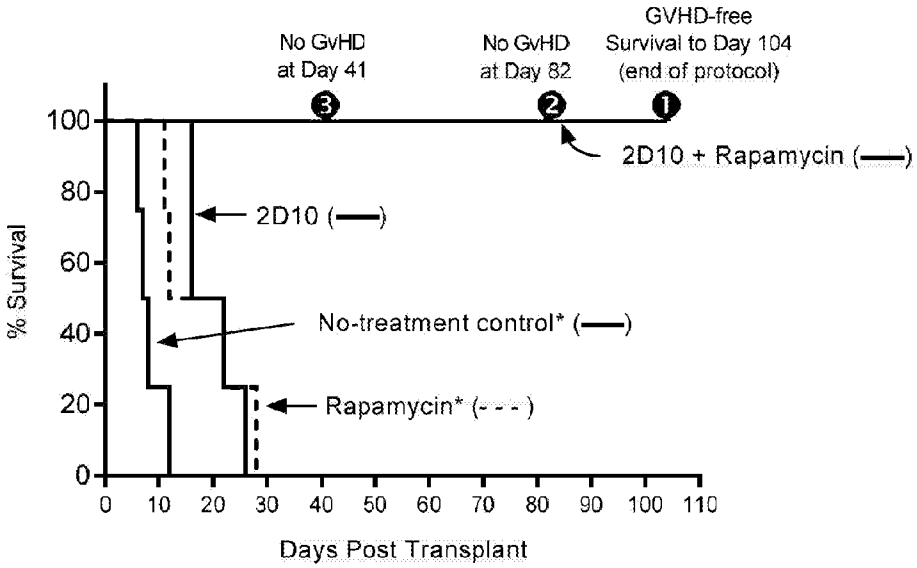


Figure 7


No GvHD
at Day 41
No GvHD
at Day 82
GVHD-free
Survival to Day 104
(end of protocol)
3
2
1
2D10 + Rapamycin (——)
2D10 (——)
No-treatment control* (——)
Rapamycin* (- - -)
% Survival
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100 110
Days Post Transplant

SEKVENSLISTE

Sekvenslisten er udeladt af skriftet og kan hentes fra det Europæiske Patent Register.

The Sequence Listing was omitted from the document and can be downloaded from the European Patent Register.