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Expansion of tumor infiltrating lymphocytes (TILs) with tumor necrosis factor receptor superfamily (TNFRSF) agonists and therapeutic combinations of TILs and TNFRSF agonists

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(54) Title: EXPANSION OF TUMOR INFILTRATING LYMPHOCYTES (TILS) WITH TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY (TNFRSF) AGONISTS AND THERAPEUTIC COMBINATIONS OF TILS AND TNFRSF AGONISTS

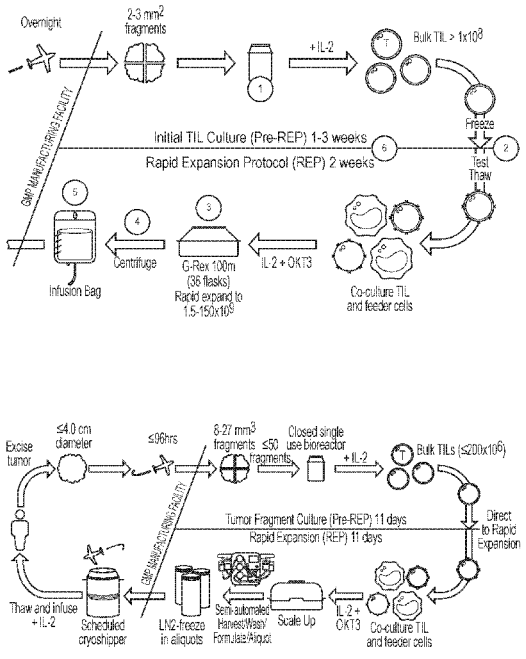

FIG. 1

(57) Abstract: Methods of expanding tumor infiltrating lymphocytes (TILs) using a tumor necrosis factor receptor superfamily (TNFRSF) agonist, such as a 4- IBB agonist, a CD27 agonist, a glucocorticoid-induced TNF receptor-related agonist, an OX40 agonist, a HVEM agonist, or a CD95 agonist, and uses of such expanded TILs in the treatment of diseases such as cancer are disclosed herein. In addition, in some embodiments, therapeutic combinations of TILs and TNFRSF agonists useful in the treatment of diseases such as cancer, including compositions, uses, and dosing regimens thereof, are disclosed herein.

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EXPANSION OF TUMOR INFILTRATING LYMPHOCYTES (TILS) WITH TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY (TNFRSF) AGONISTS AND THERAPEUTIC COMBINATIONS OF TILS AND TNFRSF AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This international application claims the benefit of priority to U.S. Provisional Application No. 62/443,556, filed January 6, 2017, U.S. Provisional Application No. 62/460,477, filed February 17, 2017, U.S. Provisional Application No. 62/532,807, filed July 14, 2017, and Provisional Application No. 62/567,151, filed October 2, 2017, the entirety of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] Methods of expanding tumor infiltrating lymphocytes (TILs) using a tumor necrosis factor receptor superfamily (TNFRSF) agonist, such as a 4-1BB agonist, a CD27 agonist, a glucocorticoid-induced TNF receptor-related agonist, an OX40 agonist, a HVEM agonist, or a CD95 agonist, and uses of expanded TILs in the treatment of diseases such as cancer are disclosed herein. In addition, therapeutic combinations of TILs and TNFRSF agonists, including compositions and uses thereof in the treatment of diseases such as cancer are disclosed herein.

BACKGROUND OF THE INVENTION

[0003] Treatment of bulky, refractory cancers using adoptive autologous transfer of tumor infiltrating lymphocytes (TILs) represents a powerful approach to therapy for patients with poor prognoses. Gattinoni, *et al.*, *Nat. Rev. Immunol.* **2006,** *6,* 383-393. TILs are dominated by T cells, and IL-2-based TIL expansion followed by a "rapid expansion process" (REP) has become a preferred method for TIL expansion because of its speed and efficiency. Dudley, *et al.*, *Science* **2002,** *298,* 850-54; Dudley, *et al.*, *J. Clin. Oncol.* **2005,** *23,* 2346-57; Dudley, *et al.*, *J. Clin. Oncol.* **2008**, *26,* 5233-39; Riddell, *et al.*, *Science* **1992,** *257,* 238-41; Dudley, *et al.*, *J. Immunother.* **2003**, *26,* 332-42. A number of approaches to improve clinical responses to TIL therapy in melanoma and to expand TIL therapy to other tumor types have been explored with limited success, and the field remains challenging. Goff, *et al., J. Clin. Oncol.* **2016,** *34,* 2389-97; Dudley, *et al.*, *J. Clin. Oncol.* **2008**, *26,* 5233-39; Rosenberg, *et al.*, *Clin. Cancer Res.* **2011,** *17,* 4550-57. Much focus has been placed on selection of TILs during expansion to either select

particular subsets (such as $CD8^+$ T cells) or to target driver mutations such as a mutated ERBB2IP epitope or driver mutations in the KRAS oncogene. Tran, *et al.*, *N. Engl. J. Med.* **2016,** *375,* 2255-62; Tran, *et al., Science* **2014,** *344,* 641-45. However, such selection approaches, even if they can be developed to show efficacy in larger clinical trials, add significantly to the duration, complexity, and cost of performing TIL therapy and limit the potential for widespread use of TIL therapy in different types of cancers.

[0004] 4-1BB (also known as CD137 and TNFRSF9), which was first identified as an inducible costimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein member of the TNFRSF. Watts, *Annu. Rev. Immunol.* **2005,** *23,* 23–68. 4-1BB is a type 2 transmembrane glycoprotein that is expressed on activated T lymphocytes, and to a larger extent on $CD8^+$ than $CD4^+$ T cells. 4-1BB is also expressed on dendritic cells, follicular dendritic cells, natural killer (NK) cells, granulocytes, cells of blood vessel walls at sites of inflammation, tumor vasculature, and atherosclerotic endothelium. The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells. 4-1BB is an activation-induced T-cell costimulatory molecule. Signaling through 4-1BB upregulates survival genes, enhances cell division, induces cytokine production, and prevents activation-induced sell death in T cells. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated NK and NK T cells (NKT cells); regulatory T cells; dendritic cells (DC) including follicular DCs; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils, and activated B cells. 4-1BB strongly enhances the proliferation and effector function of $CD8^+$ T cells. Crosslinking of 4-1BB enhances T cell proliferation, IL-2 secretion survival and cytolytic activity. Additionally, anti-4-1BB monoclonal antibodies possess strong antitumor properties, which in turn are the result of their powerful CD8+ T-cell activating, IFN-g producing, and cytolytic marker–inducing capabilities. Vinay and Kwon, *Mol. Cancer Therapeutics* **2012,** *11,* 1062-70; Lee, *et al.*, *PLoS One*, **2013,** *8,* e69677, 1-11.

[0005] Interaction of 4-1BB on activated normal human B cells with its ligand at the time of B cell receptor engagement stimulates proliferation and enhances survival. The potential impact of 4-1BB engagement in B cell lymphoma has been investigated in at least two published studies. Evaluation of several types of human primary NHL samples indicated that 4-1BB was

expressed predominantly on infiltrating T cells rather than the lymphoma cells. Houot, *et al.*, *Blood,* **2009,** *114,* 3431-38. The addition of 4-1BB agonists to *in vitro* cultures of B lymphoma cells with, rituximab and NK cells resulted in increased lymphoma killing. Kohrt, *et al.*, Blood, **2011,** *117,* 2423-32. In addition, B cell immunophenotyping was performed in two experiments using PF-05082566 in cynomolgus monkeys with doses from 0.001-100 mg/kg; in these experiments peripheral blood B cell numbers were either unchanged or decreased, as described in International Patent Application Publication No. WO 2015/119923.

[0006] 4-1BB is undetectable on the surface of naïve T cells but expression increases upon activation. Upon 4-1BB activation, two pro-survival members of the TNFR-associated factor (TRAF) family, TRAF1 and TRAF2, are recruited to the 4-1BB cytoplasmic tail, resulting in downstream activation of NFkB and the Mitogen Activated Protein (MAP) kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to upregulation of Bfl-1 and Bel-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner. Sabbagh, *et al.*, *J. Immunol.* **2008,** *180,* 8093-8101. Reports have shown that 4-1BB agonist monoclonal antibodies (mAbs) increase costimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T cell memory responses. Lynch, *et al.*, *Immunol Rev.*, **2008**, *222*, 277-286. 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models. Vinay, *et al.*, *J. Mol. Med.* **2006,** *84,* 726-36.

[0007] The OX40 receptor (OX40) (also known as TNFRSF4, CD134, ACT-4, and ACT35) is a member of the TNF receptor family which is expressed on activated $CD4^+$ T cells (see WO 95/12673). Triggering of this receptor via the OX40 ligand, named OX40L, gp34 or ACT-4-ligand, which is present on activated B-cells and dendritic cells, enhances the proliferation of $CD4^+$ T cells during an immune response and influences the formation of $CD4^+$ memory T-cells. Furthermore, the OX40-OX40L system mediates adhesion of activated T cells to endothelial cells, thus directing the activated $CD4^+$ T cells to the site of inflammation.

[0008] It has been shown that $OX40^+$ T cells are present within tumor lesions containing tumor infiltrating lymphocytes and in tumor cell positive draining lymph nodes. Weinberg, *et*

al., *J. Immunol.*, **2000**, *164*, 2160-2169. It was shown in several tumor models in mice that engagement of the OX40 receptor *in vivo* during tumor priming significantly delayed and prevented the appearance of tumors as compared to control treated mice. Weinberg, *et al.*, *J. Immunol.*, **2000,** *164,* 2160-2169. Hence, it has been contemplated to enhance the immune response of a mammal to an antigen by engaging the OX40-receptor by administering an OX40-receptor binding agent (International Patent Application Publication No. WO 1999/042585; Weinberg, *et al.*, *J. Immunol.*, **2000**, *164*, 2160-2169). Preclinical studies demonstrated that treatment of tumor bearing hosts with OX40 agonists, including both anti-OX40 monoclonal antibodies and OX40L-Fc fusion proteins, resulted in tumor regression in several preclinical models. Linch, *et al.*, *Front. Oncol.* **2015,** *34,* 1-14.

[0009] CD27, also known as TNFRSF7, has overlapping activity with other TNFRSF members including CD40, 4-1BB, and OX40. CD27 plays a critical role in T cell survival, activation, and effector function, and also plays a role in the proliferative and cytotoxic activity of NK cells. CD27 is constitutively expressed on the majority of T cells, including naïve T cells. The ligand for CD27 is CD70, which is found on T cells, B cells, and dendritic cells. Oshima, *et al.*, *Int. Immunol.* **1998,** *10,* 517-26. CD27 drives the expansion of $CD4^+$ and $CD8^+$ T cells, acting after CD28 to sustain T effector cell survival, and influences secondary responses more than primary responses. However, CD27 activation has also been associated with tumor growth through enhancement of the immunosuppressive effects of regulatory T cells. Claus, *et al.*, *Cancer Res.* **2012,** *72,* 3664-76. Other data has indicated that the immunostimulatory effects of CD27 may outweigh this tumor promoting effect. Aulwurm, *et al.*, *Int. J. Cancer* **2006,** *118,* 1728-35. In mouse models, an agonistic CD27 monoclonal antibody showed antitumor efficiacy and induction of tumor immunity. He, *et al.*, *J. Immunol.* **2013,** *191,* 4174-83.

[0010] Glucocorticoid-induced TNFR-related protein (GITR) is a costimulatory checkpoint molecule that is also known as tumor necrosis factor receptor superfamily member 18 (TNFRSF18), activation-inducible TNFR family receptor (AITR), and CD357. GITR is expressed on several cell types, including regulatory T cells (Tregs) and effector T cells, B cells, NK cells, and antigen-presenting cells. Nocentini and Riccardi, *Eur. J. Immunol.* **2005,** *35,* 1016-1022. GITR is activated by its conjugate GITR ligand (GITRL). GITR plays a role in stimulating an immune response, and antigen binding proteins to GITR have utility in treating a variety of GITR-related diseases or disorders in which it is desirable to increase an immune

response. Ko, *et al.*, *J. Exp. Med.* **2005,** *202,* 885-91; Shimizu, *et al., Nature Immunology* **2002,** *3,* 135-142; Cohen, *et al.*, *Cancer Res.* **2006,** *66,* 4904-12; Azuma, *Crit. Rev. Immunol.* **2010,** *30,* 547-57. For example, T cell stimulation through GITR attenuates Treg–mediated suppression and enhances tumor-killing by $CD4^+$ and $CD8^+$ T cells. GITR is constitutively expressed at high levels in Tregs (such as $CD4^+CD25^+$ or $CD8^+CD25^+$ cells) and is additionally upregulated upon activation of these cells. Nocentini and Riccardi, *Eur. J. Immunol.* **2005,** *35,* 1016-1022. GITR is a co-activating signal to both $CD4^+$ and $CD8^+$ naïve T cells, and induces and enhances proliferation and effector function, particularly in situations where T cell receptor (TCR) stimulation is suboptimal. Schaer, *et al., Curr. Opin. Immunol.* **2012,** *24,* 217-224. The enhanced immune response caused by antigen binding GITR proteins, such as fusion proteins and anti-GITR antibodies (including agonistic antibodies), is of interest in a variety of immunotherapy applications, such as the treatment of cancers, autoimmune diseases, inflammatory diseases, or infections.

[0011] Herpesvirus entry mediator (HVEM), also known as TNFRSF14 and CD270, was first isolated as a receptor for herpes simplex virus-1 (HSV-1). Montgomery, *et al.*, *Cell* **1996,** *87,* 427-36. HVEM binds to the TNF family ligands LIGHT and lymphotoxin alpha homotrimer (Ltα3). Mauri, *et al.*, *Immunity* **1998,** *8,* 21-30. T cell activation can occur through the HVEM-LIGHT interaction, and the interaction provides a costimulatory signal to T cells that is independent of CD28 signaling and can be observed in the presence of suboptimal levels of CD3 antibody (OKT-3). Tamada, *et al.*, *J. Immunol.* **2000,** *165,* 4397-404; Harrop, *et al.*, *J. Biol. Chem.* **1998,** *273,* 27548-56; Tamada, *et al.*, *Nat. Med.* **2000,** *6,* 283-89; Yu, *et al.*, *Nat. Immunol.* **2004**, *5,* 141-49. HVEM comprises four cysteine-rich domains (CRDs). del Rio, *et al.*, *J. Leukoc. Biol.* **2010,** *87,* 223-35. CRD2 and CRD3 are required for HVEM trimerization with the TNFRSF ligand LIGHT, which delivers a co-stimulatory signal to T cells through HVEM. In contrast, CRD1 and CRD2 bind to the co-inhibitory B and T lymphocyte attenuator (BTLA) receptor and CD160 in a monomeric manner, providing an inhibitory signal to T cells. Studies of the HVEM-LIGHT interaction suggest that it primarily has a CD28-independent costimulatory effect on CD8+ T cells, but also affects CD4+ T cells. Liu, *et al.*, *Int. Immunol.* **2003**, *15,* 861-70; Scheu, *et al.*, *J. Exp. Med.* **2002,** *195,* 1613-24.

[0012] CD95, also known as Fas, APO-1, and TNFRSF6, is a 45 kDa type-I transmembrane protein which, unlike 4-1BB, OX40, GITR, CD27, and HVEM, contains a death domain.

Kischkel, *et al.*, *EMBO J.* **1995,** *14*, 5579-88; Krammer, *Nature* **2000,** *407,* 789-95. The binding of the inducible CD95 ligand (CD95L) to CD95 on activated T cells leads to apoptotic cell death, and thus it is not normally associated with the same costimulatory function as 4-1BB, OX40, GITR, CD27, and HVEM. Strauss, *et al.*, *J. Exp. Med.* **2009,** *206,* 1379-93. However, CD95 also behaves as a dual function receptor that provides for anti-apoptotic and costimulatory effects on T cells under some conditions. Paulsen, *et al.*, *Cell Death Differ.* **2011,** *18,* 619-31. CD95 engagement modulates TCR-driven signal initiation in a dose-dependent manner, wherein high doses of CD95 agonists or cellular CD95L silence T cells, while lower doses of these agonists strongly enhance TCR-driven T cell activation and proliferation.

[0013] The present invention provides the unexpected finding that TNFRSF agonists, such as a 4-1BB agonist, a CD27 agonist, a GITR agonist, an OX40 agonist, a HVEM agonist, or a CD95 agonist, are useful in the expansion of TILs from tumors from which it is known to be difficult to obtain TILs and treat the tumor with TILs, and are further useful in the treatment of patients in combination with TIL therapy.

SUMMARY OF THE INVENTION

[0014] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF

agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer.

[0015] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is selected from the group consisting of a 4-1BB agonist, an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof.

[0016] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101 and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0017] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-

CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is a 4-1BB agonist fusion protein.

[0018] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a 4-1BB agonist fusion protein, and the 4-1BB agonist fusion protein comprises (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure

according to structure I-A or structure I-B.

[0019] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a OX40 agonist, and the OX40 agonist is selected from the group consisting of tavolixizumab, GSK3174998, MEDI6469, MEDI6383, MOXR0916, PF-04518600, Creative Biolabs MOM-18455, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0020] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at

least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is an OX40 agonist, and the OX40 agonist is an OX40 agonist fusion protein.

[0021] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is an OX40 agonist fusion protein, and the OX40 agonist fusion protein comprises (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[0022] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a CD27 agonist, and the CD27 agonist is varlilumab, or a fragment, derivative, variant, or biosimilar thereof.

[0023] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a CD27 agonist, and wherein the CD27 agonist is an CD27 agonist fusion protein.

[0024] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least

50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a CD27 agonist, and the CD27 agonist fusion protein comprises (i) a first soluble CD27 binding domain, (ii) a first peptide linker, (iii) a second soluble CD27 binding domain, (iv) a second peptide linker, and (v) a third soluble CD27 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[0025] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a GITR agonist, and the GITR agonist is selected from the group consisting of TRX518, 6C8, 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, 31H6, 2155, 698, 706, 827, 1649, 1718, 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, 9H6, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0026] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is an GITR agonist, and the GITR agonist is a GITR agonist fusion protein.

[0027] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a GITR agonist fusion protein, and the GITR agonist fusion protein comprises (i) a first soluble GITR binding domain, (ii) a first peptide linker, (iii) a second soluble GITR binding domain, (iv) a second peptide linker, and (v) a third soluble GITR binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[0028] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist,

and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a HVEM agonist.

[0029] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is an HVEM agonist, and the HVEM

agonist is a HVEM agonist fusion protein.

[0030] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is a HVEM agonist fusion protein, and wherein the HVEM agonist fusion protein comprises (i) a first soluble HVEM binding domain, (ii) a first peptide linker, (iii) a second soluble HVEM binding domain, (iv) a second peptide linker, and (v) a third soluble HVEM binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[0031] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with the TNFRSF agonist starting on the day after administration of the third population of TILs to the patient, wherein the TNFRSF agonist is administered intravenously at a dose of between 0.1 mg/kg and 50 mg/kg every four weeks for up to eight cycles.

[0032] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least

50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with the TNFRSF agonist prior to the step of resecting of a tumor from the patient, wherein the TNFRSF agonist is administered intravenously at a dose of between 0.1 mg/kg and 50 mg/kg every four weeks for up to eight cycles.

[0033] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is selected from the group consisting of urelumab, utomilumab, EU-101, tavolixizumab, Creative Biolabs MOM-18455, and

fragments, derivatives, variants, biosimilars, and combinations thereof.

[0034] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the first cell culture medium comprises a second TNFRSF agonist.

[0035] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist,

and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is added to the first cell culture medium during the initial expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks.

[0036] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is added to the second cell culture medium during the rapid expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks.

[0037] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 μg/mL and 100 μg/mL.

[0038] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 20 μg/mL and 40 μg/mL.

[0039] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF

agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the first cell culture medium.

[0040] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 3000 IU/mL in the first cell culture medium.

[0041] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, The method of Claim 31, wherein IL-2 is present at an initial concentration of about 800 to about 1100 IU/mL in the first cell culture medium.

[0042] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF

agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 1000 IU/mL in the first cell culture medium.

[0043] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the second cell culture medium.

[0044] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 3000 IU/mL in the second cell culture medium.

[0045] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF

agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 800 to about 1100 IU/mL in the second cell culture medium.

[0046] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-2 is present at an initial concentration of about 1000 IU/mL in the second cell culture medium.

[0047] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-15 is present in the first cell culture medium.

[0048] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-15 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the first cell culture medium.

[0049] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-15 is present in the second cell culture medium.

[0050] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at

least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-15 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the second cell culture medium.

[0051] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-21 is present in the first cell culture medium.

[0052] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-21 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the first cell culture medium.

[0053] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture

medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein IL-21 is present in the second cell culture medium.

[0054] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a

patient with the cancer, wherein IL-21 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the second cell culture medium.

[0055] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein OKT-3 antibody is present at an initial concentration of about 10 ng/mL to about 60 ng/mL in the second cell culture medium.

[0056] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture

medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

[0057] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the initial expansion is performed using a gas permeable container.

[0058] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the rapid expansion is performed using a gas permeable container.

[0059] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at

least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

[0060] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient, wherein the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m^2/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days.

[0061] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a decrescendo IL-2 regimen starting on the day after administration of the third population of TILs to the patient, wherein the decrescendo IL-2 regimen comprises aldesleukin administered intravenously at a dose of 18,000,000 IU/m^2 on day 1, 9,000,000 IU/m^2 on day 2, and 4,500,000 IU/m^2 on days 3 and 4.

[0062] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with pegylated IL-2 after administration of the third population of TILs to the patient at a dose of 0.10 mg/day to 50 mg/day.

[0063] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist,

and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a high-dose IL-2 regimen starting on the day after administration of the third population of TILs to the patient.

[0064] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a high-dose IL-2 regimen starting on the day after administration of the third population of TILs to the patient, wherein the high-dose IL-2 regimen comprises 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

[0065] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, and sarcoma.

[0066] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma.

[0067] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture

medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor prior to resecting the tumor from the patient.

[0068] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor prior to resecting the tumor from the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab,

pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0069] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor after resecting the tumor from the patient.

[0070] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture

medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor after resecting the tumor from the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0071] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF

agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor after administering the third population of TILs to the patient.

[0072] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer, further comprising the step of treating the patient with a PD-1 inhibitor or PD-L1 inhibitor after administering the third population of TILs to the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0073] In an embodiment, the invention provides a process for the preparation of a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(b) obtaining a first population of TILs;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less; and

(e) harvesting the third population of TILs.

[0074] In an embodiment, the invention provides a population of tumor infiltrating lymphocytes (TILs) obtainable from a process comprising the steps of:

(b) obtaining a first population of TILs;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less; and

(e) harvesting the third population of TILs.

[0075] In an embodiment, the invention provides a population of TILs is for use in the treatement of cancer. In an embodiment, the invention provides a pharmaceutical composition comprising a population of tumor infiltrating lymphocytes (TILs) for use in treating a cancer wherein the population of tumor infiltrating lymphocytes (TILs) is obtainable by a process comprising the steps of:

(b) obtaining a first population of TILs;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less; and

(e) harvesting the third population of TILs.

[0076] In an embodiment, the first population of TILs is obtained from a tumor. In an embodiment, the tumor is firstly resected from a patient. In an embodiment, the first population of TILs is obtained from the tumor which has been resected from a patient. In an embodiment, the population of TILs is for adminsitration in a therapeutically effective amount to a patient with cancer.

[0077] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 11 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), and a TNFRSF agonist, and wherein the rapid expansion is performed over a period of 11 days or less;

(e) harvesting the third population of TILs; and

(f) optionally cryopreserving the third population of TILs in a dimethylsulfoxide-based media.

[0078] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 11 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), and a

TNFRSF agonist, and wherein the rapid expansion is performed over a period of 11 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to the patient.

[0079] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 11 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), and a TNFRSF agonist, and wherein the rapid expansion is performed over a period of 11 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to the patient,

wherein the TNFRSF agonist is selected from the group consisting of a 4-1BB agonist, an OX40 agonist, and a combination thereof.

[0080] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 11 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), and a TNFRSF agonist, and wherein the rapid expansion is performed over a period of 11 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to the patient,

wherein the TNFRSF agonist is selected from the group consisting of a 4-1BB agonist, an OX40 agonist, and a combination thereof, and

wherein the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101, a fusion protein, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0081] In an embodiment, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs

is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 11 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), and a TNFRSF agonist, and wherein the rapid expansion is performed over a period of 11 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to the patient,

wherein the TNFRSF agonist is selected from the group consisting of a 4-1BB agonist, an OX40 agonist, and a combination thereof, and

wherein the TNFRSF agonist is a OX40 agonist, and the OX40 agonist is selected from the group consisting of tavolixizumab, GSK3174998, MEDI6469, MEDI6383, MOXR0916, PF-04518600, Creative Biolabs MOM-18455, and fragments, derivatives, variants, biosimilars, and combinations thereof.

wherein the OX4 agonist is present at the start of step (d) at a concentration between 1 μg/mL and 30 μg/mL.

[0082] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the TNFRSF agonist is present at the start of step (d) at a concentration between 5 μg/mL and 20 μg/mL.

[0083] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the TNFRSF agonist is present at the start of step (d) at a concentration of about 10 μg/mL.

[0084] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the TNFRSF agonist is maintained throughout step (d) at a concentration

between 1 μg/mL and 30 μg/mL.

[0085] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the TNFRSF agonist is maintained throughout step (d) at a concentration between 5 μg/mL and 20 μg/mL.

[0086] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the TNFRSF agonist is maintained throughout step (d) at a concentration of about 10 μg/mL.

[0087] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the third population of TILs exhibits an increased ratio of $CD8^+$ TILs to $CD4^+$ TILs in comparison to the reference ratio of $CD8^+$ TILs to $CD4^+$ TILs in the second population of TILs. In an embodiment, the increased ratio is selected from the group consisting of at least 1% greater than the reference ratio, at least 2% greater than the reference ratio, at least 5% greater than the reference ratio, at least 10% greater than the reference ratio, at least 15% greater than the reference ratio, at least 20% greater than the reference ratio, at least 25% greater than the reference ratio, at least 30% greater than the reference ratio, at least 35% greater than the reference ratio, at least 40% greater than the reference ratio, at least 45% greater than the reference ratio, and at least 50% greater than the reference ratio. In an embodiment, the increased ratio is between 5% and 80% greater than the reference ratio. In an embodiment, the increased ratio is between 10% and 70% greater than the reference ratio. In an embodiment, the increased ratio is between 15% and 60% greater than the reference ratio. In an of the foregoing embodiments, the reference ratio is obtained from a third TIL population that is a responder to the TNFRSF agonist.

[0088] In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the cancer is selected from the group consisting of melanoma, uveal (ocular) melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer (head and neck squamous cell cancer), renal cell carcinoma, colorectal cancer, pancreatic cancer, glioblastoma, cholangiocarcinoma, and sarcoma. In an embodiment, the invention provides a method of any of the foregoing embodiments, wherein the cancer is selected from the group consisting of cutaneous melanoma, uveal (ocular) melanoma, platinum-resistant ovarian cancer, pancreatic ductal adenocarcinoma, osteosarcoma, triple-negative breast

cancer, and non-small-cell lung cancer.

[0089] In an embodiment, any of the foregoing embodiments may be combined with any of the following embodiments.

[0090] In an embodiment, the process is an *in vitro* or an *ex vivo* process.

[0091] In an embodiment, the TNFRSF agonist is selected from the group consisting of a 4-1BB agonist, an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof.

[0092] In an embodiment, the TNFRSF agonist is a 4-1BB agonist.

[0093] In an embodiment, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101 and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0094] In an embodiment, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is a 4-1BB agonist fusion protein.

[0095] In an embodiment, the TNFRSF agonist is a 4-1BB agonist fusion protein, and the 4-1BB agonist fusion protein comprises (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[0096] In an embodiment, the TNFRSF agonist is a OX40 agonist.

[0097] In an embodiment, the TNFRSF agonist is a OX40 agonist, and the OX40 agonist is selected from the group consisting of tavolixizumab, GSK3174998, MEDI6469, MEDI6383, MOXR0916, PF-04518600, Creative Biolabs MOM-18455, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[0098] In an embodiment, the TNFRSF agonist is an OX40 agonist, and the OX40 agonist is an OX40 agonist fusion protein.

[0099] In an embodiment, the TNFRSF agonist is an OX40 agonist fusion protein, and the OX40 agonist fusion protein comprises (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[00100] In an embodiment, the TNFRSF agonist is a CD27 agonist.

[00101] In an embodiment, the TNFRSF agonist is a CD27 agonist, and the CD27 agonist is varlilumab, or a fragment, derivative, variant, or biosimilar thereof.

[00102] In an embodiment, the TNFRSF agonist is a CD27 agonist, and wherein the CD27 agonist is an CD27 agonist fusion protein.

[00103] In an embodiment, the TNFRSF agonist is a CD27 agonist, and the CD27 agonist fusion protein comprises (i) a first soluble CD27 binding domain, (ii) a first peptide linker, (iii) a second soluble CD27 binding domain, (iv) a second peptide linker, and (v) a third soluble CD27 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[00104] In an embodiment, the TNFRSF agonist is a GITR agonist.

[00105] In an embodiment, the TNFRSF agonist is a GITR agonist, and the GITR agonist is selected from the group consisting of TRX518, 6C8, 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, 31H6, 2155, 698, 706, 827, 1649, 1718, 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, 9H6, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00106] In an embodiment, the TNFRSF agonist is an GITR agonist, and the GITR agonist is a GITR agonist fusion protein.

[00107] In an embodiment, the TNFRSF agonist is a GITR agonist fusion protein, and the GITR agonist fusion protein comprises (i) a first soluble GITR binding domain, (ii) a first peptide linker, (iii) a second soluble GITR binding domain, (iv) a second peptide linker, and (v)

a third soluble GITR binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[00108] In an embodiment, the TNFRSF agonist is a HVEM agonist.

[00109] In an embodiment, the TNFRSF agonist is an HVEM agonist, and the HVEM agonist is a HVEM agonist fusion protein.

[00110] In an embodiment, the TNFRSF agonist is a HVEM agonist fusion protein, and wherein the HVEM agonist fusion protein comprises (i) a first soluble HVEM binding domain, (ii) a first peptide linker, (iii) a second soluble HVEM binding domain, (iv) a second peptide linker, and (v) a third soluble HVEM binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain comprises a Fc fragment domain and hinge domain, and wherein the fusion protein is a dimeric structure according to structure I-A or structure I-B.

[00111] In an embodiment, the TNFRSF agonist is selected from the group consisting of urelumab, utomilumab, EU-101, tavolixizumab, Creative Biolabs MOM-18455, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00112] In an embodiment, the first cell culture medium comprises a second TNFRSF agonist.

[00113] In an embodiment, the TNFRSF agonist is added to the first cell culture medium during the initial expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks.

[00114] In an embodiment, the TNFRSF agonist is added to the second cell culture medium during the rapid expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks.

[00115] In an embodiment, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 μg/mL and 100 μg/mL.

[00116] In an embodiment, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 20 μg/mL and 40 μg/mL.

[00117] Further details of the TNFRSF agonists are provided herein.

[00118] In an embodiment, IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the first cell culture medium.

[00119] In an embodiment, IL-2 is present at an initial concentration of about 3000 IU/mL in the first cell culture medium.

[00120] In an embodiment, IL-2 is present at an initial concentration of about 800 to about 1100 IU/mL in the first cell culture medium.

[00121] In an embodiment, IL-2 is present at an initial concentration of about 1000 IU/mL in the first cell culture medium.

[00122] In an embodiment, IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the second cell culture medium.

[00123] In an embodiment, IL-2 is present at an initial concentration of about 3000 IU/mL in the second cell culture medium.

[00124] In an embodiment, IL-2 is present at an initial concentration of about 800 to about 1100 IU/mL in the second cell culture medium.

[00125] In an embodiment, IL-2 is present at an initial concentration of about 1000 IU/mL in the second cell culture medium.

[00126] In an embodiment, IL-15 is present in the first cell culture medium.

[00127] In an embodiment, IL-15 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the first cell culture medium.

[00128] In an embodiment, IL-15 is present in the second cell culture medium.

[00129] In an embodiment, IL-15 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the second cell culture medium.

[00130] In an embodiment, IL-21 is present in the first cell culture medium.

[00131] In an embodiment, IL-21 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the first cell culture medium.

[00132] In an embodiment, IL-21 is present in the second cell culture medium.

[00133] In an embodiment, IL-21 is present at an initial concentration of about 5 ng/mL to about 20 ng/mL in the second cell culture medium.

[00134] In an embodiment, OKT-3 antibody is present at an initial concentration of about 10 ng/mL to about 60 ng/mL in the second cell culture medium.

[00135] In an embodiment, OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

[00136] In an embodiment, the initial expansion is performed using a gas permeable container.

[00137] In an embodiment, the rapid expansion is performed using a gas permeable container.

[00138] In an embodiment, the invention provides a population of tumor infiltrating lymphocytes (TILs) for use in treating a cancer wherein the population of tumor infiltrating lymphocytes (TILs) is obtainable by a process of the invention as described herein.

[00139] In an embodiment, the invention provides a pharmaceutical composition comprising a population of tumor infiltrating lymphocytes (TILs) for use in a method of treating a cancer wherein the population of tumor infiltrating lymphocytes (TILs) is obtainable by a process of the invention as described herein.

[00140] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a TNFRSF.

[00141] In an embodiment, the invention provides a combination of a population of TILs obtainable by a process of the invention as described herein and a TNFRSF for use in the treatment of cancer.

[00142] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a TNFRSF agonist wherein the TNFRSF agonist is for administration on the day after administration of the third population of TILs to the patient,

and wherein the TNFRSF agonist is administered intravenously at a dose of between 0.1 mg/kg and 50 mg/kg every four weeks for up to eight cycles.

[00143] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a TNFRSF agonist wherein the TNFRSF agonist is for administration prior to the step of resecting of a tumor from the patient, and wherein the TNFRSF agonist for administration intravenously at a dose of between 0.1 mg/kg and 50 mg/kg every four weeks for up to eight cycles.

[00144] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a non-myeloablative lymphodepletion regimen.

[00145] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient.

[00146] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient, wherein the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m^2/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days. Further details of the non-myeloablative lymphodepletion regimen are provided herein, e.g., under the Heading "Non-Myeloablative Lymphodepletion with Chemotherapy".

[00147] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a IL-2 regimen.

[00148] In an embodiment, the IL-2 regimen is a decrescendo IL-2 regimen.

[00149] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a decrescendo IL-2 regimen starting on the day after administration of the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient, wherein the decrescendo IL-2 regimen

comprises aldesleukin administered intravenously at a dose of 18,000,000 IU/m^2 on day 1, 9,000,000 IU/m^2 on day 2, and 4,500,000 IU/m^2 on days 3 and 4.

[00150] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with pegylated IL-2.

[00151] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in a method of treating cancer in combination with pegylated IL-2 administered after administration of the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient at a dose of 0.10 mg/day to 50 mg/day.

[00152] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in a method of treating cancer in combination with a high-dose IL-2 regimen.

[00153] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in a method of treating cancer in combination with a high-dose IL-2 regimen starting on the day after administration of the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient.

[00154] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a high-dose IL-2 regimen starting on the day after administration of the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient, wherein the high-dose IL-2 regimen comprises 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

[00155] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer, wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, and sarcoma.

[00156] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer, wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma.

[00157] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor.

[00158] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00159] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor, wherein the PD-1 inhibitor or PD-L1 inhibitor is for administration prior to resecting the tumor from the patient.

[00160] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor prior to resecting the tumor from the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00161] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in method of treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor.

[00162] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00163] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in a method of treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor after resecting the tumor from the patient.

[00164] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor after resecting the tumor from the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the

group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00165] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor, wherein the PD-1 or PD-L1 inhibitor is for administration after administering the third population of TILs and/or a pharmaceutical composition comprising the third population of TILs to the patient.

[00166] In an embodiment, the population of TILs and/or the pharmaceutical composition is for use in treating cancer in combination with a PD-1 inhibitor or PD-L1 inhibitor which is for administrationafter administering the third population of TILs to the patient, wherein the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof. Further details of the PD-1 inhibitor and the PD-L1 inhibitor are described herein e.g. under the heading "Combinations with PD-1 and PD-L1 Inhibitors".In some embodiments, the population of TILs and/ or the pharmaceutical composition comprising a population of TILs further comprise one or more features as described herein, for example, under the headings "Pharmaceutical Compositions, Dosages, and Dosing Regimens for TILs" and "Pharmaceutical Compositions, Dosages, and Dosing Regimens for TNFRSF Agonists".

BRIEF DESCRIPTION OF THE DRAWINGS

[00167] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[00168] FIG. 1 illustrates a TIL expansion and treatment process. TNFRSF agonists of the present disclosure may be used in both the pre-REP stage (top half of figure) or REP stage (bottom half of figure) and may be added when IL-2 is added to each cell culture. Step 1 refers to the addition of 4 tumor fragments into 10 G-Rex 10 flasks. At step 2, approximately 40×10^6 TILs or greater are obtained. At step 3, a split occurs into 36 G-Rex 100 flasks for REP. TILs are harvested by centrifugation at step 4. Fresh TIL product is obtained at step 5 after a total process time of approximate 43 days, at which point TILs may be infused into a patient.

[00169] FIG. 2 illustrates a treatment protocol for use with TILs expanded with TNFRSF agonists of the present disclosure. Surgery (and tumor resection) occurs at the start, and

lymphodepletion chemo refers to non-myeloablative lymphodepletion with chemotherapy as described elsewhere herein. TNFRSF agonists of the present disclosure may also be used during therapy as described herein after administration of TILs.

[00170] FIG. 3 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 4B5 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a green fluorescent protein (GFP) reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00171] FIG. 4 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 1C4 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00172] FIG. 5 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 9B4 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00173] FIG. 6 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 1D7 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00174] FIG. 7 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 1D10 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00175] FIG. 8 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 3C2 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00176] FIG. 9 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 10D12 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00177] FIG. 10 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 8D2 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00178] FIG. 11 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 4G6 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00179] FIG. 12 illustrates the results of an assay to determine if 4-1BB-Fc hybridoma 8E3 activates 4-1BB signaling on Jurkat cells expressing NF-kB using a GFP reporter in a dose dependent manner. "Secondary" refers to activation of a secondary antibody.

[00180] FIG. 13 illustrates an exemplary TIL expansion and manufacturing protocol (Process 2A).

[00181] FIG. 14 illustrates exemplary method steps undertaken in Process 2A.

[00182] FIG. 15 illustrates an exemplary TIL expansion protocol.

[00183] FIG. 16 illustrates binding affinity for Creative Biolabs (CB) and BPS Biosciences (BPS) 4-1BB agonist antibodies as assessed by percentage of 4-1BB+ cells by flow cytometry. CB 4-1BB agonist exhibited the highest binding affinity.

[00184] FIG. 17 illustrates binding affinity for Creative Biolabs (CB) and BPS Biosciences (BPS) 4-1BB agonist antibodies as assessed by mean fluorescence intensity (MFI). CB 4-1BB agonist exhibited the highest binding affinity.

[00185] FIG. 18 illustrates the results of an assessment of NF-κB pathway activation of anti-4-1BB agonistic antibodies.

[00186] FIG. 19 illustrates binding affinity for Creative Biolabs OX40 agonist antibody as assessed by percentage of $OX40^+$ cells by flow cytometry.

[00187] FIG. 20 illustrates binding affinity for Creative Biolabs OX40 agonist antibodies as assessed by mean fluorescence intensity (MFI).

[00188] FIG. 21 illustrates comparable binding affinity between Creative Biolabs anti-OX40 agonist antibody (at five concentrations shown) and a commercial anti-OX40 (clone Ber-ACT35) agonist. The first letter of each tumor designation indicates histology: C = cervical; H = head and neck (head and neck squamous cell carcinoma); L = lung; and M = melanoma.

[00189] FIG. 22 illustrates the results of an assessment of NF-κB pathway activation of anti-OX40 agonist antibody. OX40 reporter cells were treated with either anti-OX40 alone or Isotype

control at the concentrations of 1, 2, 4, 8, and 16 μg/mL with or without PBMC feeder cells for 24 hours. The cells were lysed using One-Step Luciferase reagent, and luciferase activity was measured by luminometer.

[00190] FIG. 23 illustrates the experimental design for 4-1BB and OX40 agonist experiments during pre-REP.

[00191] FIG. 24 illustrates the tumor histologies used in the experimental design of FIG. 23.

[00192] FIG. 25 illustrates the data analysis strategy used to assess the impact of 4-1BB and anti-OX40 agonists used during pre-REP on TIL performance and properties.

[00193] FIG. 26 illustrates total cell count results for cell expansion using CB 4-1BB agonist (N = 3). NT = not tested (control). The p value was > 0.99.

[00194] FIG. 27 illustrates total cell count results for cell expansion using CB OX40 agonist (N = 5). NT = not tested (control). The p value was 0.06.

[00195] FIG. 28 illustrates total cell count results for cell expansion using CB 4-1BB agonist and OX-40 agonist (N = 2). NT = not tested (control).

[00196] FIG. 29 illustrates total $CD8^+$ cell count results for cell expansion using CB 4-1BB agonist (N = 3). The p value was 0.5.

[00197] FIG. 30 illustrates total $CD8^+$ cell count results for cell expansion using CB OX40 agonist (N = 5). The p value was 0.03.

[00198] FIG. 31 illustrates total $CD8^+$ cell count results for cell expansion using CB 4-1BB agonist and OX-40 agonist (N = 2). NT = not tested (control).

[00199] FIG. 32 illustrates total $CD8^+/CD4^+$ cell count ratio results for cell expansion using CB 4-1BB agonist (N = 3). The p value was 0.2.

[00200] FIG. 33 illustrates total $CD8^+/CD4^+$ cell count ratio results for cell expansion using CB OX40 agonist (N = 5). The p value was 0.12.

[00201] FIG. 34 illustrates total $CD8^+/CD4^+$ cell count ratio results for cell expansion using CB 4-1BB agonist and OX-40 agonist (N = 2). NT = not tested (control).

[00202] FIG. 35 illustrates the experimental scheme for REP propagation of pre-REP TILs expanded in the presence of 4-1BB or OX40 agonists.

[00203] FIG. 36 illustrates fold expansion of TILs expanded in REP from pre-REP TILs expaned in the presence of CB 4-1BB agonist versus TILs not treated in the pre-REP (NT).

[00204] FIG. 37 illustrates fold expansion of TILs expanded in REP from pre-REP TILs expaned in the presence of CB OX40 agonist versus TILs not treated in the pre-REP (NT).

[00205] FIG. 38 illustrates fold expansion of TILs expanded in REP from pre-REP TILs expaned in the presence of CB 4-1BB agonist and CB OX40 agonist versus TILs not treated in the pre-REP (NT).

[00206] FIG. 39 illustrates the histologies of twenty-one TIL lines used for assessment of CB OX40 agonist during the REP phase.

[00207] FIG. 40 illustrates the experimental scheme for assessment of CB OX40 agonist during the REP phase.

[00208] FIG. 41 illustrates that the presence of an OX40 agonistic antibody preferentially expands $CD8^+$ TIL during REP (shown as a percentage of $CD3^+CD4^+$ cells).

[00209] FIG. 42 illustrates that the presence of an OX40 agonistic antibody preferentially expands $CD8^+$ TIL during REP (shown as a percentage of $CD3^+CD8^+$ cells).

[00210] FIG. 43 illustrates that in non-responder TIL lines, down-regulation of OX40 was not observed in $CD4^+$ subset following anti-OX40 treatment.

[00211] FIG. 44 illustrates experimental details for CB OX40 agonist dose titration in non-responder and responder TIL lines.

[00212] FIG. 45 illustrates the results of CB OX40 agonist dose titration in responder TIL lines.

[00213] FIG. 46 illustrates the results of CB OX40 agonist dose titration in non-responder TIL lines.

[00214] FIG. 47 illustrates comparable TCRvb repertoire profiles for responder L4005.

[00215] FIG. 48 illustrates comparable TCRvb repertoire profiles for responder H3005.

[00216] FIG. 49 illustrates comparable TCRvb repertoire profiles for responder M1022.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

[00217] SEQ ID NO:1 is the amino acid sequence of the heavy chain of muromonab.

[00218] SEQ ID NO:2 is the amino acid sequence of the light chain of muromonab.

[00219] SEQ ID NO:3 is the amino acid sequence of a recombinant human IL-2 protein.

[00220] SEQ ID NO:4 is the amino acid sequence of aldesleukin.

[00221] SEQ ID NO:5 is the amino acid sequence of a recombinant human IL-4 protein.

[00222] SEQ ID NO:6 is the amino acid sequence of a recombinant human IL-7 protein.

[00223] SEQ ID NO:7 is the amino acid sequence of a recombinant human IL-15 protein.

[00224] SEQ ID NO:8 is the amino acid sequence of a recombinant human IL-21 protein.

[00225] SEQ ID NO:9 is the amino acid sequence of human 4-1BB.

[00226] SEQ ID NO:10 is the amino acid sequence of murine 4-1BB.

[00227] SEQ ID NO:11 is the heavy chain for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00228] SEQ ID NO:12 is the light chain for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00229] SEQ ID NO:13 is the heavy chain variable region (V_H) for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00230] SEQ ID NO:14 is the light chain variable region (V_L) for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00231] SEQ ID NO:15 is the heavy chain CDRl for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00232] SEQ ID NO:16 is the heavy chain CDR2 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00233] SEQ ID NO:17 is the heavy chain CDR3 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00234] SEQ ID NO:18 is the light chain CDR1 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00235] SEQ ID NO:19 is the light chain CDR2 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00236] SEQ ID NO:20 is the light chain CDR3 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00237] SEQ ID NO:21 is the heavy chain for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00238] SEQ ID NO:22 is the light chain for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00239] SEQ ID NO:23 is the heavy chain variable region (V_H) for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00240] SEQ ID NO:24 is the light chain variable region (V_L) for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00241] SEQ ID NO:25 is the heavy chain CDR1 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00242] SEQ ID NO:26 is the heavy chain CDR2 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00243] SEQ ID NO:27 is the heavy chain CDR3 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00244] SEQ ID NO:28 is the light chain CDR1 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00245] SEQ ID NO:29 is the light chain CDR2 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00246] SEQ ID NO:30 is the light chain CDR3 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00247] SEQ ID NO:31 is an Fc domain for a TNFRSF agonist fusion protein.

[00248] SEQ ID NO:32 is a linker for a TNFRSF agonist fusion protein.

[00249] SEQ ID NO:33 is a linker for a TNFRSF agonist fusion protein.

[00250] SEQ ID NO:34 is a linker for a TNFRSF agonist fusion protein.

[00251] SEQ ID NO:35 is a linker for a TNFRSF agonist fusion protein.

[00252] SEQ ID NO:36 is a linker for a TNFRSF agonist fusion protein.

[00253] SEQ ID NO:37 is a linker for a TNFRSF agonist fusion protein.

[00254] SEQ ID NO:38 is a linker for a TNFRSF agonist fusion protein.

[00255] SEQ ID NO:39 is a linker for a TNFRSF agonist fusion protein.

[00256] SEQ ID NO:40 is a linker for a TNFRSF agonist fusion protein.

[00257] SEQ ID NO:41 is a linker for a TNFRSF agonist fusion protein.

[00258] SEQ ID NO:42 is an Fc domain for a TNFRSF agonist fusion protein.

[00259] SEQ ID NO:43 is a linker for a TNFRSF agonist fusion protein.

[00260] SEQ ID NO:44 is a linker for a TNFRSF agonist fusion protein.

[00261] SEQ ID NO:45 is a linker for a TNFRSF agonist fusion protein.

[00262] SEQ ID NO:46 is a 4-1BB ligand (4-1BBL) amino acid sequence.

[00263] SEQ ID NO:47 is a soluble portion of 4-1BBL polypeptide.

[00264] SEQ ID NO:48 is a heavy chain variable region (V_H) for the 4-1BB agonist antibody 4B4-1-1 version 1.

[00265] SEQ ID NO:49 is a light chain variable region (V_L) for the 4-1BB agonist antibody 4B4-1-1 version 1.

[00266] SEQ ID NO:50 is a heavy chain variable region (V_H) for the 4-1BB agonist antibody 4B4-1-1 version 2.

[00267] SEQ ID NO:51 is a light chain variable region (V_L) for the 4-1BB agonist antibody 4B4-1-1 version 2.

[00268] SEQ ID NO:52 is a heavy chain variable region (V_H) for the 4-1BB agonist antibody

H39E3-2.

[00269] SEQ ID NO:53 is a light chain variable region (V_L) for the 4-1BB agonist antibody H39E3-2.

[00270] SEQ ID NO:54 is the amino acid sequence of human OX40.

[00271] SEQ ID NO:55 is the amino acid sequence of murine OX40.

[00272] SEQ ID NO:56 is the heavy chain for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00273] SEQ ID NO:57 is the light chain for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00274] SEQ ID NO:58 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00275] SEQ ID NO:59 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00276] SEQ ID NO:60 is the heavy chain CDRl for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00277] SEQ ID NO:61 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00278] SEQ ID NO:62 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00279] SEQ ID NO:63 is the light chain CDR1 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00280] SEQ ID NO:64 is the light chain CDR2 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00281] SEQ ID NO:65 is the light chain CDR3 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00282] SEQ ID NO:66 is the heavy chain for the OX40 agonist monoclonal antibody 11D4.

[00283] SEQ ID NO:67 is the light chain for the OX40 agonist monoclonal antibody 11D4.

[00284] SEQ ID NO:68 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 11D4.

[00285] SEQ ID NO:69 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 11D4.

[00286] SEQ ID NO:70 is the heavy chain CDRl for the OX40 agonist monoclonal antibody 11D4.

[00287] SEQ ID NO:71 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody 11D4.

[00288] SEQ ID NO:72 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody 11D4.

[00289] SEQ ID NO:73 is the light chain CDR1 for the OX40 agonist monoclonal antibody 11D4.

[00290] SEQ ID NO:74 is the light chain CDR2 for the OX40 agonist monoclonal antibody 11D4.

[00291] SEQ ID NO:75 is the light chain CDR3 for the OX40 agonist monoclonal antibody 11D4.

[00292] SEQ ID NO:76 is the heavy chain for the OX40 agonist monoclonal antibody 18D8.

[00293] SEQ ID NO:77 is the light chain for the OX40 agonist monoclonal antibody 18D8.

[00294] SEQ ID NO:78 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 18D8.

[00295] SEQ ID NO:79 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 18D8.

[00296] SEQ ID NO:80 is the heavy chain CDRl for the OX40 agonist monoclonal antibody 18D8.

[00297] SEQ ID NO:81 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody 18D8.

[00298] SEQ ID NO:82 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody

18D8.

[00299] SEQ ID NO:83 is the light chain CDR1 for the OX40 agonist monoclonal antibody 18D8.

[00300] SEQ ID NO:84 is the light chain CDR2 for the OX40 agonist monoclonal antibody 18D8.

[00301] SEQ ID NO:85 is the light chain CDR3 for the OX40 agonist monoclonal antibody 18D8.

[00302] SEQ ID NO:86 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody Hu119-122.

[00303] SEQ ID NO:87 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody Hu119-122.

[00304] SEQ ID NO:88 is the heavy chain CDRl for the OX40 agonist monoclonal antibody Hu119-122.

[00305] SEQ ID NO:89 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody Hu119-122.

[00306] SEQ ID NO:90 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody Hu119-122.

[00307] SEQ ID NO:91 is the light chain CDR1 for the OX40 agonist monoclonal antibody Hu119-122.

[00308] SEQ ID NO:92 is the light chain CDR2 for the OX40 agonist monoclonal antibody Hu119-122.

[00309] SEQ ID NO:93 is the light chain CDR3 for the OX40 agonist monoclonal antibody Hu119-122.

[00310] SEQ ID NO:94 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody Hu106-222.

[00311] SEQ ID NO:95 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody Hu106-222.

[00312] SEQ ID NO:96 is the heavy chain CDRl for the OX40 agonist monoclonal antibody Hu106-222.

[00313] SEQ ID NO:97 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody Hu106-222.

[00314] SEQ ID NO:98 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody Hu106-222.

[00315] SEQ ID NO:99 is the light chain CDR1 for the OX40 agonist monoclonal antibody Hu106-222.

[00316] SEQ ID NO:100 is the light chain CDR2 for the OX40 agonist monoclonal antibody Hu106-222.

[00317] SEQ ID NO:101 is the light chain CDR3 for the OX40 agonist monoclonal antibody Hu106-222.

[00318] SEQ ID NO:102 is an OX40 ligand (OX40L) amino acid sequence.

[00319] SEQ ID NO:103 is a soluble portion of OX40L polypeptide.

[00320] SEQ ID NO:104 is an alternative soluble portion of OX40L polypeptide.

[00321] SEQ ID NO:105 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 008.

[00322] SEQ ID NO:106 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 008.

[00323] SEQ ID NO:107 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 011.

[00324] SEQ ID NO:108 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 011.

[00325] SEQ ID NO:109 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 021.

[00326] SEQ ID NO:110 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 021.

[00327] SEQ ID NO:111 is the heavy chain variable region (V_H) for the OX40 agonist monoclonal antibody 023.

[00328] SEQ ID NO:112 is the light chain variable region (V_L) for the OX40 agonist monoclonal antibody 023.

[00329] SEQ ID NO:113 is the heavy chain variable region (V_H) for an OX40 agonist monoclonal antibody.

[00330] SEQ ID NO:114 is the light chain variable region (V_L) for an OX40 agonist monoclonal antibody.

[00331] SEQ ID NO:115 is the heavy chain variable region (V_H) for an OX40 agonist monoclonal antibody.

[00332] SEQ ID NO:116 is the light chain variable region (V_L) for an OX40 agonist monoclonal antibody.

[00333] SEQ ID NO:117 is the heavy chain variable region (V_H) for a humanized OX40 agonist monoclonal antibody.

[00334] SEQ ID NO:118 is the heavy chain variable region (V_H) for a humanized OX40 agonist monoclonal antibody.

[00335] SEQ ID NO:119 is the light chain variable region (V_L) for a humanized OX40 agonist monoclonal antibody.

[00336] SEQ ID NO:120 is the light chain variable region (V_L) for a humanized OX40 agonist monoclonal antibody.

[00337] SEQ ID NO:121 is the heavy chain variable region (V_H) for a humanized OX40 agonist monoclonal antibody.

[00338] SEQ ID NO:122 is the heavy chain variable region (V_H) for a humanized OX40 agonist monoclonal antibody.

[00339] SEQ ID NO:123 is the light chain variable region (V_L) for a humanized OX40 agonist monoclonal antibody.

[00340] SEQ ID NO:124 is the light chain variable region (V_L) for a humanized OX40 agonist

monoclonal antibody.

[00341] SEQ ID NO:125 is the heavy chain variable region (V_H) for an OX40 agonist monoclonal antibody.

[00342] SEQ ID NO:126 is the light chain variable region (V_L) for an OX40 agonist monoclonal antibody.

[00343] SEQ ID NO:127 is the amino acid sequence of human CD27.

[00344] SEQ ID NO:128 is the amino acid sequence of macaque CD27.

[00345] SEQ ID NO:129 is the heavy chain for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00346] SEQ ID NO:130 is the light chain for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00347] SEQ ID NO:131 is the heavy chain variable region (V_H) for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00348] SEQ ID NO:132 is the light chain variable region (V_L) for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00349] SEQ ID NO:133 is the heavy chain CDR1 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00350] SEQ ID NO:134 is the heavy chain CDR2 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00351] SEQ ID NO:135 is the heavy chain CDR3 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00352] SEQ ID NO:136 is the light chain CDR1 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00353] SEQ ID NO:137 is the light chain CDR2 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00354] SEQ ID NO:138 is the light chain CDR3 for the CD27 agonist monoclonal antibody varlilumab (CDX-1127).

[00355] SEQ ID NO:139 is an CD27 ligand (CD70) amino acid sequence.

[00356] SEQ ID NO:140 is a soluble portion of CD70 polypeptide.

[00357] SEQ ID NO:141 is an alternative soluble portion of CD70 polypeptide.

[00358] SEQ ID NO:142 is the amino acid sequence of human GITR (human tumor necrosis factor receptor superfamily member 18 (TNFRSF18) protein).

[00359] SEQ ID NO:143 is the amino acid sequence of murine GITR (murine tumor necrosis factor receptor superfamily member 18 (TNFRSF18) protein).

[00360] SEQ ID NO:144 is the amino acid sequence of the heavy chain variant HuN6C8 (glycosylated) of the 6C8 humanized GITR agonist monoclonal antibody, with an N (asparagine) in CDR2, corresponding to SEQ ID NO:60 in U.S. Patent No. 7,812,135.

[00361] SEQ ID NO:145 is the amino acid sequence of the heavy chain variant HuN6C8 (aglycosylated) of the 6C8 humanized GITR agonist monoclonal antibody, with an N (asparagine) in CDR2, corresponding to SEQ ID NO:61 in U.S. Patent No. 7,812,135.

[00362] SEQ ID NO:146 is the amino acid sequence of the heavy chain variant HuQ6C8 (glycosylated) of the 6C8 humanized GITR agonist monoclonal antibody, with an Q (glutamine) in CDR2, corresponding to SEQ ID NO:62 in U.S. Patent No. 7,812,135.

[00363] SEQ ID NO:147 is the amino acid sequence of the heavy chain variant HuQ6C8 (aglycosylated) of the 6C8 humanized GITR agonist monoclonal antibody, with an Q (glutamine) in CDR2, corresponding to SEQ ID NO:63 in U.S. Patent No. 7,812,135.

[00364] SEQ ID NO:148 is the amino acid sequence of the light chain of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:58 in U.S. Patent No. 7,812,135.

[00365] SEQ ID NO:149 is the amino acid sequence of the leader sequence that may optionally be included with the amino acid sequences of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, or SEQ ID NO:147 in GITR agonist monoclonal antibodies.

[00366] SEQ ID NO:150 is the amino acid sequence of the leader sequence that may optionally be included with the amino acid sequence of SEQ ID NO:148 in GITR agonist monoclonal antibodies.

[00367] SEQ ID NO:151 is the amino acid sequence of the heavy chain variable region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:1 in U.S. Patent No. 7,812,135.

[00368] SEQ ID NO:152 is the amino acid sequence of the heavy chain variable region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:66 in U.S. Patent No. 7,812,135.

[00369] SEQ ID NO:153 is the amino acid sequence of the light chain variable region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:2 in U.S. Patent No. 7,812,135.

[00370] SEQ ID NO:154 is the amino acid sequence of the heavy chain CDR1 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:3 in U.S. Patent No. 7,812,135.

[00371] SEQ ID NO:155 is the amino acid sequence of the heavy chain CDR2 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:4 in U.S. Patent No. 7,812,135.

[00372] SEQ ID NO:156 is the amino acid sequence of the heavy chain CDR2 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:19 in U.S. Patent No. 7,812,135.

[00373] SEQ ID NO:157 is the amino acid sequence of the heavy chain CDR3 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:5 in U.S. Patent No. 7,812,135.

[00374] SEQ ID NO:158 is the amino acid sequence of the heavy chain CDR1 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:6 in U.S. Patent No. 7,812,135.

[00375] SEQ ID NO:159 is the amino acid sequence of the heavy chain CDR2 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:7 in U.S. Patent No. 7,812,135.

[00376] SEQ ID NO:160 is the amino acid sequence of the heavy chain CDR3 region of the 6C8 humanized GITR agonist monoclonal antibody, corresponding to SEQ ID NO:8 in U.S.

Patent No. 7,812,135.

[00377] SEQ ID NO:161 is the amino acid sequence of the heavy chain variant HuN6C8 (glycosylated) of the 6C8 chimeric GITR agonist monoclonal antibody, with an N (asparagine) in CDR2, corresponding to SEQ ID NO:23 in U.S. Patent No. 7,812,135.

[00378] SEQ ID NO:162 is the amino acid sequence of the heavy chain variant HuQ6C8 (aglycosylated) of the 6C8 chimeric GITR agonist monoclonal antibody, with an Q (glutamine) in CDR2, corresponding to SEQ ID NO:24 in U.S. Patent No. 7,812,135.

[00379] SEQ ID NO:163 is the amino acid sequence of the light chain of the 6C8 chimeric GITR agonist monoclonal antibody, corresponding to SEQ ID NO:22 in U.S. Patent No. 7,812,135.

[00380] SEQ ID NO:164 is the amino acid sequence of the GITR agonist 36E5 heavy chain variable region from U.S. Patent No. 8,709,424.

[00381] SEQ ID NO:165 is the amino acid sequence of the GITR agonist 36E5 light chain variable region from U.S. Patent No. 8,709,424.

[00382] SEQ ID NO:166 is the amino acid sequence of the GITR agonist 3D6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00383] SEQ ID NO:167 is the amino acid sequence of the GITR agonist 3D6 light chain variable region from U.S. Patent No. 8,709,424.

[00384] SEQ ID NO:168 is the amino acid sequence of the GITR agonist 61G6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00385] SEQ ID NO:169 is the amino acid sequence of the GITR agonist 61G6 light chain variable region from U.S. Patent No. 8,709,424.

[00386] SEQ ID NO:170 is the amino acid sequence of the GITR agonist 6H6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00387] SEQ ID NO:171 is the amino acid sequence of the GITR agonist 6H6 light chain variable region from U.S. Patent No. 8,709,424.

[00388] SEQ ID NO:172 is the amino acid sequence of the GITR agonist 61F6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00389] SEQ ID NO:173 is the amino acid sequence of the GITR agonist 61F6 light chain variable region from U.S. Patent No. 8,709,424.

[00390] SEQ ID NO:174 is the amino acid sequence of the GITR agonist 1D8 heavy chain variable region from U.S. Patent No. 8,709,424.

[00391] SEQ ID NO:175 is the amino acid sequence of the GITR agonist 1D8 light chain variable region from U.S. Patent No. 8,709,424.

[00392] SEQ ID NO:176 is the amino acid sequence of the GITR agonist 17F10 heavy chain variable region from U.S. Patent No. 8,709,424.

[00393] SEQ ID NO:177 is the amino acid sequence of the GITR agonist 17F10 light chain variable region from U.S. Patent No. 8,709,424.

[00394] SEQ ID NO:178 is the amino acid sequence of the GITR agonist 35D8 heavy chain variable region from U.S. Patent No. 8,709,424.

[00395] SEQ ID NO:179 is the amino acid sequence of the GITR agonist 35D8 light chain variable region from U.S. Patent No. 8,709,424.

[00396] SEQ ID NO:180 is the amino acid sequence of the GITR agonist 49A1 heavy chain variable region from U.S. Patent No. 8,709,424.

[00397] SEQ ID NO:181 is the amino acid sequence of the GITR agonist 49A1 light chain variable region from U.S. Patent No. 8,709,424.

[00398] SEQ ID NO:182 is the amino acid sequence of the GITR agonist 9E5 heavy chain variable region from U.S. Patent No. 8,709,424.

[00399] SEQ ID NO:183 is the amino acid sequence of the GITR agonist 9E5 light chain variable region from U.S. Patent No. 8,709,424.

[00400] SEQ ID NO:184 is the amino acid sequence of the GITR agonist 31H6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00401] SEQ ID NO:185 is the amino acid sequence of the GITR agonist 31H6 light chain variable region from U.S. Patent No. 8,709,424.

[00402] SEQ ID NO:186 is the amino acid sequence of the humanized GITR agonist 36E5

heavy chain variable region from U.S. Patent No. 8,709,424.

[00403] SEQ ID NO:187 is the amino acid sequence of the humanized GITR agonist 36E5 light chain variable region from U.S. Patent No. 8,709,424.

[00404] SEQ ID NO:188 is the amino acid sequence of the humanized GITR agonist 3D6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00405] SEQ ID NO:189 is the amino acid sequence of the humanized GITR agonist 3D6 light chain variable region from U.S. Patent No. 8,709,424.

[00406] SEQ ID NO:190 is the amino acid sequence of the humanized GITR agonist 61G6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00407] SEQ ID NO:191 is the amino acid sequence of the humanized GITR agonist 61G6 light chain variable region from U.S. Patent No. 8,709,424.

[00408] SEQ ID NO:192 is the amino acid sequence of the humanized GITR agonist 6H6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00409] SEQ ID NO:193 is the amino acid sequence of the humanized GITR agonist 6H6 light chain variable region from U.S. Patent No. 8,709,424.

[00410] SEQ ID NO:194 is the amino acid sequence of the humanized GITR agonist 61F6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00411] SEQ ID NO:195 is the amino acid sequence of the humanized GITR agonist 61F6 light chain variable region from U.S. Patent No. 8,709,424.

[00412] SEQ ID NO:196 is the amino acid sequence of the humanized GITR agonist 1D8 heavy chain variable region from U.S. Patent No. 8,709,424.

[00413] SEQ ID NO:197 is the amino acid sequence of the humanized GITR agonist 1D8 light chain variable region from U.S. Patent No. 8,709,424.

[00414] SEQ ID NO:198 is the amino acid sequence of the humanized GITR agonist 17F10 heavy chain variable region from U.S. Patent No. 8,709,424.

[00415] SEQ ID NO:199 is the amino acid sequence of the humanized GITR agonist 17F10 light chain variable region from U.S. Patent No. 8,709,424.

[00416] SEQ ID NO:200 is the amino acid sequence of the humanized GITR agonist 35D8 heavy chain variable region from U.S. Patent No. 8,709,424.

[00417] SEQ ID NO:201 is the amino acid sequence of the humanized GITR agonist 35D8 light chain variable region from U.S. Patent No. 8,709,424.

[00418] SEQ ID NO:202 is the amino acid sequence of the humanized GITR agonist 49A1 heavy chain variable region from U.S. Patent No. 8,709,424.

[00419] SEQ ID NO:203 is the amino acid sequence of the humanized GITR agonist 49A1 light chain variable region from U.S. Patent No. 8,709,424.

[00420] SEQ ID NO:204 is the amino acid sequence of the humanized GITR agonist 9E5 heavy chain variable region from U.S. Patent No. 8,709,424.

[00421] SEQ ID NO:205 is the amino acid sequence of the humanized GITR agonist 9E5 light chain variable region from U.S. Patent No. 8,709,424.

[00422] SEQ ID NO:206 is the amino acid sequence of the humanized GITR agonist 31H6 heavy chain variable region from U.S. Patent No. 8,709,424.

[00423] SEQ ID NO:207 is the amino acid sequence of the humanized GITR agonist 31H6 light chain variable region from U.S. Patent No. 8,709,424.

[00424] SEQ ID NO:208 is the amino acid sequence of the GITR agonist 2155 variable heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00425] SEQ ID NO:209 is the amino acid sequence of the GITR agonist 2155 variable light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00426] SEQ ID NO:210 is the amino acid sequence of the GITR agonist 2155 humanized (HC1) heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00427] SEQ ID NO:211 is the amino acid sequence of the GITR agonist 2155 humanized (HC2) heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00428] SEQ ID NO:212 is the amino acid sequence of the GITR agonist 2155 humanized (HC3a) heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00429] SEQ ID NO:213 is the amino acid sequence of the humanized (HC3b) GITR agonist

heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00430] SEQ ID NO:214 is the amino acid sequence of the humanized (HC4) GITR agonist heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00431] SEQ ID NO:215 is the amino acid sequence of the 2155 humanized (LC1) GITR agonist light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00432] SEQ ID NO:216 is the amino acid sequence of the 2155 humanized (LC2a) GITR agonist light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00433] SEQ ID NO:217 is the amino acid sequence of the 2155 humanized (LC2b) GITR agonist light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00434] SEQ ID NO:218 is the amino acid sequence of the 2155 humanized (LC3) GITR agonist light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00435] SEQ ID NO:219 is the amino acid sequence of the GITR agonist 698 variable heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00436] SEQ ID NO:220 is the amino acid sequence of the GITR agonist 698 variable light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00437] SEQ ID NO:221 is the amino acid sequence of the GITR agonist 706 variable heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00438] SEQ ID NO:222 is the amino acid sequence of the GITR agonist 706 variable light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00439] SEQ ID NO:223 is the amino acid sequence of the GITR agonist 827 variable heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00440] SEQ ID NO:224 is the amino acid sequence of the GITR agonist 827 variable light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00441] SEQ ID NO:225 is the amino acid sequence of the GITR agonist 1718 variable heavy chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00442] SEQ ID NO:226 is the amino acid sequence of the GITR agonist 1718 variable light chain from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00443] SEQ ID NO:227 is the amino acid sequence of the GITR agonist 2155 heavy chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00444] SEQ ID NO:228 is the amino acid sequence of the GITR agonist 2155 heavy chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00445] SEQ ID NO:229 is the amino acid sequence of the GITR agonist 2155 heavy chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00446] SEQ ID NO:230 is the amino acid sequence of the GITR agonist 2155 light chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00447] SEQ ID NO:231 is the amino acid sequence of the GITR agonist 2155 light chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00448] SEQ ID NO:232 is the amino acid sequence of the GITR agonist 2155 light chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00449] SEQ ID NO:233 is the amino acid sequence of the GITR agonists 698 and 706 heavy chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00450] SEQ ID NO:234 is the amino acid sequence of the GITR agonists 698 and 706 heavy chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00451] SEQ ID NO:235 is the amino acid sequence of the GITR agonists 698 and 706 heavy chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00452] SEQ ID NO:236 is the amino acid sequence of the GITR agonist 698 light chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00453] SEQ ID NO:237 is the amino acid sequence of the GITR agonists 698, 706, 827, and 1649 light chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00454] SEQ ID NO:238 is the amino acid sequence of the GITR agonists 698, 706, 827, and 1649 light chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00455] SEQ ID NO:239 is the amino acid sequence of the GITR agonists 706, 827, and 1649 light chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00456] SEQ ID NO:240 is the amino acid sequence of the GITR agonists 827 and 1649

heavy chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00457] SEQ ID NO:241 is the amino acid sequence of the GITR agonist 827 heavy chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00458] SEQ ID NO:242 is the amino acid sequence of the GITR agonist 1649 heavy chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00459] SEQ ID NO:243 is the amino acid sequence of the GITR agonist 1718 heavy chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00460] SEQ ID NO:244 is the amino acid sequence of the GITR agonist 1718 heavy chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00461] SEQ ID NO:245 is the amino acid sequence of the GITR agonist 1718 heavy chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00462] SEQ ID NO:246 is the amino acid sequence of the GITR agonist 1718 light chain CDR3 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00463] SEQ ID NO:247 is the amino acid sequence of the GITR agonist 1718 light chain CDR2 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00464] SEQ ID NO:248 is the amino acid sequence of the GITR agonist 1718 light chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00465] SEQ ID NO:249 is the amino acid sequence of the GITR agonists 827 and 1649 heavy chain CDR1 from U.S. Patent Application Publication No. US 2013/0108641 A1.

[00466] SEQ ID NO:250 is the amino acid sequence of the GITR agonist 1D7 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00467] SEQ ID NO:251 is the amino acid sequence of the GITR agonist 1D7 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00468] SEQ ID NO:252 is the amino acid sequence of the GITR agonist 1D7 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00476] SEQ ID NO:260 is the amino acid sequence of the GITR agonist 33C9 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00477] SEQ ID NO:261 is the amino acid sequence of the GITR agonist 33C9 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00478] SEQ ID NO:262 is the amino acid sequence of the GITR agonist 33C9 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00479] SEQ ID NO:263 is the amino acid sequence of the GITR agonist 33C9 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00480] SEQ ID NO:264 is the amino acid sequence of the GITR agonist 33C9 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00481] SEQ ID NO:265 is the amino acid sequence of the GITR agonist 33C9 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00482] SEQ ID NO:266 is the amino acid sequence of the GITR agonist 33C9 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00483] SEQ ID NO:267 is the amino acid sequence of the GITR agonist 33C9 light chain

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[00484] SEQ ID NO:268 is the amino acid sequence of the GITR agonist 33C9 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00490] SEQ ID NO:274 is the amino acid sequence of the GITR agonist 33F6 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00491] SEQ ID NO:275 is the amino acid sequence of the GITR agonist 33F6 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00494] SEQ ID NO:278 is the amino acid sequence of the GITR agonist 33F6 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00496] SEQ ID NO:280 is the amino acid sequence of the GITR agonist 34G4 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00500] SEQ ID NO:284 is the amino acid sequence of the GITR agonist 34G4 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00501] SEQ ID NO:285 is the amino acid sequence of the GITR agonist 34G4 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00503] SEQ ID NO:287 is the amino acid sequence of the GITR agonist 34G4 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00504] SEQ ID NO:288 is the amino acid sequence of the GITR agonist 34G4 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00506] SEQ ID NO:290 is the amino acid sequence of the GITR agonist 35B10 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00510] SEQ ID NO:294 is the amino acid sequence of the GITR agonist 35B10 heavy chain

CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00511] SEQ ID NO:295 is the amino acid sequence of the GITR agonist 35B10 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00513] SEQ ID NO:297 is the amino acid sequence of the GITR agonist 35B10 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00514] SEQ ID NO:298 is the amino acid sequence of the GITR agonist 35B10 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00516] SEQ ID NO:300 is the amino acid sequence of the GITR agonist 41E11 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00519] SEQ ID NO:303 is the amino acid sequence of the GITR agonist 41E11 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00520] SEQ ID NO:304 is the amino acid sequence of the GITR agonist 41E11 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00521] SEQ ID NO:305 is the amino acid sequence of the GITR agonist 41E11 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00523] SEQ ID NO:307 is the amino acid sequence of the GITR agonist 41E11 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00524] SEQ ID NO:308 is the amino acid sequence of the GITR agonist 41E11 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00525] SEQ ID NO:309 is the amino acid sequence of the GITR agonist 41E11 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00526] SEQ ID NO:310 is the amino acid sequence of the GITR agonist 41G5 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00529] SEQ ID NO:313 is the amino acid sequence of the GITR agonist 41G5 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00530] SEQ ID NO:314 is the amino acid sequence of the GITR agonist 41G5 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00531] SEQ ID NO:315 is the amino acid sequence of the GITR agonist 41G5 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00532] SEQ ID NO:316 is the amino acid sequence of the GITR agonist 41G5 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00533] SEQ ID NO:317 is the amino acid sequence of the GITR agonist 41G5 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00534] SEQ ID NO:318 is the amino acid sequence of the GITR agonist 41G5 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00535] SEQ ID NO:319 is the amino acid sequence of the GITR agonist 41G5 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00536] SEQ ID NO:320 is the amino acid sequence of the GITR agonist 42A11 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00537] SEQ ID NO:321 is the amino acid sequence of the GITR agonist 42A11 light chain

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[00538] SEQ ID NO:322 is the amino acid sequence of the GITR agonist 42A11 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00539] SEQ ID NO:323 is the amino acid sequence of the GITR agonist 42A11 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00540] SEQ ID NO:324 is the amino acid sequence of the GITR agonist 42A11 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00541] SEQ ID NO:325 is the amino acid sequence of the GITR agonist 42A11 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00542] SEQ ID NO:326 is the amino acid sequence of the GITR agonist 42A11 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00543] SEQ ID NO:327 is the amino acid sequence of the GITR agonist 42A11 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00544] SEQ ID NO:328 is the amino acid sequence of the GITR agonist 42A11 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00545] SEQ ID NO:329 is the amino acid sequence of the GITR agonist 42A11 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00546] SEQ ID NO:330 is the amino acid sequence of the GITR agonist 44C1 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00547] SEQ ID NO:331 is the amino acid sequence of the GITR agonist 44C1 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00548] SEQ ID NO:332 is the amino acid sequence of the GITR agonist 44C1 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00549] SEQ ID NO:333 is the amino acid sequence of the GITR agonist 44C1 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00550] SEQ ID NO:334 is the amino acid sequence of the GITR agonist 44C1 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00551] SEQ ID NO:335 is the amino acid sequence of the GITR agonist 44C1 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00552] SEQ ID NO:336 is the amino acid sequence of the GITR agonist 44C1 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00553] SEQ ID NO:337 is the amino acid sequence of the GITR agonist 44C1 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00554] SEQ ID NO:338 is the amino acid sequence of the GITR agonist 44C1 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00555] SEQ ID NO:339 is the amino acid sequence of the GITR agonist 44C1 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00556] SEQ ID NO:340 is the amino acid sequence of the GITR agonist 45A8 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00557] SEQ ID NO:341 is the amino acid sequence of the GITR agonist 45A8 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00558] SEQ ID NO:342 is the amino acid sequence of the GITR agonist 45A8 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00559] SEQ ID NO:343 is the amino acid sequence of the GITR agonist 45A8 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00560] SEQ ID NO:344 is the amino acid sequence of the GITR agonist 45A8 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00561] SEQ ID NO:345 is the amino acid sequence of the GITR agonist 45A8 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00562] SEQ ID NO:346 is the amino acid sequence of the GITR agonist 45A8 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00563] SEQ ID NO:347 is the amino acid sequence of the GITR agonist 45A8 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00564] SEQ ID NO:348 is the amino acid sequence of the GITR agonist 45A8 light chain

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[00565] SEQ ID NO:349 is the amino acid sequence of the GITR agonist 45A8 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00566] SEQ ID NO:350 is the amino acid sequence of the GITR agonist 46E11 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00570] SEQ ID NO:354 is the amino acid sequence of the GITR agonist 46E11 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00571] SEQ ID NO:355 is the amino acid sequence of the GITR agonist 46E11 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00576] SEQ ID NO:360 is the amino acid sequence of the GITR agonist 48H12 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00578] SEQ ID NO:362 is the amino acid sequence of the GITR agonist 48H12 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00580] SEQ ID NO:364 is the amino acid sequence of the GITR agonist 48H12 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00583] SEQ ID NO:367 is the amino acid sequence of the GITR agonist 48H12 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00602] SEQ ID NO:386 is the amino acid sequence of the GITR agonist 49D9 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00603] SEQ ID NO:387 is the amino acid sequence of the GITR agonist 49D9 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

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[00609] SEQ ID NO:393 is the amino acid sequence of the GITR agonist 49E2 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00610] SEQ ID NO:394 is the amino acid sequence of the GITR agonist 49E2 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00611] SEQ ID NO:395 is the amino acid sequence of the GITR agonist 49E2 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00612] SEQ ID NO:396 is the amino acid sequence of the GITR agonist 49E2 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00613] SEQ ID NO:397 is the amino acid sequence of the GITR agonist 49E2 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00614] SEQ ID NO:398 is the amino acid sequence of the GITR agonist 49E2 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00615] SEQ ID NO:399 is the amino acid sequence of the GITR agonist 49E2 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00616] SEQ ID NO:400 is the amino acid sequence of the GITR agonist 48A9 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00617] SEQ ID NO:401 is the amino acid sequence of the GITR agonist 48A9 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00618] SEQ ID NO:402 is the amino acid sequence of the GITR agonist 48A9 variable heavy

chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00619] SEQ ID NO:403 is the amino acid sequence of the GITR agonist 48A9 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00620] SEQ ID NO:404 is the amino acid sequence of the GITR agonist 48A9 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00621] SEQ ID NO:405 is the amino acid sequence of the GITR agonist 48A9 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00622] SEQ ID NO:406 is the amino acid sequence of the GITR agonist 48A9 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00623] SEQ ID NO:407 is the amino acid sequence of the GITR agonist 48A9 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00624] SEQ ID NO:408 is the amino acid sequence of the GITR agonist 48A9 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00625] SEQ ID NO:409 is the amino acid sequence of the GITR agonist 48A9 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00626] SEQ ID NO:410 is the amino acid sequence of the GITR agonist 5H7 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00627] SEQ ID NO:411 is the amino acid sequence of the GITR agonist 5H7 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00628] SEQ ID NO:412 is the amino acid sequence of the GITR agonist 5H7 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00629] SEQ ID NO:413 is the amino acid sequence of the GITR agonist 5H7 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00630] SEQ ID NO:414 is the amino acid sequence of the GITR agonist 5H7 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00631] SEQ ID NO:415 is the amino acid sequence of the GITR agonist 5H7 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00632] SEQ ID NO:416 is the amino acid sequence of the GITR agonist 5H7 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00633] SEQ ID NO:417 is the amino acid sequence of the GITR agonist 5H7 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00634] SEQ ID NO:418 is the amino acid sequence of the GITR agonist 5H7 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00635] SEQ ID NO:419 is the amino acid sequence of the GITR agonist 5H7 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00636] SEQ ID NO:420 is the amino acid sequence of the GITR agonist 7A10 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00637] SEQ ID NO:421 is the amino acid sequence of the GITR agonist 7A10 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00638] SEQ ID NO:422 is the amino acid sequence of the GITR agonist 7A10 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00639] SEQ ID NO:423 is the amino acid sequence of the GITR agonist 7A10 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00640] SEQ ID NO:424 is the amino acid sequence of the GITR agonist 7A10 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00641] SEQ ID NO:425 is the amino acid sequence of the GITR agonist 7A10 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00642] SEQ ID NO:426 is the amino acid sequence of the GITR agonist 7A10 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00643] SEQ ID NO:427 is the amino acid sequence of the GITR agonist 7A10 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00644] SEQ ID NO:428 is the amino acid sequence of the GITR agonist 7A10 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00645] SEQ ID NO:429 is the amino acid sequence of the GITR agonist 7A10 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00646] SEQ ID NO:430 is the amino acid sequence of the GITR agonist 9H6 heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00647] SEQ ID NO:431 is the amino acid sequence of the GITR agonist 9H6 light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00648] SEQ ID NO:432 is the amino acid sequence of the GITR agonist 9H6 variable heavy chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00649] SEQ ID NO:433 is the amino acid sequence of the GITR agonist 9H6 variable light chain from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00650] SEQ ID NO:434 is the amino acid sequence of the GITR agonist 9H6 heavy chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00651] SEQ ID NO:435 is the amino acid sequence of the GITR agonist 9H6 heavy chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00652] SEQ ID NO:436 is the amino acid sequence of the GITR agonist 9H6 heavy chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00653] SEQ ID NO:437 is the amino acid sequence of the GITR agonist 9H6 light chain CDR1 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00654] SEQ ID NO:438 is the amino acid sequence of the GITR agonist 9H6 light chain CDR2 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00655] SEQ ID NO:439 is the amino acid sequence of the GITR agonist 9H6 light chain CDR3 from U.S. Patent Application Publication No. US 2015/0064204 A1.

[00656] SEQ ID NO:440 is an GITR ligand (GITRL) amino acid sequence.

[00657] SEQ ID NO:441 is a soluble portion of GITRL polypeptide.

[00658] SEQ ID NO:442 is the amino acid sequence of human HVEM (CD270).

[00659] SEQ ID NO:443 is a HVEM ligand (LIGHT) amino acid sequence.

[00660] SEQ ID NO:444 is a soluble portion of LIGHT polypeptide.

[00661] SEQ ID NO:445 is an alternative soluble portion of LIGHT polypeptide.

[00662] SEQ ID NO:446 is an alternative soluble portion of LIGHT polypeptide.

[00663] SEQ ID NO:447 is the amino acid sequence of human CD95 isoform 1.

[00664] SEQ ID NO:448 is the amino acid sequence of human CD95 isoform 2.

[00665] SEQ ID NO:449 is the amino acid sequence of human CD95 isoform 3.

[00666] SEQ ID NO:450 is the amino acid sequence of human CD95 isoform 4.

[00667] SEQ ID NO:451 is the heavy chain variable region (V_H) for the CD95 agonist monoclonal antibody E09.

[00668] SEQ ID NO:452 is the light chain variable region (V_L) for the CD95 agonist monoclonal antibody E09.

[00669] SEQ ID NO:453 is the heavy chain CDRl for the CD95 agonist monoclonal antibody E09.

[00670] SEQ ID NO:454 is the heavy chain CDR2 for the CD95 agonist monoclonal antibody E09.

[00671] SEQ ID NO:455 is the heavy chain CDR3 for the CD95 agonist monoclonal antibody E09.

[00672] SEQ ID NO:456 is the light chain CDR1 for the CD95 agonist monoclonal antibody E09.

[00673] SEQ ID NO:457 is the light chain CDR2 for the CD95 agonist monoclonal antibody E09.

[00674] SEQ ID NO:458 is the light chain CDR3 for the CD95 agonist monoclonal antibody E09.

[00675] SEQ ID NO:459 is a CD95 ligand (CD95L) amino acid sequence.

[00676] SEQ ID NO:460 is a soluble portion of CD95L polypeptide.

[00677] SEQ ID NO:461 is an alternative soluble portion of CD95L polypeptide.

[00678] SEQ ID NO:462 is an alternative soluble portion of CD95L polypeptide.

[00679] SEQ ID NO:463 is the heavy chain amino acid sequence of the PD-1 inhibitor nivolumab.

[00680] SEQ ID NO:464 is the light chain amino acid sequence of the PD-1 inhibitor nivolumab.

[00681] SEQ ID NO:465 is the heavy chain variable region (V_H) amino acid sequence of the PD-1 inhibitor nivolumab.

[00682] SEQ ID NO:466 is the light chain variable region (V_L) amino acid sequence of the PD-1 inhibitor nivolumab.

[00683] SEQ ID NO:467 is the heavy chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab.

[00684] SEQ ID NO:468 is the heavy chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab.

[00685] SEQ ID NO:469 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab.

[00686] SEQ ID NO:470 is the light chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab.

[00687] SEQ ID NO:471 is the light chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab.

[00688] SEQ ID NO:472 is the light chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab.

[00689] SEQ ID NO:473 is the heavy chain amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00690] SEQ ID NO:474 is the light chain amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00691] SEQ ID NO:475 is the heavy chain variable region (V_H) amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00692] SEQ ID NO:476 is the light chain variable region (V_L) amino acid sequence of the

PD-1 inhibitor pembrolizumab.

[00693] SEQ ID NO:477 is the heavy chain CDR1 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00694] SEQ ID NO:478 is the heavy chain CDR2 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00695] SEQ ID NO:479 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00696] SEQ ID NO:480 is the light chain CDR1 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00697] SEQ ID NO:481 is the light chain CDR2 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00698] SEQ ID NO:482 is the light chain CDR3 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00699] SEQ ID NO:483 is the heavy chain amino acid sequence of the PD-L1 inhibitor durvalumab.

[00700] SEQ ID NO:484 is the light chain amino acid sequence of the PD-L1 inhibitor durvalumab.

[00701] SEQ ID NO:485 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor durvalumab.

[00702] SEQ ID NO:486 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor durvalumab.

[00703] SEQ ID NO:487 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00704] SEQ ID NO:488 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00705] SEQ ID NO:489 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00706] SEQ ID NO:490 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00707] SEQ ID NO:491 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00708] SEQ ID NO:492 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00709] SEQ ID NO:493 is the heavy chain amino acid sequence of the PD-L1 inhibitor avelumab.

[00710] SEQ ID NO:494 is the light chain amino acid sequence of the PD-L1 inhibitor avelumab.

[00711] SEQ ID NO:495 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor avelumab.

[00712] SEQ ID NO:496 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor avelumab.

[00713] SEQ ID NO:497 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor avelumab.

[00714] SEQ ID NO:498 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor avelumab.

[00715] SEQ ID NO:499 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor avelumab.

[00716] SEQ ID NO:500 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor avelumab.

[00717] SEQ ID NO:501 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor avelumab.

[00718] SEQ ID NO:502 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor avelumab.

[00719] SEQ ID NO:503 is the heavy chain amino acid sequence of the PD-L1 inhibitor

atezolizumab.

[00720] SEQ ID NO:504 is the light chain amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00721] SEQ ID NO:505 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00722] SEQ ID NO:506 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00723] SEQ ID NO:507 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00724] SEQ ID NO:508 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00725] SEQ ID NO:509 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00726] SEQ ID NO:510 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00727] SEQ ID NO:511 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00728] SEQ ID NO:512 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor atezolizumab.

DETAILED DESCRIPTION OF THE INVENTION

[00729] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

Definitions

[00730] The terms “co-administration,” “co-administering,” “administered in combination with,” “administering in combination with,” “simultaneous,” and “concurrent,” as used herein, encompass administration of two or more active pharmaceutical ingredients (in a preferred embodiment of the present invention, for example, at least one TNFRSF agonist and a plurality

of TILs) to a subject so that both active pharmaceutical ingredients and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more active pharmaceutical ingredients are present. Simultaneous administration in separate compositions and administration in a composition in which both agents are present are preferred.

[00731] The term "rapid expansion" means an increase in the number of antigen-specific TILs of at least about 3-fold (or 4-, 5-, 6-, 7-, 8-, or 9-fold) over a period of a week, more preferably at least about 10-fold (or 20-, 30-, 40-, 50-, 60-, 70-, 80-, or 90-fold) over a period of a week, or most preferably at least about 100-fold over a period of a week. A number of rapid expansion protocols are described herein.

[00732] By "tumor infiltrating lymphocytes" or "TILs" herein is meant a population of cells originally obtained as white blood cells that have left the bloodstream of a subject and migrated into a tumor. TILs include, but are not limited to, $CD8^+$ cytotoxic T cells (lymphocytes), Th1 and Th17 $CD4^+$ T cells, natural killer cells, dendritic cells and M1 macrophages. TILs include both primary and secondary TILs. "Primary TILs" are those that are obtained from patient tissue samples as outlined herein (sometimes referred to as "freshly harvested"), and "secondary TILs" are any TIL cell populations that have been expanded or proliferated as discussed herein, including, but not limited to bulk TILs and expanded TILs ("REP TILs" or "post-REP TILs").

[00733] By "population of cells" (including TILs) herein is meant a number of cells that share common traits. In general, populations generally range from 1 X 10^6 to 1 X 10^{10} in number, with different TIL populations comprising different numbers. For example, initial growth of primary TILs in the presence of IL-2 results in a population of bulk TILs of roughly 1×10^8 cells. REP expansion is generally done to provide populations of 1.5×10^9 to 1.5×10^{10} cells for infusion.

[00734] The term "central memory T cell" refers to a subset of T cells that in the human are CD45R0+ and constitutively express CCR7 ($CCR7^{hi}$) and CD62L ($CD62^{hi}$). The surface phenotype of central memory T cells also includes TCR, CD3, CD127 (IL-7R), and IL-15R. Transcription factors for central memory T cells include BCL-6, BCL-6B, MBD2, and BMI1. Central memory T cells primarily secret IL-2 and CD40L as effector molecules after

TCR triggering. Central memory T cells are predominant in the CD4 compartment in blood, and in the human are proportionally enriched in lymph nodes and tonsils.

[00735] The term "anti-CD3 antibody" refers to an antibody or variant thereof, *e.g.*, a monoclonal antibody and including human, humanized, chimeric or murine antibodies which are directed against the CD3 receptor in the T cell antigen receptor of mature T cells. Anti-CD3 antibodies include OKT-3, also known as muromonab. Anti-CD3 antibodies also include the UHCT1 clone, also known as T3 and CD3ε. Other anti-CD3 antibodies include, for example, otelixizumab, teplizumab, and visilizumab.

[00736] The term "OKT-3" (also referred to herein as "OKT3") refers to a monoclonal antibody or biosimilar or variant thereof, including human, humanized, chimeric, or murine antibodies, directed against the CD3 receptor in the T cell antigen receptor of mature T cells, and includes commercially-available forms such as OKT-3 (30 ng/mL, MACS GMP CD3 pure, Miltenyi Biotech, Inc., San Diego, CA, USA) and muromonab or variants, conservative amino acid substitutions, glycoforms, or biosimilars thereof. The amino acid sequences of the heavy and light chains of muromonab are given in Table 1 (SEQ ID NO:1 and SEQ ID NO:2).

TABLE 1. Amino acid sequences of muromonab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:1 Muromonab heavy chain	QVQLQQSGAE LARPGASVKM SCKASGYTFT RYTMHWVKQR PGQGLEWIGY INPSRGYTNY NQKFKDKATL TTDKSSSTAY MQLSSLTSED SAVYYCARYY DDHYCLDYWG QGTTLTVSSA KTTAPSVYPL APVCGGTTGS SVTLGCLVKG YFPEPVTLTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVT SSTWPSQSIT CNVAHPASST KVDKKIEPRP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 240 300 360 420 450
SEQ ID NO:2 Muromonab light chain	QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMNWYQQKSG TSPKRWIYDT SKLASGVPAH FRGSGSGTSY SLTISGMEAE DAATYYCQQW SSNPFTFGSG TKLEINRADT APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS TSPIVKSFNR NEC	60 120 180 213

[00737] The term "IL-2" (also referred to herein as "IL2") refers to the T cell growth factor known as interleukin-2, and includes all forms of IL-2 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-2 is described, *e.g.*, in Nelson, *J. Immunol.* **2004,** *172,* 3983-88 and Malek, *Annu. Rev. Immunol.* **2008,** *26,* 453-79, the disclosures of which are incorporated by reference herein. The amino acid sequence of recombinant human IL-2 suitable for use in the invention is given in Table 2 (SEQ

ID NO:3). For example, the term IL-2 encompasses human, recombinant forms of IL-2 such as aldesleukin (PROLEUKIN, available commercially from multiple suppliers in 22 million IU per single use vials), as well as the form of recombinant IL-2 commercially supplied by CellGenix, Inc., Portsmouth, NH, USA (CELLGRO GMP) or ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-209-b) and other commercial equivalents from other vendors. Aldesleukin (des-alanyl-1, serine-125 human IL-2) is a nonglycosylated human recombinant form of IL-2 with a molecular weight of approximately 15 kDa. The amino acid sequence of aldesleukin suitable for use in the invention is given in Table 2 (SEQ ID NO:4). The term IL-2 also encompasses pegylated forms of IL-2, as described herein, including the pegylated IL2 prodrug NKTR-214, available from Nektar Therapeutics, South San Francisco, CA, USA. NKTR-214 and pegylated IL-2 suitable for use in the invention is described in U.S. Patent Application Publication No. US 2014/0328791 A1 and International Patent Application Publication No. WO 2012/065086 Al, the disclosures of which are incorporated by reference herein. Alternative forms of conjugated IL-2 suitable for use in the invention are described in U.S. Patent Nos. 4,766,106, 5,206,344, 5,089,261 and 4902,502, the disclosures of which are incorporated by reference herein. Formulations of IL-2 suitable for use in the invention are described in U.S. Patent No. 6,706,289, the disclosure of which is incorporated by reference herein.

TABLE 2. Amino acid sequences of interleukins.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:3 recombinant human IL-2 (rhIL-2)	MAPTSSSTKK TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEV LNLAQSKNFH LRPRDLISNI NVIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFCQSII STLT	60 120 134
SEQ ID NO:4 Aldesleukin	PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFYMPKKAT ELKHLQCLEE ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT	60 120 132
SEQ ID NO:5 recombinant human IL-4 (rhIL-4)	MHKCDITLQE IIKTLNSLTE QKTLCTELTV TDIFAASKNT TEKETFCRAA TVLRQFYSHH EKDTRCLGAT AQQFHRHKQL IRFLKRLDRN LWGLAGLNSC PVKEANQSTL ENFLERLKTI MREKYSKCSS	60 120 130
SEQ ID NO:6 recombinant human IL-7 (rhIL-7)	MDCDIEGKDG KQYESVLMVS IDQLLDSMKE IGSNCLNNEF NFFKRHICDA NKEGMFLFRA ARKLRQFLKM NSTGDFDLHL LKVSEGTTIL LNCTGQVKGR KPAALGEAQP TKSLEENKSL KEQKKLNDLC FLKRLLQEIK TCWNKILMGT KEH	60 120 153
SEQ ID NO:7 recombinant human IL-15 (rhIL-15)	MNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV ISLESGDASI HDTVENLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM FINTS	60 115
SEQ ID NO:8 recombinant human IL-21 (rhIL-21)	MQDRHMIRMR QLIDIVDQLK NYVNDLVPEF LPAPEDVETN CEWSAFSCFQ KAQLKSANTG NNERIINVSI KKLKRKPPST NAGRRQKHRL TCPSCDSYEK KPPKEFLERF KSLLQKMIHQ HLSSRTHGSE DS	60 120 132

[00738] The term "IL-4" (also referred to herein as "IL4") refers to the cytokine known as interleukin 4, which is produced by Th2 T cells and by eosinophils, basophils, and mast cells. IL-4 regulates the differentiation of naïve helper T cells (Th0 cells) to Th2 T cells. Steinke and Borish, *Respir. Res.* **2001,** *2,* 66-70. Upon activation by IL-4, Th2 T cells subsequently produce additional IL-4 in a positive feedback loop. IL-4 also stimulates B cell proliferation and class II MHC expression, and induces class switching to IgE and IgG_1 expression from B cells. Recombinant human IL-4 suitable for use in the invention is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-211) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-15 recombinant protein, Cat. No. Gibco CTP0043). The amino acid sequence of recombinant human IL-4 suitable for use in the invention is given in Table 2 (SEQ ID NO:5).

[00739] The term "IL-7" (also referred to herein as "IL7") refers to a glycosylated tissue-derived cytokine known as interleukin 7, which may be obtained from stromal and epithelial cells, as well as from dendritic cells. Fry and Mackall, *Blood* **2002,** *99,* 3892-904. IL-7 can stimulate the development of T cells. IL-7 binds to the IL-7 receptor, a heterodimer consisting of IIL-7 receptor alpha and common gamma chain receptor, which in a series of signals important for T cell development within the thymus and survival within the periphery. Recombinant human IL-7 suitable for use in the invention is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-254) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-7 recombinant protein, Cat. No. Gibco PHC0071). The amino acid sequence of recombinant human IL-7 suitable for use in the invention is given in Table 2 (SEQ ID NO:6).

[00740] The term "IL-15" (also referred to herein as "IL15") refers to the T cell growth factor known as interleukin-15, and includes all forms of IL-15 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-15 is described, *e.g.*, in Fehniger and Caligiuri, *Blood* **2001,** *97,* 14-32, the disclosure of which is incorporated by reference herein. IL-15 shares β and γ signaling receptor subunits with IL-2. Recombinant human IL-15 is a single, non-glycosylated polypeptide chain containing 114 amino acids (and an N-terminal methionine) with a molecular mass of 12.8 kDa. Recombinant human IL-15 is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-230-b) and ThermoFisher Scientific, Inc.,

Waltham, MA, USA (human IL-15 recombinant protein, Cat. No. 34-8159-82). The amino acid sequence of recombinant human IL-15 suitable for use in the invention is given in Table 2 (SEQ ID NO:7).

[00741] The term "IL-21" (also referred to herein as "IL21") refers to the pleiotropic cytokine protein known as interleukin-21, and includes all forms of IL-21 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-21 is described, *e.g.*, in Spolski and Leonard, *Nat. Rev. Drug. Disc.* **2014,** *13,* 379-95, the disclosure of which is incorporated by reference herein. IL-21 is primarily produced by natural killer T cells and activated human $CD4^+$ T cells. Recombinant human IL-21 is a single, non-glycosylated polypeptide chain containing 132 amino acids with a molecular mass of 15.4 kDa. Recombinant human IL-21 is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-408-b) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-21 recombinant protein, Cat. No. 14-8219-80). The amino acid sequence of recombinant human IL-21 suitable for use in the invention is given in Table 2 (SEQ ID NO:8).

[00742] The term "*in vivo*" refers to an event that takes place in a mammalian subject's body.

[00743] The term "*ex vivo*" refers to an event that takes place outside of a mammalian subject's body, in an artificial environment.

[00744] The term "*in vitro*" refers to an event that takes places in a test system. *In vitro* assays encompass cell-based assays in which alive or dead cells may be are employed and may also encompass a cell-free assay in which no intact cells are employed.

[00745] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, or the manner of administration. The term also applies to a dose that will induce a particular response in target cells (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in

combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[00746] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[00747] The terms "QD," "qd," or "q.d." mean *quaque die*, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean *bis in die*, twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean *ter in die*, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean *quater in die*, four times a day, or four times daily.

[00748] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Preferred inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Preferred organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve hydrogen transfer between the cocrystal and the drug, and instead

involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

[00749] The terms "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" are intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions, processes and methods.

[00750] The term "antigen" refers to a substance that induces an immune response. In some embodiments, an antigen is a molecule capable of being bound by an antibody or a T cell receptor (TCR) if presented by major histocompatibility complex (MHC) molecules. The term "antigen", as used herein, also encompasses T cell epitopes. An antigen is additionally capable of being recognized by the immune sytem. In some embodiments, an antigen is capable of inducing a humoral immune response or a cellular immune response leading to the activation of B lymphocytes and/or T lynphocytes. In some cases, this may require that the antigen contains or is linked to a Th cell epitope. An antigen can also have one or more epitopes (e.g., B- and T-epitopes). In some embodiments, an antigen will preferably react, typically in a highly specific and selective manner, with its corresponding antibody or TCR and not with the multitude of other antibodies or TCRs which may be induced by ther antigens.

[00751] The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is

comprised of one domain, C_L. The V_H and V_L regions of an antibody may be further subdivided into regions of hypervariability, which are referred to as complementarity determining regions (CDR) or hypervariable regions (HVR), and which can be interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen epitope or epitopes. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

[00752] The terms "monoclonal antibody," "mAb," "monoclonal antibody composition," or their plural forms refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies specific to TNFRSF receptors can be made using knowledge and skill in the art of injecting test subjects with suitable antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies will be described in more detail below.

[00753] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1 domains; (ii) a F(ab′)2 fragment, a bivalent fragment comprising two Fab fragments linked

by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward, *et al., Nature,* **1989,** *341,* 544-546), which may consist of a V_H or a V_L domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain Fv (scFv); see, *e.g.*, Bird, *et al.*, *Science* **1988,** *242,* 423-426; and Huston, *et al.*, *Proc. Natl. Acad. Sci. USA* **1988,** *85,* 5879-5883). Such scFv antibodies are also intended to be encompassed within the terms "antigen-binding portion" or "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[00754] The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). The term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00755] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In an embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[00756] The term "recombinant human antibody", as used herein, includes all human

antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (such as a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be 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 V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[00757] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

[00758] The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[00759] The term "human antibody derivatives" refers to any modified form of the human antibody, including a conjugate of the antibody and another active pharmaceutical ingredient or antibody. The terms "conjugate," "antibody-drug conjugate", "ADC," or "immunoconjugate" refers to an antibody, or a fragment thereof, conjugated to another therapeutic moiety, which can be conjugated to antibodies described herein using methods available in the art.

[00760] The terms "humanized antibody," "humanized antibodies," and "humanized" are intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Humanized forms of non-human (for example, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the

most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a 15 hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones, *et al.*, *Nature* **1986,** *321,* 522-525; Riechmann, *et al.*, *Nature* **1988,** *332,* 323-329; and Presta, *Curr. Op. Struct. Biol.* **1992,** *2,* 593-596. The TNFRSF agonists described herein may also be modified to employ any Fc variant which is known to impart an improvement (*e.g.*, reduction) in effector function and/or FcR binding. The Fc variants may include, for example, any one of the amino acid substitutions disclosed in International Patent Application Publication Nos. WO 1988/07089 A1, WO 1996/14339 A1, WO 1998/05787 A1, WO 1998/23289 A1, WO 1999/51642 A1, WO 99/58572 A1, WO 2000/09560 A2, WO 2000/32767 A1, WO 2000/42072 A2, WO 2002/44215 A2, WO 2002/060919 A2, WO 2003/074569 A2, WO 2004/016750 A2, WO 2004/029207 A2, WO 2004/035752 A2, WO 2004/063351 A2, WO 2004/074455 A2, WO 2004/099249 A2, WO 2005/040217 A2, WO 2005/070963 A1, WO 2005/077981 A2, WO 2005/092925 A2, WO 2005/123780 A2, WO 2006/019447 A1, WO 2006/047350 A2, and WO 2006/085967 A2; and U.S. Patent Nos. 5,648,260; 5,739,277; 5,834,250; 5,869,046; 6,096,871; 6,121,022; 6,194,551; 6,242,195; 6,277,375; 6,528,624; 6,538,124; 6,737,056; 6,821,505; 6,998,253; and 7,083,784; the disclosures of which are incorporated by reference herein.

[00761] The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

[00762] A "diabody" is a small antibody fragment with two antigen-binding sites. The fragments comprises a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H-V_L or V_L-V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, European Patent No. EP 404,097, International Patent Publication No. WO 93/11161; and Bolliger, *et al.*, *Proc. Natl. Acad. Sci. USA* **1993,** *90,* 6444-6448.

[00763] The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8−/− cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/0110704 or Yamane-Ohnuki, *et al., Biotechnol. Bioeng.*, **2004,** *87,* 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by

reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, *et al., J. Biol. Chem.* **2002,** *277,* 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana, *et al.*, *Nat. Biotech.* **1999,** *17*, 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, *et al.*, *Biochem.* **1975,** *14,* 5516-5523.

[00764] "Pegylation" refers to a modified antibody or fusion protein, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C_1-C_{10}) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The protein or antibody to be pegylated may be an aglycosylated protein or antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention, as described for example in European Patent Nos. EP 0154316 and EP 0401384 and U.S. Patent No. 5,824,778, the disclosures of each of which are incorporated by reference herein.

[00765] The terms "fusion protein" or "fusion polypeptide" refer to proteins that combine the properties of two or more individual proteins. Such proteins have at least two heterologous polypeptides covalently linked either directly or via an amino acid linker. The polypeptides forming the fusion protein are typically linked C-terminus to N-terminus, although they can also

be linked C-terminus to C-terminus, N-terminus to N-terminus, or N-terminus to C-terminus. The polypeptides of the fusion protein can be in any order and may include more than one of either or both of the constituent polypeptides. The term encompasses conservatively modified variants, polymorphic variants, alleles, mutants, subsequences, interspecies homologs, and immunogenic fragments of the antigens that make up the fusion protein. Fusion proteins of the disclosure can also comprise additional copies of a component antigen or immunogenic fragment thereof. The fusion protein may contain one or more binding domains linked together and further linked to an Fc domain, such as an IgG Fc domain. Fusion proteins may be further linked together to mimic a monoclonal antibody and provide six or more binding domains. Fusion proteins may be produced by recombinant methods as is known in the art. Preparation of fusion proteins are known in the art and are described, *e.g.*, in International Patent Application Publication Nos. WO 1995/027735 A1, WO 2005/103077 A1, WO 2008/025516 A1, WO 2009/007120 A1, WO 2010/003766 A1, WO 2010/010051 A1, WO 2010/078966 A1, U.S. Patent Application Publication Nos. US 2015/0125419 A1 and US 2016/0272695 A1, and U.S. Patent No. 8,921,519, the disclosures of each of which are incorporated by reference herein.

[00766] The term "heterologous" when used with reference to portions of a nucleic acid or protein indicates that the nucleic acid or protein comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, *e.g.*, a promoter from one source and a coding region from another source, or coding regions from different sources. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[00767] The term "conservative amino acid substitutions" means amino acid sequence modifications which do not abrogate the binding of an antibody or fusion protein to the antigen. Conservative amino acid substitutions include the substitution of an amino acid in one class by an amino acid of the same class, where a class is defined by common physicochemical amino acid side chain properties and high substitution frequencies in homologous proteins found in nature, as determined, for example, by a standard Dayhoff frequency exchange matrix or BLOSUM matrix. Six general classes of amino acid side chains have been categorized and include: Class I (Cys); Class II (Ser, Thr, Pro, Ala, Gly); Class III (Asn, Asp, Gln, Glu); Class IV

(His, Arg, Lys); Class V (Ile, Leu, Val, Met); and Class VI (Phe, Tyr, Trp). For example, substitution of an Asp for another class III residue such as Asn, Gln, or Glu, is a conservative substitution. Thus, a predicted nonessential amino acid residue in an antibody is preferably replaced with another amino acid residue from the same class. Methods of identifying amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, *e.g.*, Brummell, *et al.*, *Biochemistry* **1993,** *32,* 1180-1187; Kobayashi, *et al.*, *Protein Eng.* **1999,** *12,* 879-884 (1999); and Burks, *et al.*, *Proc. Natl. Acad. Sci. USA* **1997,** *94,* 412-417.

[00768] The terms "sequence identity," "percent identity," and "sequence percent identity" (or synonyms thereof, *e.g.*, "99% identical") in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences. Suitable programs to determine percent sequence identity include for example the BLAST suite of programs available from the U.S. Government's National Center for Biotechnology Information BLAST web site. Comparisons between two sequences can be carried using either the BLASTN or BLASTP algorithm. BLASTN is used to compare nucleic acid sequences, while BLASTP is used to compare amino acid sequences. ALIGN, ALIGN-2 (Genentech, South San Francisco, California) or MegAlign, available from DNASTAR, are additional publicly available software programs that can be used to align sequences. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain embodiments, the default parameters of the alignment software are used.

[00769] Certain embodiments of the present invention comprise a variant of an antibody or fusion protein. As used herein, the term "variant" encompasses but is not limited to antibodies or fusion proteins which comprise an amino acid sequence which differs from the amino acid sequence of a reference antibody by way of one or more substitutions, deletions and/or additions at certain positions within or adjacent to the amino acid sequence of the reference antibody. The variant may comprise one or more conservative substitutions in its amino acid sequence as compared to the amino acid sequence of a reference antibody. Conservative substitutions may

involve, *e.g.*, the substitution of similarly charged or uncharged amino acids. The variant retains the ability to specifically bind to the antigen of the reference antibody.

[00770] Nucleic acid sequences implicitly encompass conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues. Batzer, *et al.*, *Nucleic Acid Res.* **1991,** *19,* 5081; Ohtsuka, *et al.*, *J. Biol. Chem.* **1985,** *260,* 2605-2608; Rossolini, *et al.*, *Mol. Cell. Probes* **1994,** *8,* 91-98. The term nucleic acid is used interchangeably with cDNA, mRNA, oligonucleotide, and polynucleotide.

[00771] The term "biosimilar" means a biological product, including a monoclonal antibody or fusion protein, that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Furthermore, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use by the European Medicines Agency. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies. Biological products or biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. For example, if the reference monoclonal antibody is rituximab, an biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab is a "biosimilar to" rituximab or is a "biosimilar thereof" of rituximab. In Europe, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use by the European Medicines Agency (EMA). The relevant legal basis for similar biological applications in Europe is Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended and therefore in Europe, the biosimilar may be authorised, approved for authorisation or subject of an application for authorisation under Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC. The already authorized original biological medicinal product may be referred to as

a "reference medicinal product" in Europe. Some of the requirements for a product to be considered a biosimilar are outlined in the CHMP Guideline on Similar Biological Medicinal Products. In addition, product specific guidelines, including guidelines relating to monoclonal antibody biosimilars, are provided on a product-by-product basis by the EMA and published on its website. A biosimilar as described herein may be similar to the reference medicinal product by way of quality characteristics, biological activity, mechanism of action, safety profiles and/or efficacy. In addition, the biosimilar may be used or be intended for use to treat the same conditions as the reference medicinal product. Thus, a biosimilar as described herein may be deemed to have similar or highly similar quality characteristics to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar biological activity to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have a similar or highly similar safety profile to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar efficacy to a reference medicinal product. As described herein, a biosimilar in Europe is compared to a reference medicinal product which has been authorised by the EMA. However, in some instances, the biosimilar may be compared to a biological medicinal product which has been authorised outside the European Economic Area (a non-EEA authorised "comparator") in certain studies. Such studies include for example certain clinical and in vivo non-clinical studies. As used herein, the term "biosimilar" also relates to a biological medicinal product which has been or may be compared to a non-EEA authorised comparator. Certain biosimilars are proteins such as antibodies, antibody fragments (for example, antigen binding portions) and fusion proteins. A protein biosimilar may have an amino acid sequence that has minor modifications in the amino acid structure (including for example deletions, additions, and/or substitutions of amino acids) which do not significantly affect the function of the polypeptide. The biosimilar may comprise an amino acid sequence having a sequence identity of 97% or greater to the amino acid sequence of its reference medicinal product, e.g., 97%, 98%, 99% or 100%. The biosimilar may comprise one or more post-translational modifications, for example, although not limited to, glycosylation, oxidation, deamidation, and/or truncation which is/are different to the post-translational modifications of the reference medicinal product, provided that the differences do not result in a change in safety and/or efficacy of the medicinal product. The biosimilar may have an identical or different

glycosylation pattern to the reference medicinal product. Particularly, although not exclusively, the biosimilar may have a different glycosylation pattern if the differences address or are intended to address safety concerns associated with the reference medicinal product. Additionally, the biosimilar may deviate from the reference medicinal product in for example its strength, pharmaceutical form, formulation, excipients and/or presentation, providing safety and efficacy of the medicinal product is not compromised. In some embodiments, a biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product. The biosimilar may comprise differences in for example pharmacokinetic (PK) and/or pharmacodynamic (PD) profiles as compared to the reference medicinal product but is still deemed sufficiently similar to the reference medicinal product as to be authorised or considered suitable for authorisation. In certain circumstances, the biosimilar exhibits different binding characteristics as compared to the reference medicinal product, wherein the different binding characteristics are considered by a Regulatory Authority such as the EMA not to be a barrier for authorisation as a similar biological product. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies.

[00772] As used herein, the term "4-1BB agonist" may refer to any antibody or protein that specifically binds to 4-1BB (CD137) antigen. By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to non-4-1BB molecules. The 4-1BB agonist may be any 4-1BB agonist known in the art. In particular, it is one of the 4-1BB agonists described in more detail herein. An isolated binding molecule that specifically binds 4-1BB may, however, have cross-reactivity to 4-1BB molecules from other species. 4-1BB agonistic antibodies and proteins may also specifically bind to *e.g.*, human 4-1BB (h4-1BB or hCD137) on T cells.

[00773] As used herein, the term "OX40 agonist" may refer to any antibody or protein that specifically binds to OX40 (CD134) antigen. By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to non-OX40 molecules. The OX40 agonist may be any OX40 agonist known in the art. In particular, it is one of the OX40 agonists described in more detail herein. An isolated binding molecule that specifically binds OX40 may, however, have cross-reactivity to OX40 molecules from other species. OX40 agonistic antibodies and proteins may also specifically bind to *e.g.*, human OX40 (hOX40 or hCD134) on

T cells.

[00774] As used herein, the term "CD27 agonist" may refer to any antibody or protein that specifically binds to CD27 antigen. By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to non-CD27 molecules. The CD27 agonist may be any CD27 agonist known in the art. In particular, it is one of the CD27 agonists described in more detail herein. An isolated binding molecule that specifically binds CD27 may, however, have cross-reactivity to CD27 molecules from other species. CD27 agonistic antibodies and proteins may also specifically bind to *e.g.*, human CD27 (hCD27) on T cells.

[00775] As used herein, the term "GITR agonist" includes molecules that contain at least one antigen binding site that specifically binds to GITR (CD357). By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to non-GITR molecules. The GITR agonist may be any GITR agonist known in the art. In particular, it is one of the GITR agonists described in more detail herein. An isolated binding molecule that specifically binds GITR may, however, have cross-reactivity to GITR molecules from other species. GITR agonistic antibodies and proteins may also specifically bind to *e.g.*, human GITR (hGITR) on T cells and dendritic cells.

[00776] As used herein, the term "HVEM agonist" includes molecules that contain at least one antigen binding site that specifically binds to HVEM (CD270). By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to non-HVEM molecules. The HVEM agonist may be any HVEM agonist known in the art. In particular, it is one of the HVEM agonists described in more detail herein. An isolated binding molecule that specifically binds HVEM may, however, have cross-reactivity to HVEM molecules from other species. HVEM agonistic antibodies and proteins may also specifically bind to *e.g.*, human HVEM (hHVEM) on T cells.

[00777] The term "hematological malignancy" refers to mammalian cancers and tumors of the hematopoietic and lymphoid tissues, including but not limited to tissues of the blood, bone marrow, lymph nodes, and lymphatic system. Hematological malignancies are also referred to as "liquid tumors." Hematological malignancies include, but are not limited to, acute lymphoblastic leukemia (ALL), chronic lymphocytic lymphoma (CLL), small lymphocytic lymphoma (SLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML),

acute monocytic leukemia (AMoL), Hodgkin's lymphoma, and non-Hodgkin's lymphomas. The term "B cell hematological malignancy" refers to hematological malignancies that affect B cells.

[00778] The term "solid tumor" refers to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign or malignant. The term "solid tumor cancer" refers to malignant, neoplastic, or cancerous solid tumors. Solid tumor cancers include, but are not limited to, sarcomas, carcinomas, and lymphomas, such as cancers of the lung, breast, prostate, colon, rectum, and bladder. The tissue structure of solid tumors includes interdependent tissue compartments including the parenchyma (cancer cells) and the supporting stromal cells in which the cancer cells are dispersed and which may provide a supporting microenvironment.

[00779] The term "microenvironment," as used herein, may refer to the solid or hematological tumor microenvironment as a whole or to an individual subset of cells within the microenvironment. The tumor microenvironment, as used herein, refers to a complex mixture of "cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dominant metastases to thrive," as described in Swartz, *et al.*, *Cancer Res.*, **2012**, *72*, 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment.

[00780] For the avoidance of doubt, it is intended herein that particular features (for example integers, characteristics, values, uses, diseases, formulae, compounds or groups) described in conjunction with a particular aspect, embodiment or example of the invention are to be understood as applicable to any other aspect, embodiment or example described herein unless incompatible therewith. Thus such features may be used where appropriate in conjunction with any of the definition, claims or embodiments defined herein. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of the features and/or steps are mutually exclusive. The invention is not restricted to any details of any disclosed embodiments. The invention extends to any novel one, or novel combination, of the features disclosed in this specification (including any

accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00781] The terms "about" and "approximately" mean within a statistically meaningful range of a value. Such a range can be within an order of magnitude, preferably within 50%, more preferably within 20%, more preferably still within 10%, and even more preferably within 5% of a given value or range. The allowable variation encompassed by the terms "about" or "approximately" depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art. Moreover, as used herein, the terms "about" and "approximately" mean that dimensions, sizes, formulations, parameters, shapes and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, a dimension, size, formulation, parameter, shape or other quantity or characteristic is "about" or "approximate" whether or not expressly stated to be such. It is noted that embodiments of very different sizes, shapes and dimensions may employ the described arrangements.

[00782] The transitional terms "comprising," "consisting essentially of," and "consisting of," when used in the appended claims, in original and amended form, define the claim scope with respect to what unrecited additional claim elements or steps, if any, are excluded from the scope of the claim(s). The term "comprising" is intended to be inclusive or open-ended and does not exclude any additional, unrecited element, method, step or material. The term "consisting of" excludes any element, step or material other than those specified in the claim and, in the latter instance, impurities ordinary associated with the specified material(s). The term "consisting essentially of" limits the scope of a claim to the specified elements, steps or material(s) and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. All compositions, methods, and kits described herein that embody the present invention can, in alternate embodiments, be more specifically defined by any of the transitional terms "comprising," "consisting essentially of," and "consisting of."

4-1BB (CD137) Agonists

[00783] In an embodiment, the TNFRSF agonist is a 4-1BB (CD137) agonist. The 4-1BB agonist may be any 4-1BB binding molecule known in the art. The 4-1BB binding molecule

may be a monoclonal antibody or fusion protein capable of binding to human or mammalian 4-1BB. The 4-1BB agonists or 4-1BB binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The 4-1BB agonist or 4-1BB binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to 4-1BB. In an embodiment, the 4-1BB agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the 4-1BB agonist is an antigen binding protein that is a humanized antibody. In some embodiments, 4-1BB agonists for use in the presently disclosed methods and compositions include anti-4-1BB antibodies, human anti-4-1BB antibodies, mouse anti-4-1BB antibodies, mammalian anti-4-1BB antibodies, monoclonal anti-4-1BB antibodies, polyclonal anti-4-1BB antibodies, chimeric anti-4-1BB antibodies, anti-4-1BB adnectins, anti-4-1BB domain antibodies, single chain anti-4-1BB fragments, heavy chain anti-4-1BB fragments, light chain anti-4-1BB fragments, anti-4-1BB fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. Agonistic anti-4-1BB antibodies are known to induce strong immune responses. Lee, *et al.*, *PLOS One* **2013**, *8,* e69677. In a preferred embodiment, the 4-1BB agonist is an agonistic, anti-4-1BB humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line). In an embodiment, the 4-1BB agonist is EU-101 (Eutilex Co. Ltd.), utomilumab, or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof. In a preferred embodiment, the 4-1BB agonist is utomilumab or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof.

[00784] In a preferred embodiment, the 4-1BB agonist or 4-1BB binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric 4-1BB agonist, such as a trimeric or hexameric 4-1BB agonist (with three or six ligand binding domains), may induce superior receptor (4-1BBL) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF

binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[00785] Agonistic 4-1BB antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the 4-1BB agonist is a monoclonal antibody or fusion protein that binds specifically to 4-1BB antigen in a manner sufficient to reduce toxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein which abrogates Fc region functionality.

[00786] In some embodiments, the 4-1BB agonists are characterized by binding to human 4-1BB (SEQ ID NO:9) with high affinity and agonistic activity. In an embodiment, the 4-1BB agonist is a binding molecule that binds to human 4-1BB (SEQ ID NO:9). In an embodiment, the 4-1BB agonist is a binding molecule that binds to murine 4-1BB (SEQ ID NO:10). The amino acid sequences of 4-1BB antigen to which a 4-1BB agonist or binding molecule binds are summarized in Table 3.

TABLE 3. Amino acid sequences of 4-1BB antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:9 human 4-1BB, Tumor necrosis factor receptor superfamily, member 9 (Homo sapiens)	MGNSCYNIVA TLLLVLNFER TRSLQDPCSN CPAGTFCDNN RNQICSPCPP NSFSSAGGQR 60 TCDICRQCKG VFRTRKECSS TSNAECDCTP GFHCLGAGCS MCEQDCKQGQ ELTKKGCKDC 120 CFGTFNDQKR GICRPWTNCS LDGKSVLVNG TKERDVVCGP SPADLSPGAS SVTPPAPARE 180 PGHSPQIISF FLALTSTALL FLLFFLTLRF SVVKRGRKKL LYIFKQPFMR PVQTTQEEDG 240 CSCRFPEEEE GGCEL 255
SEQ ID NO:10 murine 4-1BB, Tumor necrosis factor receptor superfamily, member 9 (Mus musculus)	MGNNCYNVVV IVLLLVGCEK VGAVQNSCDN CQPGTFCRKY NPVCKSCPPS TFSSIGGQPN 60 CNICRVCAGY FRFKKFCSST HNAECECIEG FHCLGPQCTR CEKDCRPGQE LTKQGCKTCS 120 LGTFNDQNGT GVCRPWTNCS LDGRSVLKTG TTEKDVVCGP PVVSFSPSTT ISVTPEGGPG 180 GHSLQVLTLF LALTSALLLA LIFITLLFSV LKWIRKKFPH IFKQPFKKTT GAAQEEDACS 240 CRCPQEEEGG GGGYEL 256

[00787] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds human or murine 4-1BB with a K_D of about 100 pM or lower, binds

human or murine 4-1BB with a K_D of about 90 pM or lower, binds human or murine 4-1BB with a K_D of about 80 pM or lower, binds human or murine 4-1BB with a K_D of about 70 pM or lower, binds human or murine 4-1BB with a K_D of about 60 pM or lower, binds human or murine 4-1BB with a K_D of about 50 pM or lower, binds human or murine 4-1BB with a K_D of about 40 pM or lower, or binds human or murine 4-1BB with a K_D of about 30 pM or lower.

[00788] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8×10^5 l/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine 4-1BB with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00789] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine 4-1BB with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine 4-1BB with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine 4-1BB with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[00790] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with an IC_{50} of about 10 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 9 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 8 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 7 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 6 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 5 nM or lower, binds to human or murine 4-1BB

with an IC_{50} of about 4 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 3 nM or lower, binds to human or murine 4-1BB with an IC_{50} of about 2 nM or lower, or binds to human or murine 4-1BB with an IC_{50} of about 1 nM or lower.

[00791] In a preferred embodiment, the 4-1BB agonist is utomilumab, also known as PF-05082566 or MOR-7480, or a fragment, derivative, variant, or biosimilar thereof. Utomilumab is available from Pfizer, Inc. Utomilumab is an immunoglobulin G2-lambda, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor (TNFR) superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* (fully human) monoclonal antibody. The amino acid sequences of utomilumab are set forth in Table 4. Utomilumab comprises glycosylation sites at Asn59 and Asn292; heavy chain intrachain disulfide bridges at positions 22-96 (V_H-V_L), 143-199 (C_H1-C_L), 256-316 (C_H2) and 362-420 (C_H3); light chain intrachain disulfide bridges at positions 22'-87' (V_H-V_L) and 136'-195' (C_H1-C_L); interchain heavy chain-heavy chain disulfide bridges at IgG2A isoform positions 218-218, 219-219, 222-222, and 225-225, at IgG2A/B isoform positions 218-130, 219-219, 222-222, and 225-225, and at IgG2B isoform positions 219-130 (2), 222-222, and 225-225; and interchain heavy chain-light chain disulfide bridges at IgG2A isoform positions 130-213' (2), IgG2A/B isoform positions 218-213' and 130-213', and at IgG2B isoform positions 218-213' (2). The preparation and properties of utomilumab and its variants and fragments are described in U.S. Patent Nos. 8,821,867; 8,337,850; and 9,468,678, and International Patent Application Publication No. WO 2012/032433 A1, the disclosures of each of which are incorporated by reference herein. Preclinical characteristics of utomilumab are described in Fisher, *et al.*, *Cancer Immunolog. & Immunother.* **2012,** *61,* 1721-33. Current clinical trials of utomilumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02444793, NCT01307267, NCT02315066, and NCT02554812.

[00792] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:11 and a light chain given by SEQ ID NO:12. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light

chains that are each at least 98% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively.

[00793] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of utomilumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:13, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:14, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14.

[00794] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively, and conservative amino acid substitutions thereof.

[00795] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal

antibody approved by drug regulatory authorities with reference to utomilumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab.

TABLE 4. Amino acid sequences for 4-1BB agonist antibodies related to utomilumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:11 heavy chain for utomilumab	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMGK IYPGDSYTNY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGY GIFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP G	60 120 180 240 300 360 420 441
SEQ ID NO:12 light chain for utomilumab	SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD KNRPSGIPER FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS	60 120 180 214
SEQ ID NO:13 heavy chain	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMG KIYPGDSYTN YSPSFQGQVT ISADKSISTA YLQWSSLKAS DTAMYYCARG YGIFDYWGQ GTLVTVSS	60 118

variable region for utomilumab		
SEQ ID NO:14 light chain variable region for utomilumab	SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD KNRPSGIPER FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVL	60 108
SEQ ID NO:15 heavy chain CDR1 for utomilumab	STYWIS	6
SEQ ID NO:16 heavy chain CDR2 for utomilumab	KIYPGDSYTN YSPSFQG	17
SEQ ID NO:17 heavy chain CDR3 for utomilumab	RGYGIFDY	8
SEQ ID NO:18 light chain CDR1 for utomilumab	SGDNIGDQYA H	11
SEQ ID NO:19 light chain CDR2 for utomilumab	QDKNRPS	7
SEQ ID NO:20 light chain CDR3 for utomilumab	ATYTGFGSLA V	11

[00796] In a preferred embodiment, the 4-1BB agonist is the monoclonal antibody urelumab, also known as BMS-663513 and 20H4.9.h4a, or a fragment, derivative, variant, or biosimilar thereof. Urelumab is available from Bristol-Myers Squibb, Inc., and Creative Biolabs, Inc. Urelumab is an immunoglobulin G4-kappa, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* (fully human) monoclonal antibody. The amino acid sequences of urelumab are set forth in Table 5. Urelumab comprises N-glycosylation sites at positions 298 (and 298''); heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 262-322 (C_H2) and 368-426 (C_H3) (and at positions 22''-95'', 148''-204'', 262''-322'', and 368''-426''); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 136'-196' (C_H1-C_L) (and at positions 23'''-88''' and 136'''-196'''); interchain heavy chain-heavy chain disulfide bridges at positions 227-227'' and 230-230''; and interchain heavy chain-light chain disulfide bridges at 135-216' and 135''-216'''. The preparation and properties of urelumab and its variants and fragments are described in U.S. Patent Nos. 7,288,638 and 8,962,804, the disclosures of which are incorporated by reference herein. The preclinical and clinical characteristics of urelumab are described in Segal, *et al.*, *Clin. Cancer Res.* **2016,** *available at* http:/dx.doi.org/ 10.1158/1078-0432.CCR-16-1272. Current clinical trials of urelumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT01775631, NCT02110082, NCT02253992, and NCT01471210.

[00797] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:21

and a light chain given by SEQ ID NO:22. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

[00798] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of urelumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:23, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:24, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24.

[00799] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3

domains having the sequences set forth in SEQ ID NO:25, SEQ ID NO:26, and SEQ ID NO:27, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:28, SEQ ID NO:29, and SEQ ID NO:30, respectively, and conservative amino acid substitutions thereof.

[00800] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to urelumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab.

TABLE 5. Amino acid sequences for 4-1BB agonist antibodies related to urelumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:21 heavy chain for urelumab	QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQS PEKGLEWIGE INHGGYVTYN PSLESRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARDYG PGNYDWYFDL WGRGTLVTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTK TYTCNVDHKP SNTKVDKRVE SKYGPPCPPC PAPEFLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK	60 120 180 240 300 360 420 448
SEQ ID NO:22 light chain for urelumab	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPALTF CGGTKVEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	60 120 180 216
SEQ ID NO:23 variable heavy chain for urelumab	MKHLWFFLLL VAAPRWVLSQ VQLQQWGAGL LKPSETLSLT CAVYGGSFSG YYWSWIRQSP EKGLEWIGEI NHGGYVTYNP SLESRVTISV DTSKNQFSLK LSSVTAADTA VYYCARDYGP	60 120
SEQ ID NO:24 variable light chain for urelumab	MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ	60 110
SEQ ID NO:25 heavy chain CDR1 for urelumab	GYYWS	5
SEQ ID NO:26 heavy chain CDR2 for urelumab	EINHGGYVTY NPSLES	16
SEQ ID NO:27 heavy chain CDR3 for urelumab	DYGPGNYDWY FDL	13
SEQ ID NO:28 light chain CDR1 for urelumab	RASQSVSSYL A	11
SEQ ID NO:29 light chain CDR2 for urelumab	DASNRAT	7
SEQ ID NO:30 light chain CDR3 for urelumab	QQRSDWPPAL T	11

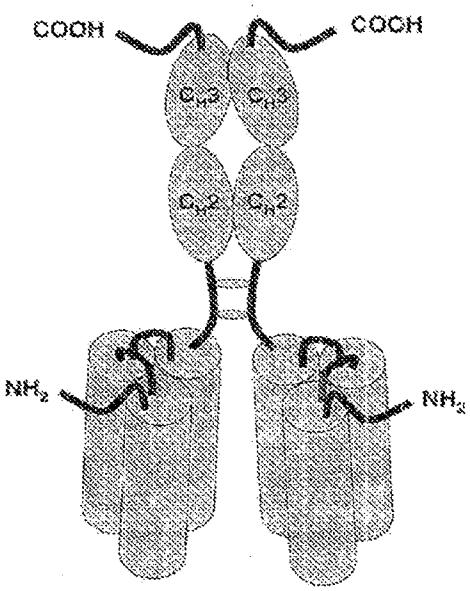
[00801] In an embodiment, the 4-1BB agonist is selected from the group consisting of 1D8, 3Elor, 4B4 (BioLegend 309809), H4-1BB-M127 (BD Pharmingen 552532), BBK2 (Thermo Fisher MS621PABX), 145501 (Leinco Technologies B591), the antibody produced by cell line deposited as ATCC No. HB-11248 and disclosed in U.S. Patent No. 6,974,863, 5F4 (BioLegend 31 1503), C65-485 (BD Pharmingen 559446), antibodies disclosed in U.S. Patent Application Publication No. US 2005/0095244, antibodies disclosed in U.S. Patent No. 7,288,638 (such as 20H4.9-IgGl (BMS-663031)), antibodies disclosed in U.S. Patent No. 6,887,673 (such as 4E9 or BMS-554271), antibodies disclosed in U.S. Patent No. 7,214,493, antibodies disclosed in U.S. Patent No. 6,303,121, antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in U.S. Patent No. 6,905,685 (such as 4E9 or BMS-554271), antibodies disclosed in U.S. Patent No. 6,362,325 (such as 1D8 or BMS-469492; 3H3 or BMS-469497; or 3El), antibodies disclosed

in U.S. Patent No. 6,974,863 (such as 53A2); antibodies disclosed in U.S. Patent No. 6,210,669 (such as 1D8, 3B8, or 3El), antibodies described in U.S. Patent No. 5,928,893, antibodies disclosed in U.S. Patent No. 6,303,121, antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in International Patent Application Publication Nos. WO 2012/177788, WO 2015/119923, and WO 2010/042433, and fragments, derivatives, conjugates, variants, or biosimilars thereof, wherein the disclosure of each of the foregoing patents or patent application publications is incorporated by reference here.

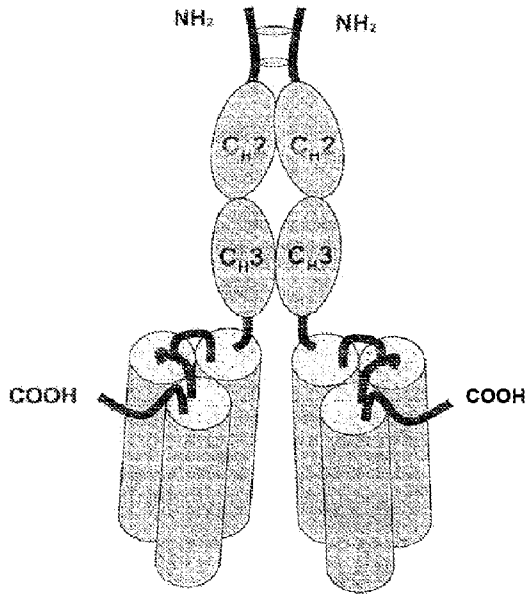
[00802] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein described in International Patent Application Publication Nos. WO 2008/025516 A1, WO 2009/007120 A1, WO 2010/003766 A1, WO 2010/010051 A1, and WO 2010/078966 A1; U.S. Patent Application Publication Nos. US 2011/0027218 A1, US 2015/0126709 A1, US 2011/0111494 A1, US 2015/0110734 A1, and US 2015/0126710 A1; and U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein.

[00803] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof:

(I-A)



(I-B)



In structures I-A and I-B, the cylinders refer to individual polypeptide binding domains. Structures I-A and I-B comprise three linearly-linked TNFRSF binding domains derived from *e.g.*, 4-1BBL or an antibody that binds 4-1BB, which fold to form a trivalent protein, which is then linked to a second triavelent protein through IgG1-Fc (including C_H3 and C_H2 domains) is then used to link two of the trivalent proteins together through disulfide bonds (small elongated ovals), stabilizing the structure and providing an agonists capable of bringing together the intracellular signaling domains of the six receptors and signaling proteins to form a signaling complex. The TNFRSF binding domains denoted as cylinders may be scFv domains comprising, *e.g.*, a V_H and a V_L chain connected by a linker that may comprise hydrophilic residues and Gly and Ser sequences for flexibility, as well as Glu and Lys for solubility. Any scFv domain design may be used, such as those described in de Marco, *Microbial Cell Factories*, **2011,** *10*, 44; Ahmad, *et al.*, *Clin. & Dev. Immunol.* **2012,** 980250; Monnier, *et al.*, *Antibodies,* **2013,** *2,* 193-208; or in references incorporated elsewhere herein. Fusion protein structures of this form are described in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein.

[00804] Amino acid sequences for the other polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion

of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides.

TABLE 6. Amino acid sequences for TNFRSF fusion proteins, including 4-1BB fusion proteins, with C-terminal Fc-antibody fragment fusion protein design (structure I-A).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:31 Fc domain	KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 230
SEQ ID NO:32 linker	GGPGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:33 linker	GGSGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:34 linker	GGPGSSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:35 linker	GGSGSSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:36 linker	GGPGSSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:37 linker	GGSGSSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:38 linker	GGPGSSGSGS SDKTHTCPPC PAPE	24
SEQ ID NO:39 linker	GGPGSSGSGS DKTHTCPPCP APE	23
SEQ ID NO:40 linker	GGPSSSGSDK THTCPPCPAP E	21
SEQ ID NO:41 linker	GGSSSSSSSS GSDKTHTCPP CPAPE	25

[00805] Amino acid sequences for the other polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

TABLE 7. Amino acid sequences for TNFRSF fusion proteins, including 4-1BB fusion proteins, with N-terminal Fc-antibody fragment fusion protein design (structure I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:42 Fc domain	METDTLLLWV LLLWVPAGNG DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG	60 120 180 240 246
SEQ ID NO:43 linker	SGSGSGSGSG S	11
SEQ ID NO:44 linker	SSSSSSGSGS GS	12

SEQ ID NO:45 linker	SSSSSSGSGS GSGSGS	16

[00806] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains selected from the group consisting of a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain of urelumab, a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table 8, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00807] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:46. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a soluble 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:47.

[00808] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 8, wherein the V_H and V_L domains are connected by a linker.

TABLE 8. Additional polypeptide domains useful as 4-1BB binding domains in fusion proteins or as scFv 4-1BB agonist antibodies.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:46 4-1BBL	MEYASDASLD PEAPWPPAPR ARACRVLPWA LVAGLLLLLL LAAACAVFLA CPWAVSGARA SPGSAASPRL REGPELSPDD PAGLLDLRQG MFAQLVAQNV LLIDGPLSWY SDPGLAGVSL TGGLSYKEDT KELVVAKAGV YYVFFQLELR RVVAGEGSGS VSLALHLQPL RSAAGAAALA LTVDLPPASS EARNSAFGFQ GRLLHLSAGQ RLGVHLHTEA RARHAWQLTQ GATVLGLFRV TPEIPAGLPS PRSE	60 120 180 240 254
SEQ ID NO:47 4-1BBL soluble domain	LRQGMFAQLV AQNVLLIDGP LSWYSDPGLA GVSLTGGLSY KEDTKELVVA KAGVYYVFFQ LELRRVVAGE GSGSVSLALH LQPLRSAAGA AALALTVDLP PASSEARNSA FGFQGRLLHL SAGQRLGVHL HTEARARHAW QLTQGATVLG LFRVTPEIPA GLPSPRSE	60 120 168
SEQ ID NO:48 variable heavy chain for 4B4-1-1 version 1	QVQLQQPGAE LVKPGASVKL SCKASGYTFS SYWMHWVKQR PGQVLEWIGE INPGNGHTNY NEKFKSKATL TVDKSSSTAY MQLSSLTSED SAVYYCARSF TTARGFAYWG QGTLVTVS	60 118
SEQ ID NO:49 variable light chain for 4B4-1-1 version 1	DIVMTQSPAT QSVTPGDRVS LSCRASQTIS DYLHWYQQKS HESPRLLIKY ASQSISGIPS RFSGSGSGSD FTLSINSVEP EDVGVYYCQD GHSFPPTFGG GTKLEIK	60 107
SEQ ID NO:50 variable heavy chain for 4B4-1-1 version 2	QVQLQQPGAE LVKPGASVKL SCKASGYTFS SYWMHWVKQR PGQVLEWIGE INPGNGHTNY NEKFKSKATL TVDKSSSTAY MQLSSLTSED SAVYYCARSF TTARGFAYWG QGTLVTVSA	60 119
SEQ ID NO:51 variable light chain for 4B4-1-1 version 2	DIVMTQSPAT QSVTPGDRVS LSCRASQTIS DYLHWYQQKS HESPRLLIKY ASQSISGIPS RFSGSGSGSD FTLSINSVEP EDVGVYYCQD GHSFPPTFGG GTKLEIKR	60 108
SEQ ID NO:52 variable heavy chain for H39E3-2	MDWTWRILFL VAAATGAHSE VQLVESGGGL VQPGGSLRLS CAASGFTFSD YWMSWVRQAP GKGLEWVADI KNDGSYTNYA PSLTNRFTIS RDNAKNSLYL QMNSLRAEDT AVYYCARELT	60 120
SEQ ID NO:53 variable light chain for H39E3-2	MEAPAQLLFL LLLWLPDTTG DIVMTQSPDS LAVSLGERAT INCKSSQSLL SSGNQKNYL WYQQKPGQPP KLLIYYASTR QSGVPDRFSG SGSGTDFTLT ISSLQAEDVA	60 110

[00809] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain, wherein each of the soluble 4-1BB domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the 4-1BB binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[00810] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein each TNF superfamily cytokine domain is a 4-1BB binding domain.

[00811] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[00812] In an embodiment, the 4-1BB agonist agonist is BPS Bioscience 4-1BB agonist antibody catalog no. 79097-2, commercially available from BPS Bioscience, San Diego, CA, USA. In an embodiment, the 4-1BB agonist agonist is Creative Biolabs 4-1BB agonist antibody catalog no. MOM-18179, commercially available from Creative Biolabs, Shirley, NY, USA.

OX40 (CD134) Agonists

[00813] In an embodiment, the TNFRSF agonist is an OX40 (CD134) agonist. The OX40 agonist may be any OX40 binding molecule known in the art. The OX40 binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian OX40. The OX40 agonists or OX40 binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The OX40 agonist or OX40 binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab′) fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to OX40. In an embodiment, the OX40 agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the OX40 agonist is an antigen binding protein that is a humanized antibody. In some embodiments, OX40 agonists for use in the presently disclosed methods and compositions include anti-OX40 antibodies, human anti-OX40 antibodies, mouse

anti-OX40 antibodies, mammalian anti-OX40 antibodies, monoclonal anti-OX40 antibodies, polyclonal anti-OX40 antibodies, chimeric anti-OX40 antibodies, anti-OX40 adnectins, anti-OX40 domain antibodies, single chain anti-OX40 fragments, heavy chain anti-OX40 fragments, light chain anti-OX40 fragments, anti-OX40 fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the OX40 agonist is an agonistic, anti-OX40 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[00814] In a preferred embodiment, the OX40 agonist or OX40 binding molecule may also be a fusion protein. OX40 fusion proteins comprising an Fc domain fused to OX40L are described, for example, in Sadun, *et al.*, *J. Immunother.* **2009,** *182,* 1481-89. In a preferred embodiment, a multimeric OX40 agonist, such as a trimeric or hexameric OX40 agonist (with three or six ligand binding domains), may induce superior receptor (OX40L) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[00815] Agonistic OX40 antibodies and fusion proteins are known to induce strong immune responses. Curti, *et al.*, *Cancer Res.* **2013**, *73,* 7189-98. In a preferred embodiment, the OX40 agonist is a monoclonal antibody or fusion protein that binds specifically to OX40 antigen in a manner sufficient to reduce toxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein which abrogates Fc region functionality.

[00816] In some embodiments, the OX40 agonists are characterized by binding to human OX40 (SEQ ID NO:54) with high affinity and agonistic activity. In an embodiment, the OX40

agonist is a binding molecule that binds to human OX40 (SEQ ID NO:54). In an embodiment, the OX40 agonist is a binding molecule that binds to murine OX40 (SEQ ID NO:55). The amino acid sequences of OX40 antigen to which an OX40 agonist or binding molecule binds are summarized in Table 9.

TABLE 9. Amino acid sequences of OX40 antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:54 human OX40 (Homo sapiens)	MCVGARRLGR GPCAALLLLG LGLSTVTGLH CVGDTYPSND RCCHECRPGN GMVSRCSRSQ NTVCRPCGPG FYNDVVSSKP CKPCTWCNLR SGSERKQLCT ATQDTVCRCR AGTQPLDSYK PGVDCAPCPP GHFSPGDNQA CKPWTNCTLA GKHTLQPASN SSDAICEDRD PPATQPQETQ GPPARPITVQ PTEAWPRTSQ GPSTRPVEVP GGRAVAAILG LGLVLGLLGP LAILLALYLL RRDQRLPPDA HKPPGGGSFR TPIQEEQADA HSTLAKI	60 120 180 240 277
SEQ ID NO:55 murine OX40 (Mus musculus)	MYVWVQQPTA LLLLGLTLGV TARRLNCVKH TYPSGHKCCR ECQPGHGMVS RCDHTRDTLC HPCETGFYNE AVNYDTCKQC TQCNHRSGSE LKQNCTPTQD TVCRCRPGTQ PRQDSGYKLG VDCVPCPPGH FSPGNNQACK PWTNCTLSGK QTRHPASDSL DAVCEDRSLL ATLLWETQRP TFRPTTVQST TVWPRTSELP SPPTLVTPEG PAFAVLLGLG LGLLAPLTVL LALYLLRKAW RLPNTPKPCW GNSFRTPIQE EHTDAHFTLA KI	60 120 180 240 272

[00817] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds human or murine OX40 with a K_D of about 100 pM or lower, binds human or murine OX40 with a K_D of about 90 pM or lower, binds human or murine OX40 with a K_D of about 80 pM or lower, binds human or murine OX40 with a K_D of about 70 pM or lower, binds human or murine OX40 with a K_D of about 60 pM or lower, binds human or murine OX40 with a K_D of about 50 pM or lower, binds human or murine OX40 with a K_D of about 40 pM or lower, or binds human or murine OX40 with a K_D of about 30 pM or lower.

[00818] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine OX40 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00819] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine OX40 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine OX40

with a k_{dissoc} of about 2.3 × 10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.4 × 10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.5 × 10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.6 × 10^{-5} 1/s or slower or binds to human or murine OX40 with a k_{dissoc} of about 2.7 × 10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.8 × 10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.9 × 10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 3 × 10^{-5} 1/s or slower.

[00820] In some embodiments, the compositions, processes and methods described include OX40 agonist that binds to human or murine OX40 with an IC_{50} of about 10 nM or lower, binds to human or murine OX40 with an IC_{50} of about 9 nM or lower, binds to human or murine OX40 with an IC_{50} of about 8 nM or lower, binds to human or murine OX40 with an IC_{50} of about 7 nM or lower, binds to human or murine OX40 with an IC_{50} of about 6 nM or lower, binds to human or murine OX40 with an IC_{50} of about 5 nM or lower, binds to human or murine OX40 with an IC_{50} of about 4 nM or lower, binds to human or murine OX40 with an IC_{50} of about 3 nM or lower, binds to human or murine OX40 with an IC_{50} of about 2 nM or lower, or binds to human or murine OX40 with an IC_{50} of about 1 nM or lower.

[00821] In some embodiments, the OX40 agonist is tavolixizumab, also known as MEDI0562 or MEDI-0562. Tavolixizumab is available from the MedImmune subsidiary of AstraZeneca, Inc. Tavolixizumab is immunoglobulin G1-kappa, anti-[*Homo sapiens* TNFRSF4 (tumor necrosis factor receptor (TNFR) superfamily member 4, OX40, CD134)], humanized and chimeric monoclonal antibody. The amino acid sequences of tavolixizumab are set forth in Table 10. Tavolixizumab comprises N-glycosylation sites at positions 301 and 301'', with fucosylated complex bi-antennary CHO-type glycans; heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 265-325 (C_H2) and 371-429 (C_H3) (and at positions 22''-95'', 148''-204'', 265''-325'', and 371''-429''); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 134'-194' (C_H1-C_L) (and at positions 23'''-88''' and 134'''-194'''); interchain heavy chain-heavy chain disulfide bridges at positions 230-230'' and 233-233''; and interchain heavy chain-light chain disulfide bridges at 224-214' and 224''-214'''. Current clinical trials of tavolixizumab in a variety of solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02318394 and NCT02705482.

[00822] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:56 and a light chain given by SEQ ID NO:57. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively.

[00823] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of tavolixizumab. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:58, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:59, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, an OX40 agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59.

[00824] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, respectively, and conservative amino acid substitutions thereof.

[00825] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tavolixizumab. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab.

TABLE 10. Amino acid sequences for OX40 agonist antibodies related to tavolixizumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:56 heavy chain for tavolixizumab	QVQLQESGPG LVKPSQTLSL TCAVYGGSFS SGYWNWIRKH PGKGLEYIGY ISYNGITYHN PSLKSRITIN RDTSKNQYSL QLNSVTPEDT AVYYCARYKY DYDGGHAMDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K	60 120 180 240 300 360 420 451
SEQ ID NO:57 light chain for tavolixizumab	DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY TSKLHSGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCQQ GSALPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:58 heavy chain variable region for tavolixizumab	QVQLQESGPG LVKPSQTLSL TCAVYGGSFS SGYWNWIRKH PGKGLEYIGY ISYNGITYHN PSLKSRITIN RDTSKNQYSL QLNSVTPEDT AVYYCARYKY DYDGGHAMDY WGQGTLVT	60 118
SEQ ID NO:59 light chain variable region for tavolixizumab	DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY TSKLHSGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCQQ GSALPWTFGQ GTKVEIKR	60 108
SEQ ID NO:60 heavy chain CDR1 for tavolixizumab	GSFSSGYWN	9
SEQ ID NO:61 heavy chain CDR2 for tavolixizumab	YIGYISYNGI TYH	13
SEQ ID NO:62 heavy chain CDR3 for tavolixizumab	RYKYDYDGGH AMDY	14
SEQ ID NO:63 light chain CDR1 for tavolixizumab	QDISNYLN	8
SEQ ID NO:64 light chain CDR2 for tavolixizumab	LLIYYTSKLH S	11
SEQ ID NO:65 light chain CDR3 for tavolixizumab	QQGSALPW	8

[00826] In some embodiments, the OX40 agonist is 11D4, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 11D4 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 11D4 are set forth in Table 11.

[00827] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:66 and a light chain given by SEQ ID NO:67. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:66 and SEQ ID NO:67,

respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively.

[00828] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 11D4. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:68, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:69, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively.

[00829] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:73, SEQ ID NO:74, and SEQ ID NO:75, respectively, and conservative amino acid substitutions thereof.

[00830] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 11D4. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4.

TABLE 11. Amino acid sequences for OX40 agonist antibodies related to 11D4.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:66 heavy chain for 11D4	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP PVAGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTFRVV SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE KTISKTKGQP REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK	60 120 180 240 300 360 420 444
SEQ ID NO:67 light chain for 11D4	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:68 heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSS	60 118

variable region for 11D4		
SEQ ID NO:69 light chain variable region for 11D4	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIK	60 107
SEQ ID NO:70 heavy chain CDR1 for 11D4	SYSMN	5
SEQ ID NO:71 heavy chain CDR2 for 11D4	YISSSSSTID YADSVKG	17
SEQ ID NO:72 heavy chain CDR3 for 11D4	ESGWYLFDY	9
SEQ ID NO:73 light chain CDR1 for 11D4	RASQGISSWL A	11
SEQ ID NO:74 light chain CDR2 for 11D4	AASSLQS	7
SEQ ID NO:75 light chain CDR3 for 11D4	QQYNSYPPT	9

[00831] In some embodiments, the OX40 agonist is 18D8, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 18D8 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 18D8 are set forth in Table 12.

[00832] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:76 and a light chain given by SEQ ID NO:77. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively.

[00833] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 18D8. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:78, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:79, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively.

[00834] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:80, SEQ ID NO:81, and SEQ ID NO:82, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:83, SEQ ID NO:84, and SEQ ID NO:85, respectively, and conservative amino acid substitutions thereof.

[00835] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 18D8. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference

biological product, wherein the reference medicinal product or reference biological product is 18D8. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8.

TABLE 12. Amino acid sequences for OX40 agonist antibodies related to 18D8.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:76 heavy chain for 18D8	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGSIGY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TALYYCAKDQ STADYYFYYG MDVWGQGTTV TVSSASTKGP SVFPLAPCSR STSESTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSNF GTQTYTCNVD HKPSNTKVDK TVERKCCVEC PPCPAPPVAG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVQFNW YVDGVEVHNA KTKPREEQFN STFRVVSVLT VVHQDWLNGK EYKCKVSNKG LPAPIEKTIS KTKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPM LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 240 300 360 420 450
SEQ ID NO:77 light chain for 18D8	EIVVTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPTFGQG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC	60 120 180 213
SEQ ID NO:78 heavy chain variable region for 18D8	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGSIGY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TALYYCAKDQ STADYYFYYG MDVWGQGTTV TVSS	60 120 124
SEQ ID NO:79 light chain variable region for 18D8	EIVVTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPTFGQG TKVEIK	60 106
SEQ ID NO:80 heavy chain CDR1 for 18D8	DYAMH	5
SEQ ID NO:81 heavy chain CDR2 for 18D8	GISWNSGSIG YADSVKG	17
SEQ ID NO:82 heavy chain CDR3 for 18D8	DQSTADYYFY YGMDV	15
SEQ ID NO:83 light chain CDR1 for 18D8	RASQSVSSYL A	11
SEQ ID NO:84 light chain CDR2 for 18D8	DASNRAT	7
SEQ ID NO:85 light chain CDR3 for 18D8	QQRSNWPT	8

[00836] In some embodiments, the OX40 agonist is Hu119-122, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu119-122 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu119-122 are set forth in Table 13.

[00837] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu119-122. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:86, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:87, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively.

[00838] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:88, SEQ ID NO:89, and SEQ ID NO:90, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:91, SEQ ID NO:92, and SEQ ID NO:93, respectively, and conservative amino acid substitutions thereof.

[00839] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu119-122. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as

compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122.

TABLE 13. Amino acid sequences for OX40 agonist antibodies related to Hu119-122.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:86 heavy chain variable region for Hu119-122	EVQLVESGGG LVQPGGSLRL SCAASEYEFP SHDMSWVRQA PGKGLELVAA INSDGGSTYY PDTMERRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARHY DDYYAWFAYW GQGTMVTVSS	60 120
SEQ ID NO:87 light chain variable region for Hu119-122	EIVLTQSPAT LSLSPGERAT LSCRASKSVS TSGYSYMHWY QQKPGQAPRL LIYLASNLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRELPL TFGGGTKVEI K	60 111
SEQ ID NO:88 heavy chain CDR1 for Hu119-122	SHDMS	5
SEQ ID NO:89 heavy chain CDR2 for Hu119-122	AINSDGGSTY YPDTMER	17
SEQ ID NO:90 heavy chain CDR3 for Hu119-122	HYDDYYAWFA Y	11
SEQ ID NO:91 light chain CDR1 for Hu119-122	RASKSVSTSG YSYMH	15
SEQ ID NO:92 light chain CDR2 for Hu119-122	LASNLES	7

SEQ ID NO:93 light chain CDR3 for Hu119-122	QHSRELPLT	9

[00840] In some embodiments, the OX40 agonist is Hu106-222, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu106-222 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu106-222 are set forth in Table 14.

[00841] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu106-222. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:94, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:95, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively.

[00842] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:96, SEQ ID NO:97, and SEQ ID NO:98, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101, respectively, and conservative amino acid substitutions thereof.

[00843] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu106-222. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100%

sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222.

TABLE 14. Amino acid sequences for OX40 agonist antibodies related to Hu106-222.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:94 heavy chain variable region for Hu106-222	QVQLVQSGSE LKKPGASVKV SCKASGYTFT DYSMHWVRQA PGQGLKWMGW INTETGEPTY ADDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCANPY YDYVSYYAMD YWGQGTTVTV SS	60 120 122
SEQ ID NO:95 light chain variable region for Hu106-222	DIQMTQSPSS LSASVGDRVT ITCKASQDVS TAVAWYQQKP GKAPKLLIYS ASYLYTGVPS RFSGSGSGTD FTFTISSLQP EDIATYYCQQ HYSTPRTFGQ GTKLEIK	60 107
SEQ ID NO:96 heavy chain CDR1 for Hu106-222	DYSMH	5
SEQ ID NO:97 heavy chain CDR2 for Hu106-222	WINTETGEPT YADDFKG	17
SEQ ID NO:98 heavy chain CDR3 for Hu106-222	PYYDYVSYYA MDY	13
SEQ ID NO:99 light chain CDR1 for Hu106-222	KASQDVSTAV A	11

SEQ ID NO:100 light chain CDR2 for Hu106-222	SASYLYT	7
SEQ ID NO:101 light chain CDR3 for Hu106-222	QQHYSTPRT	9

[00844] In some embodiments, the OX40 agonist antibody is MEDI6469 (also referred to as 9B12). MEDI6469 is a murine monoclonal antibody. Weinberg, *et al.*, *J. Immunother.* **2006**, *29*, 575-585. In some embodiments the OX40 agonist is an antibody produced by the 9B12 hybridoma, deposited with Biovest Inc. (Malvern, MA, USA), as described in Weinberg, *et al.*, *J. Immunother.* **2006**, *29*, 575-585, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the antibody comprises the CDR sequences of MEDI6469. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of MEDI6469.

[00845] In an embodiment, the OX40 agonist is L106 BD (Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises the CDRs of antibody L106 (BD Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody L106 (BD Pharmingen Product #340420). In an embodiment, the OX40 agonist is ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises the CDRs of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In an embodiment, the OX40 agonist is the murine monoclonal antibody anti-mCD134/mOX40 (clone OX86), commercially available from InVivoMAb, BioXcell Inc, West Lebanon, NH.

[00846] In an embodiment, the OX40 agonist is selected from the OX40 agonists described in International Patent Application Publication Nos. WO 95/12673, WO 95/21925, WO 2006/121810, WO 2012/027328, WO 2013/028231, WO 2013/038191, and WO 2014/148895; European Patent Application EP 0672141; U.S. Patent Application Publication Nos. US 2010/136030, US 2014/377284, US 2015/190506, and US 2015/132288 (including clones 20E5 and 12H3); and U.S. Patent Nos. 7,504,101, 7,550,140, 7,622,444, 7,696,175, 7,960,515, 7,961,515, 8,133,983, 9,006,399, and 9,163,085, the disclosure of each of which is incorporated herein by reference in its entirety.

[00847] In an embodiment, the OX40 agonist is an OX40 agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[00848] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains selected from the group consisting of a variable heavy chain and variable light chain of tavolixizumab, a variable heavy chain and variable light chain of 11D4, a variable heavy chain and variable light chain of 18D8, a variable heavy chain and variable light chain of Hu119-122, a variable heavy chain and variable light chain of Hu106-222, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table 15, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00849] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising an OX40L sequence. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:102. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a soluble OX40L sequence. In an embodiment, a

OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:103. In an embodiment, a OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:104.

[00850] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 15, wherein the V_H and V_L domains are connected by a linker.

TABLE 15. Additional polypeptide domains useful as OX40 binding domains in fusion proteins (*e.g.*, structures I-A and I-B) or as scFv OX40 agonist antibodies.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:102 OX40L	MERVQPLEEN VGNAARPRFE RNKLLLVASV IQGLGLLLCF TYICLHFSAL QVSHRYPRIQ SIKVQFTEYK KEKGFILTSQ KEDEIMKVQN NSVIINCDGF YLISLKGYFS QEVNISLHYQ KDEEPLFQLK KVRSVNSLMV ASLTYKDKVY LNVTTDNTSL DDFHVNGGEL ILIHQNPGEF CVL	60 120 180 183
SEQ ID NO:103 OX40L soluble domain	SHRYPRIQSI KVQFTEYKKE KGFILTSQKE DEIMKVQNNS VIINCDGFYL ISLKGYFSQE VNISLHYQKD EEPLFQLKKV RSVNSLMVAS LTYKDKVYLN VTTDNTSLDD FHVNGGELIL IHQNPGEFCV L	60 120 131
SEQ ID NO:104 OX40L soluble domain (alternative)	YPRIQSIKVQ FTEYKKEKGF ILTSQKEDEI MKVQNNSVII NCDGFYLISL KGYFSQEVNI SLHYQKDEEP LFQLKKVRSV NSLMVASLTY KDKVYLNVTT DNTSLDDFHV NGGELILIHQ NPGEFCVL	60 120 128
SEQ ID NO:105 variable heavy chain for 008	EVQLVESGGG LVQPGGSLRL SCAASGFTFS NYTMNWVRQA PGKGLEWVSA ISGSGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKDR YSQVHYALDY WGQGTLVTVS	60 120
SEQ ID NO:106 variable light chain for 008	DIVMTQSPDS LPVTPGEPAS ISCRSSQSLL HSNGYNYLDW YLQKAGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCQQYYNHP TTFGQGTK	60 108
SEQ ID NO:107 variable heavy chain for 011	EVQLVESGGG VVQPGRSLRL SCAASGFTFS DYTMNWVRQA PGKGLEWVSS ISGGSTYYAD SRKGRFTISR DNSKNTLYLQ MNNLRAEDTA VYYCARDRYF RQQNAFDYWG QGTLVTVSSA	60 120
SEQ ID NO:108 variable light chain for 011	DIVMTQSPDS LPVTPGEPAS ISCRSSQSLL HSNGYNYLDW YLQKAGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCQQYYNHP TTFGQGTK	60 108
SEQ ID NO:109 variable heavy chain for 021	EVQLVESGGG LVQPRGSLRL SCAASGFTFS SYAMNWVRQA PGKGLEWVAV ISYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKDR YITLPNALDY WGQGTLVTVS	60 120
SEQ ID NO:110 variable light chain for 021	DIQMTQSPVS LPVTPGEPAS ISCRSSQSLL HSNGYNYLDW YLQKPGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCQQYKSNP PTFGQGTK	60 108
SEQ ID NO:111 variable heavy chain for 023	EVQLVESGGG LVHPGGSLRL SCAGSGFTFS SYAMHWVRQA PGKGLEWVSA IGTGGGTYYA DSVMGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARYDN VMGLYWFDYW GQGTLVTVSS	60 120
SEQ ID NO:112 variable light chain for 023	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPAFGG GTKVEIKR	60 108
SEQ ID NO:113 heavy chain variable region	EVQLQQSGPE LVKPGASVKM SCKASGYTFT SYVMHWVKQK PGQGLEWIGY INPYNDGTKY NEKFKGKATL TSDKSSSTAY MELSSLTSED SAVYYCANYY GSSLSMDYWG QGTSVTVSS	60 119
SEQ ID NO:114 light chain variable region	DIQMTQTTSS LSASLGDRVT ISCRASQDIS NYLNWYQQKP DGTVKLLIYY TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GNTLPWTFGG GTKLEIKR	60 108
SEQ ID NO:115 heavy chain variable region	EVQLQQSGPE LVKPGASVKI SCKTSGYTFK DYTMHWVKQS HGKSLEWIGG IYPNNGGSTY NQNFKDKATL TVDKSSSTAY MEFRSLTSED SAVYYCARMG YHGPHLDFDV WGAGTTVTVS P	60 120 121
SEQ ID NO:116 light chain variable region	DIVMTQSHKF MSTSLGDRVS ITCKASQDVG AAVAWYQQKP GQSPKLLIYW ASTRHTGVPD RFTGGGSGTD FTLTISNVQS EDLTDYFCQQ YINYPLTFGG GTKLEIKR	60 108
SEQ ID NO:117 heavy chain variable region of humanized antibody	QIQLVQSGPE LKKPGETVKI SCKASGYTFT DYSMHWVKQA PGKGLKWMGW INTETGEPTY ADDFKGRFAF SLETSASTAY LQINNLKNED TATYFCANPY YDYVSYYAMD YWGHGTSVTV SS	60 120 122
SEQ ID NO:118 heavy chain variable region of humanized antibody	QVQLVQSGSE LKKPGASVKV SCKASGYTFT DYSMHWVRQA PGQGLKWMGW INTETGEPTY ADDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCANPY YDYVSYYAMD YWGQGTTVTV SS	60 120 122
SEQ ID NO:119 light chain variable region of humanized antibody	DIVMTQSHKF MSTSVRDRVS ITCKASQDVS TAVAWYQQKP GQSPKLLIYS ASYLYTGVPD RFTGSGSGTD FTFTISSVQA EDLAVYYCQQ HYSTPRTFGG GTKLEIK	60 107

SEQ ID NO:120 light chain variable region of humanized antibody	DIVMTQSHKF MSTSVRDRVS ITCKASQDVS TAVAWYQQKP GQSPKLLIYS ASYLYTGVPD RFTGSGSGTD FTFTISSVQA EDLAVYYCQQ HYSTPRTFGG GTKLEIK	60 107
SEQ ID NO:121 heavy chain variable region of humanized antibody	EVQLVESGGG LVQPGESLKL SCESNEYEFP SHDMSWVRKT PEKRLELVAA INSDGGSTYY PDTMERRFII SRDNTKKTLY LQMSSLRSED TALYYCARHY DDYYAWFAYW GQGTLVTVSA	60 120
SEQ ID NO:122 heavy chain variable region of humanized antibody	EVQLVESGGG LVQPGGSLRL SCAASEYEFP SHDMSWVRQA PGKGLELVAA INSDGGSTYY PDTMERRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARHY DDYYAWFAYW GQGTMVTVSS	60 120
SEQ ID NO:123 light chain variable region of humanized antibody	DIVLTQSPAS LAVSLGQRAT ISCRASKSVS TSGYSYMHWY QQKPGQPPKL LIYLASNLES GVPARFSGSG SGTDFTLNIH PVEEEDAATY YCQHSRELPL TFGAGTKLEL K	60 111
SEQ ID NO:124 light chain variable region of humanized antibody	EIVLTQSPAT LSLSPGERAT LSCRASKSVS TSGYSYMHWY QQKPGQAPRL LIYLASNLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRELPL TFGGGTKVEI K	60 111
SEQ ID NO:125 heavy chain variable region	MYLGLNYVFI VFLLNGVQSE VKLEESGGGL VQPGGSMKLS CAASGFTFSD AWMDWVRQSP EKGLEWVAEI RSKANNHATY YAESVNGRFT ISRDDSKSSV YLQMNSLRAE DTGIYYCTWG EVFYFDYWGQ GTTLTVSS	60 120 138
SEQ ID NO:126 light chain variable region	MRPSIQFLGL LLFWLHGAQC DIQMTQSPSS LSASLGGKVT ITCKSSQDIN KYIAWYQHKP GKGPRLLIHY TSTLQPGIPS RFSGSGSGRD YSFSISNLEP EDIATYYCLQ YDNLLTFGAG TKLELK	60 120 126

[00851] In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble OX40 binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the OX40 binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[00852] In an embodiment, the OX40 agonist is an OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of

the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an OX40 binding domain.

[00853] In some embodiments, the OX40 agonist is MEDI6383. MEDI6383 is an OX40 agonistic fusion protein and can be prepared as described in U.S. Patent No. 6,312,700, the disclosure of which is incorporated by reference herein.

[00854] In an embodiment, the OX40 agonist is an OX40 agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[00855] In an embodiment, the OX40 agonist is Creative Biolabs OX40 agonist monoclonal antibody MOM-18455, commercially available from Creative Biolabs, Inc., Shirley, NY, USA.

[00856] In an embodiment, the OX40 agonist is OX40 agonistic antibody clone Ber-ACT35 commercially available from BioLegend, Inc., San Diego, CA, USA.

CD27 Agonists

[00857] In an embodiment, the TNFRSF agonist is a CD27 agonist. The CD27 agonist may be any CD27 binding molecule known in the art. The CD27 binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian CD27. The CD27 agonists or CD27 binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The CD27 agonist or CD27 binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab′) fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to CD27. In an embodiment, the CD27 agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the CD27 agonist is an antigen binding protein that is a humanized antibody. In some embodiments, CD27 agonists for use in the presently disclosed methods and compositions include anti-CD27 antibodies, human anti-CD27 antibodies, mouse anti-CD27 antibodies, mammalian anti-CD27 antibodies, monoclonal anti-CD27 antibodies,

polyclonal anti-CD27 antibodies, chimeric anti-CD27 antibodies, anti-CD27 adnectins, anti-CD27 domain antibodies, single chain anti-CD27 fragments, heavy chain anti-CD27 fragments, light chain anti-CD27 fragments, anti-CD27 fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the CD27 agonist is an agonistic, anti-CD27 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line). In a preferred embodiment, the CD27 agonist is varlilumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof.

[00858] In a preferred embodiment, the CD27 agonist or CD27 binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric CD27 agonist, such as a trimeric or hexameric CD27 agonist (with three or six ligand binding domains), may induce superior receptor (CD27L) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[00859] Agonistic CD27 antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the CD27 agonist is a monoclonal antibody or fusion protein that binds specifically to CD27 antigen in a manner sufficient to reduce toxicity. In some embodiments, the CD27 agonist is an agonistic CD27 monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the CD27 agonist is an agonistic CD27 monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the CD27 agonist is an agonistic CD27 monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the CD27 agonist is an agonistic CD27 monoclonal antibody or fusion protein which abrogates Fc region functionality.

[00860] In some embodiments, the CD27 agonists are characterized by binding to human CD27 (SEQ ID NO:127) with high affinity and agonistic activity. In an embodiment, the CD27 agonist is a binding molecule that binds to human CD27 (SEQ ID NO:127). In some embodiments, the CD27 agonists are characterized by binding to macaque CD27 (SEQ ID NO:128) with high affinity and agonistic activity. In an embodiment, the CD27 agonist is a

binding molecule that binds to macaque CD27 (SEQ ID NO:128). The amino acid sequences of CD27 antigens to which a CD27 agonist or binding molecule binds is summarized in Table 16.

TABLE 16. Amino acid sequences of CD27 antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:127 human CD27, Tumor necrosis factor receptor superfamily, member 7 (Homo sapiens)	MARPHPWWLC VLGTLVGLSA TPAPKSCPER HYWAQGKLCC QMCEPGTFLV KDCDQHRKAA 60 QCDPCIPGVS FSPDHHTRPH CESCRHCNSG LLVRNCTITA NAECACRNGW QCRDKECTEC 120 DPLPNPSLTA RSSQALSPHP QPTHLPYVSE MLEARTAGHM QTLADFRQLP ARTLSTHWPP 180 QRSLCSSDFI RILVIFSGMF LVFTLAGALF LHQRRKYRSN KGESPVEPAE PCRYSCPREE 240 EGSTIPIQED YRKPEPACSP 260
SEQ ID NO:128 human CD27, Tumor necrosis factor receptor superfamily, member 7 (Macaca nemestrina)	MARPHPWWLC FLGTLVGLSA TPAPKSCPER HYWAQGKLCC QMCEPGTFLV KDCDQHRKAA 60 QCHPCIPGVS FSPDHHTRPH CESCRHCNSG LLIRNCTITA NAVCACRNGW QCRDKECTEC 120 DPPPNPSLTT WPSQALGPHP QPTHLPYVNE MLEARTAGHM QTLADFRHLP ARTLSTHWPP 180 QRSLCSSDFI RILVIFSGMF LVFTLAGTLF LHQQRKYRSN KGESPMEPAE PCPYSCPREE 240 EGSTIPIQED YRKPEPASSP 260

[00861] In some embodiments, the compositions, processes and methods described include a CD27 agonist that binds human or murine CD27 with a K_D of about 100 pM or lower, binds human or murine CD27 with a K_D of about 90 pM or lower, binds human or murine CD27 with a K_D of about 80 pM or lower, binds human or murine CD27 with a K_D of about 70 pM or lower, binds human or murine CD27 with a K_D of about 60 pM or lower, binds human or murine CD27 with a K_D of about 50 pM or lower, binds human or murine CD27 with a K_D of about 40 pM or lower, or binds human or murine CD27 with a K_D of about 30 pM or lower.

[00862] In some embodiments, the compositions, processes and methods described include a CD27 agonist that binds to human or murine CD27 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine CD27 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine CD27 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine CD27 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine CD27 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine CD27 with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine CD27 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00863] In some embodiments, the compositions, processes and methods described include a CD27 agonist that binds to human or murine CD27 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine CD27 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine CD27

with a k_{dissoc} of about 2.3 × 10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.4 × 10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.5 × 10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.6 × 10^{-5} 1/s or slower or binds to human or murine CD27 with a k_{dissoc} of about 2.7 × 10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.8 × 10^{-5} 1/s or slower, binds to human or murine CD27 with a k_{dissoc} of about 2.9 × 10^{-5} 1/s or slower, or binds to human or murine CD27 with a k_{dissoc} of about 3 × 10^{-5} 1/s or slower.

[00864] In some embodiments, the compositions, processes and methods described include a CD27 agonist that binds to human or murine CD27 with an IC_{50} of about 10 nM or lower, binds to human or murine CD27 with an IC_{50} of about 9 nM or lower, binds to human or murine CD27 with an IC_{50} of about 8 nM or lower, binds to human or murine CD27 with an IC_{50} of about 7 nM or lower, binds to human or murine CD27 with an IC_{50} of about 6 nM or lower, binds to human or murine CD27 with an IC_{50} of about 5 nM or lower, binds to human or murine CD27 with an IC_{50} of about 4 nM or lower, binds to human or murine CD27 with an IC_{50} of about 3 nM or lower, binds to human or murine CD27 with an IC_{50} of about 2 nM or lower, or binds to human or murine CD27 with an IC_{50} of about 1 nM or lower.

[00865] In a preferred embodiment, the CD27 agonist is the monoclonal antibody varlilumab, also known as CDX-1127 or 1F5, or a fragment, derivative, variant, or biosimilar thereof. Varlilumab is available from Celldex Therapeutics, Inc. Varlilumab is an immunoglobulin G1-kappa, anti-[*Homo sapiens* anti-CD27 (TNFRSF7, tumor necrosis factor receptor superfamily member 7)], *Homo sapiens* monoclonal antibody. The amino acid sequences of varlilumab are set forth in Table 17. Varlilumab comprises N-glycosylation sites at positions 299 and 299''; heavy chain intrachain disulfide bridges at positions 22-96 (V_H-V_L), 146-202 (C_H1-C_L), 263-323 (C_H2) and 369-427 (C_H3) (and at positions 22''-96'', 146''-202'', 263''-323'', and 369''-427''); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 134'-194' (C_H1-C_L) (and at positions 23'''-88''' and 134'''-194'''); interchain heavy chain-heavy chain disulfide bridges at positions 228-228'' and 231-231''; and interchain heavy chain-light chain disulfide bridges at 222-214' and 222''-214'''. The preparation and properties of varlilumab are described in International Patent Application Publication No. WO 2016/145085 A2 and U.S. Patent Application Publication Nos. US 2011/0274685 A1 and US 2012/0213771 A1, the disclosures of which are incorporated by reference herein. Clinical and preclinical studies using

varlilumab are known in the art and are described, for example, in Thomas, *et al.*, *OncoImmunology* **2014,** *3,* e27255; Vitale, *et al.*, *Clin. Cancer Res.* **2012,** *18,* 3812-21; and He, *et al.*, *J. Immunol.* **2013,** *191,* 4174-83. Current clinical trials of varlilumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT01460134, NCT02543645, NCT02413827, NCT02386111, and NCT02335918.

[00866] In an embodiment, a CD27 agonist comprises a heavy chain given by SEQ ID NO:129 and a light chain given by SEQ ID NO:130. In an embodiment, a CD27 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a CD27 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively. In an embodiment, a CD27 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively. In an embodiment, a CD27 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively. In an embodiment, a CD27 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively. In an embodiment, a CD27 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:129 and SEQ ID NO:130, respectively.

[00867] In an embodiment, the CD27 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of varlilumab. In an embodiment, the CD27 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:131, and the CD27 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:132, and conservative amino acid substitutions thereof. In an embodiment, a CD27 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132, respectively. In an embodiment, a CD27 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132, respectively. In an embodiment, a CD27 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132,

respectively. In an embodiment, a CD27 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132, respectively. In an embodiment, a CD27 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132, respectively.

[00868] In an embodiment, a CD27 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:133, SEQ ID NO:134, and SEQ ID NO:135, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:136, SEQ ID NO:137, and SEQ ID NO:138, respectively, and conservative amino acid substitutions thereof.

[00869] In an embodiment, the CD27 agonist is a CD27 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to varlilumab. In an embodiment, the biosimilar monoclonal antibody comprises an CD27 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is varlilumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a CD27 agonist antibody authorized or submitted for authorization, wherein the CD27 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is varlilumab. The CD27 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is varlilumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients

comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is varlilumab.

TABLE 17. Amino acid sequences for CD27 agonist antibodies related to varlilumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:129 heavy chain for varlilumab	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYDMHWVRQA PGKGLEWVAV IWYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGS GNWGFFDYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGKG SS	60 120 180 240 300 360 420 452
SEQ ID NO:130 light chain for varlilumab	DIQMTQSPSS LSASVGDRVT ITCRASQGIS RWLAWYQQKP EKAPKSLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNTYPRTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:131 heavy chain variable region for varlilumab	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYDMHWVRQA PGKGLEWVAV IWYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGS GNWGFFDYWG QGTLVTVSS	60 119
SEQ ID NO:132 light chain variable region for varlilumab	DIQMTQSPSS LSASVGDRVT ITCRASQGIS RWLAWYQQKP EKAPKSLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNTYPRTFGQ GTKVEIK	60 107
SEQ ID NO:133 heavy chain CDR1 for varlilumab	GFTFSSYD	8
SEQ ID NO:134 heavy chain CDR2 for varlilumab	IWYDGSNK	8
SEQ ID NO:135 heavy chain CDR3 for varlilumab	ARGSGNWGFF DY	12
SEQ ID NO:136 light chain CDR1 for varlilumab	QGISRW	6
SEQ ID NO:137 light chain CDR2 for varlilumab	AASG	4
SEQ ID NO:138 light chain CDR3 for varlilumab	QQYNTYPRT	9

[00870] In an embodiment, the CD27 agonist is an CD27 agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for

connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[00871] In an embodiment, an CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains selected from the group consisting of a variable heavy chain and variable light chain of varlilumab, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00872] In an embodiment, an CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains comprising an CD70 (CD27L) sequence (Table 18). In an embodiment, an CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains comprising a sequence according to SEQ ID NO:139. In an embodiment, an CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains comprising a soluble CD70 sequence. In an embodiment, a CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains comprising a sequence according to SEQ ID NO:140. In an embodiment, a CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains comprising a sequence according to SEQ ID NO:141.

[00873] In an embodiment, an CD27 agonist fusion protein according to structures I-A or I-B comprises one or more CD27 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:131 and SEQ ID NO:132, respectively, wherein the V_H and V_L domains are connected by a linker.

TABLE 18. Additional polypeptide domains useful as CD27 binding domains in fusion proteins (*e.g.*, structures I-A and I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:139 CD70 (CD27L)	MPEEGSGCSV RRRPYGCVLR AALVPLVAGL VICLVVCIQR FAQAQQQLPL ESLGWDVAEL 60 QLNHTGPQQD PRLYWQGGPA LGRSFLHGPE LDKGQLRIHR DGIYMVHIQV TLAICSSTTA 120 SRHHPTTLAV GICSPASRSI SLLRLSFHQG CTIASQRLTP LARGDTLCTN LTGTLLPSRN 180 TDETFFGVQW VRP 193

SEQ ID NO:140 CD70 soluble domain	SLGWDVAELQ LNHTGPQQDP RLYWQGGPAL GRSFLHGPEL DKGQLRIHRD GIYMVHIQVT LAICSSTTAS RHHPTTLAVG ICSPASRSIS LLRLSFHQGC TIASQRLTPL ARGDTLCTNL TGTLLPSRNT DETFFGVQWV RP	60 120 142
SEQ ID NO:141 CD70 soluble domain (alternative)	VAELQLNHTG PQQDPRLYWQ GGPALGRSFL HGPELDKGQL RIHRDGIYMV HIQVTLAICS STTASRHHPT TLAVGICSPA SRSISLLRLS FHQGCTIASQ RLTPLARGDT LCTNLTGTLL PSRNTDETFF GVQWVRP	60 120 137

[00874] In an embodiment, the CD27 agonist is a CD27 agonistic single-chain fusion polypeptide comprising (i) a first soluble CD27 binding domain, (ii) a first peptide linker, (iii) a second soluble CD27 binding domain, (iv) a second peptide linker, and (v) a third soluble CD27 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the CD27 agonist is a CD27 agonistic single-chain fusion polypeptide comprising (i) a first soluble CD27 binding domain, (ii) a first peptide linker, (iii) a second soluble CD27 binding domain, (iv) a second peptide linker, and (v) a third soluble CD27 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble CD27 binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the CD27 binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[00875] In an embodiment, the CD27 agonist is an CD27 agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an CD27 binding domain.

[00876] In an embodiment, the CD27 agonist is a CD27 agonist described in U.S. Patent Application Publication No. US 2014/0112942 A1, US 2011/0274685 A1, or US 2012/0213771 A1, or International Patent Application Publication No. WO 2012/004367 A1, the disclosures of which are incorporated by reference herein.

[00877] In an embodiment, the CD27 agonist is a CD27 agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

GITR (CD357) Agonists

[00878] In an embodiment, the TNFRSF agonist is a GITR agonist. The GITR agonist may be any GITR binding molecule known in the art. The GITR binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian GITR. The GITR agonists or GITR binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The GITR agonist or GITR binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab′) fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to OX40. In an embodiment, the GITR agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the GITR agonist is an antigen binding protein that is a humanized antibody. In some embodiments, GITR agonists for use in the presently disclosed methods and compositions include anti-GITR antibodies, human anti-GITR antibodies, mouse anti-OX40 antibodies, mammalian anti-GITR antibodies, monoclonal anti-OX40 antibodies, polyclonal anti-OX40 antibodies, chimeric anti-OX40 antibodies, anti-OX40 adnectins, anti-OX40 domain antibodies, single chain anti-OX40 fragments, heavy chain anti-OX40 fragments, light chain anti-OX40 fragments, anti-OX40 fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the OX40 agonist is an agonistic, anti-OX40 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[00879] In a preferred embodiment, the GITR agonist or GITR binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric GITR agonist, such as a trimeric or hexameric GITR agonist (with three or six ligand binding domains), may induce superior GITR receptor clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF

binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[00880] In some embodiments, the anti-GITR antibodies are characterized by binding to hGITR (SEQ ID NO:142) with high affinity, in the presence of a stimulating agent, *e.g.*, CD3 antibody (muromonab or OKT3), and are agonistic, and abrogate the suppression of T effector cells by Treg cells. In an embodiment, the GITR binding molecule binds to human GITR (SEQ ID NO:142). In an embodiment, the GITR binding molecule binds to murine GITR (SEQ ID NO:143). The amino acid sequences of GITR antigens to which a GITR binding molecule binds are summarized in Table 19.

TABLE 19. Amino acid sequences of GITR antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:142 human GITR, tumor necrosis factor receptor superfamily member 18 (Homo sapiens)	MAQHGAMGAF RALCGLALLC ALSLGQRPTG GPGCGPGRLL LGTGTDARCC RVHTTRCCRD YPGEECCSEW DCMCVQPEFH CGDPCCTTCR HHPCPPGQGV QSQGKFSFGF QCIDCASGTF SGGHEGHCKP WTDCTQFGFL TVFPGNKTHN AVCVPGSPPA EPLGWLTVVL LAVAACVLLL TSAQLGLHIW QLRSQCMWPR ETQLLLEVPP STEDARSCQF PEEERGERSA EEKGRLGDLW V	60 120 180 240 241
SEQ ID NO:143 murine GITR, tumor necrosis factor receptor superfamily member 18 (Mus musculus)	MGAWAMLYGV SMLCVLDLGQ PSVVEEPGCG PGKVQNGSGN NTRCCSLYAP GKEDCPKERC ICVTPEYHCG DPQCKICKHY PCQPGQRVES QGDIVFGFRC VACAMGTFSA GRDGHCRLWT NCSQFGFLTM FPGNKTHNAV CIPEPLPTEQ YGHLTVIFLV MAACIFFLTT VQLGLHIWQL RRQHMCPRET QPFAEVQLSA EDACSFQFPE EERGEQTEEK CHLGGRWP	60 120 180 228

[00881] In an embodiment, the GITR agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the GITR agonist is an antigen binding protein that is a humanized antibody. In an embodiment, the GITR agonist is an antigen binding protein that agonizes the activity of human GITR. In an embodiment, the GITR binding molecule is an antigen binding protein that is a fully human IgG1 antibody. In an embodiment, the GITR agonist is an antigen binding protein that is capable of binding Fcgamma receptor (FcγR). In an embodiment, the GITR agonist is an antigen binding protein that is capable of binding Fcgamma receptor (FcγR) such that a cluster of antigen binding proteins is formed.

[00882] In some embodiments, the compositions, processes and methods described include a GITR agonist that binds human or murine GITR with a K_D of about 100 pM or lower, binds human or murine GITR with a K_D of about 90 pM or lower, binds human or murine GITR with a K_D of about 80 pM or lower, binds human or murine GITR with a K_D of about 70 pM or lower,

binds human or murine GITR with a K_D of about 60 pM or lower, binds human or murine GITR with a K_D of about 50 pM or lower, binds human or murine GITR with a K_D of about 40 pM or lower, or binds human or murine GITR with a K_D of about 30 pM or lower.

[00883] In some embodiments, the compositions, processes and methods described include a GITR agonist that binds to human or murine GITR with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine GITR with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine GITR with a k_{assoc} of about 8×10^5 l/M·s or faster, binds to human or murine GITR with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine GITR with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine GITR with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine GITR with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00884] In some embodiments, the compositions, processes and methods described include a GITR agonist that binds to human or murine GITR with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine GITR with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine GITR with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine GITR with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine GITR with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[00885] In some embodiments, the compositions, processes and methods described include a GITR agonist that binds to human or murine GITR with an IC_{50} of about 10 nM or lower, binds to human or murine GITR with an IC_{50} of about 9 nM or lower, binds to human or murine GITR with an IC_{50} of about 8 nM or lower, binds to human or murine GITR with an IC_{50} of about 7 nM or lower, binds to human or murine GITR with an IC_{50} of about 6 nM or lower, binds to human or murine GITR with an IC_{50} of about 5 nM or lower, binds to human or murine GITR with an IC_{50} of about 4 nM or lower, binds to human or murine GITR with an IC_{50} of about 3 nM or lower, binds to human or murine GITR with an IC_{50} of about 2 nM or lower, or binds to human

or murine GITR with an IC_{50} of about 1 nM or lower.

[00886] In a preferred embodiment, the GITR agonist is an agonistic, anti-GITR monoclonal antibody (*i.e.*, an antibody derived from a single cell line). Agonist anti-GITR antibodies are known to induce strong immune responses. Cohen, *et al.*, *Cancer Res.* **2006,** *66,* 4904-12; Schaer, *et al., Curr. Opin. Investig. Drugs* **2010,** *11,* 1378-1386. In a preferred embodiment, the GITR agonist is a monoclonal antibody that binds specifically to GITR antigen. In an embodiment, the GITR agonist is a GITR receptor blocker. In some embodiments, the GITR agonist is an agonistic, anti-GITR monoclonal antibody that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the GITR agonist is an agonistic, anti-GITR monoclonal antibody that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the GITR agonist is an agonistic, anti-GITR monoclonal antibody that abrogates complement-dependent cytotoxicity (CDC).

[00887] In an embodiment, the GITR agonist is the agonistic, anti-GITR monoclonal antibody TRX518 (TolerRx, Inc.), also known as 6C8 and Ch-6C8-Agly. TRX518 is a fully-humanized IgG1 anti-human GITR monoclonal antibody in which heavy chain asparagine 297 is substituted with alanine to eliminate N-linked glycosylation, which abrogates Fc region functionality, including ADCC and CDC. Rosenzweig, *et al.*, *J. Clin. Oncol.* **2010,** *28* (supplement; abstract e13028); Jung, *et al., Cur. Opin. Biotechnology* **2011,** *22,*858-867. The amino acid sequences of TRX518 are set forth in Table 20. In some embodiments, the GITR binding molecule is the anti-human-GITR monoclonal antibody 6C8, or a variant thereof. The 6C8 antibody is an anti-GITR antibody that binds to human GITR on immune cells, *e.g.*, human T cells and dendritic cells, with high affinity. Preferably, such binding molecules abrogate the suppression of T effector cells by Treg cells and are agonistic to partially activated immune cells *in vitro* in the presence of a stimulating agent, such as CD3. In some embodiments, the GITR binding molecule is the anti-murine GITR monoclonal antibody 2F8, or a variant thereof. The preparation, properties, and uses of 6C8 and 2F8 antibodies, and their variants, are described in U.S. Patent Nos. 7,812,135; 8,388,967; and 9,028,823; the disclosures of which are incorporated by reference herein.

[00888] In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, and SEQ ID NO:147, and a light chain comprising SEQ ID NO:148. In an embodiment, the

agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 99% to a sequence selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, and SEQ ID NO:147, and a light chain with a sequence identity of greater than 99% to SEQ ID NO:148. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 98% to a sequence selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, and SEQ ID NO:147, and a light chain with a sequence identity of greater than 98% to SEQ ID NO:148. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 95% to a sequence selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, and SEQ ID NO:147, and a light chain with a sequence identity of greater than 95% to SEQ ID NO:148. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 90% to a sequence selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, and SEQ ID NO:147, and a light chain with a sequence identity of greater than 90% to SEQ ID NO:148.

[00889] In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain that comprises the leader sequence of SEQ ID NO:149 and further comprises a sequence selected from the group consisting of SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146 and SEQ ID NO:147. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a light chain that comprises the leader sequence of SEQ ID NO:148 and further comprises a sequence comprising SEQ ID NO:150.

[00890] In an embodiment, the agonistic anti-GITR monoclonal antibody (such as TRX518) comprises a variable heavy chain region (V_H) selected from the group consisting of SEQ ID NO:151 and SEQ ID NO:152, and a variable light chain region (V_L) comprising SEQ ID NO:153. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a variable heavy chain region selected from the group consisting of amino acid residues 20-138 of SEQ ID NO:151 and amino acid residues 20-138 of SEQ ID NO:152, and a variable light chain region comprising amino acid residues 20-138 of SEQ ID NO:153. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a variable heavy chain region with a sequence identity of greater than 99% to a sequence selected from the group consisting of amino acid residues 20-138 of SEQ ID NO:151 and amino acid residues 20-138 of SEQ ID NO:152, and a

variable light chain region with a sequence identity of greater than 99% to a sequence comprising amino acid residues 20-138 of SEQ ID NO:153. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a variable heavy chain region with a sequence identity of greater than 98% to a sequence selected from the group consisting of amino acid residues 20-138 of SEQ ID NO:151 and amino acid residues 20-138 of SEQ ID NO:152, and a variable light chain region with a sequence identity of greater than 98% to a sequence comprising amino acid residues 20-138 of SEQ ID NO:153. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a variable heavy chain region with a sequence identity of greater than 95% to a sequence selected from the group consisting of amino acid residues 20-138 of SEQ ID NO:151 and amino acid residues 20-138 of SEQ ID NO:152, and a variable light chain region with a sequence identity of greater than 95% to a sequence comprising amino acid residues 20-138 of SEQ ID NO:153. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a variable heavy chain region with a sequence identity of greater than 90% to a sequence selected from the group consisting of amino acid residues 20-138 of SEQ ID NO:151 and amino acid residues 20-138 of SEQ ID NO:152, and a variable light chain region with a sequence identity of greater than 90% to a sequence comprising amino acid residues 20-138 of SEQ ID NO:153.

[00891] In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_H region comprising at least one CDR1 region comprising the amino acid sequence of SEQ ID NO:154; at least one CDR2 region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:155 and SEQ ID NO:156; and at least one CDR3 region comprising the amino acid sequence of SEQ ID NO:157; and a V_L region comprising at least one CDR1 region comprising the amino acid sequence of SEQ ID NO:158; at least one CDR2 region comprising the amino acid sequence of SEQ ID NO:159; and at least one CDR3 region comprising the amino acid sequence of SEQ ID NO:160. In an embodiment, the invention provides isolated nucleic acid molecules encoding a polypeptide sequence comprising a 6C8 CDR, *e. g.*, comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises the six CDRs represented by the amino acid sequences of SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an

embodiment, the GITR binding molecule that specifically binds to GITR comprises the six CDRs represented by the amino acid sequences of SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least one CDR domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least two CDR domains comprising an amino acid sequence selected from the group consisting of SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having CDR domains comprising the amino acid sequences of SEQ ID NO:158, SEQ ID NO:159, and SEQ ID NO:160. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least one CDR domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:154, SEQ ID NO:155, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least two CDR domains comprising an amino acid sequence selected from the group consisting of SEQ ID NO:154, SEQ ID NO:155, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having CDR domains comprising the amino acid sequences of SEQ ID NO:154, SEQ ID NO:155, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least one CDR domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:154, SEQ ID NO:156, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having at least two CDR domains comprising an amino acid sequence selected from the group consisting of SEQ ID NO:154, SEQ ID NO:156, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L having CDR domains comprising the amino acid sequences of SEQ ID NO:154, SEQ ID NO:156, and SEQ ID NO:157. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_H domain comprising a CDR set forth in SEQ ID NO:154 (CDR1). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_H domain comprising a CDR set forth in SEQ ID NO:155 (CDR2, "N" variant). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_H domain comprising a CDR set forth in SEQ ID NO:156 (CDR3, "Q" variant). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_H domain

comprising a CDR set forth in SEQ ID NO:157 (CDR3). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L domain comprising a CDR set forth in SEQ ID NO:158 (CDR1). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L domain comprising a CDR set forth in SEQ ID NO:159 (CDR2). In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a V_L domain comprising a CDR set forth in SEQ ID NO:160 (CDR3).

[00892] In an embodiment, the agonistic anti-GITR monoclonal antibody is a chimeric 6C8 monoclonal antibody, or an antigen-binding fragment, derivative, conjugate, or variant thereof. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain selected from the group consisting of SEQ ID NO:162 and SEQ ID NO:163, and a light chain comprising SEQ ID NO:161. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 99% to a sequence selected from the group consisting of SEQ ID NO:162 and SEQ ID NO:163, and a light chain with a sequence identity of greater than 99% to SEQ ID NO:161. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 98% to a sequence selected from the group consisting of SEQ ID NO:162 and SEQ ID NO:163, and a light chain with a sequence identity of greater than 98% to SEQ ID NO:161. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 95% to a sequence selected from the group consisting of SEQ ID NO:162 and SEQ ID NO:163, and a light chain with a sequence identity of greater than 95% to SEQ ID NO:161. In an embodiment, the agonistic anti-GITR monoclonal antibody comprises a heavy chain with a sequence identity of greater than 90% to a sequence selected from the group consisting of SEQ ID NO:162 and SEQ ID NO:163, and a light chain with a sequence identity of greater than 90% to SEQ ID NO:161.

[00893] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to TRX518 or 6C8. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the

reference medicinal product or reference biological product is TRX518 or 6C8. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is TRX518 or 6C8. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is TRX518 or 6C8. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is TRX518 or 6C8.

TABLE 20. Amino acid sequences for GITR agonist antibodies related to TRX518 and 6C8.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:144 humanized 6C8 heavy chain variant	QVTLRESGPA LVKPTQTLTL TCTFSGFSLS TSGMGVGWIR QPPGKALEWL AHIWWDDDKY YNPSLKSRLT ISKDTSKNQV VLTMTNMDPV DTATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449
SEQ ID NO:145 humanized 6C8 heavy chain variant	QVTLRESGPA LVKPTQTLTL TCTFSGFSLS TSGMGVGWIR QPPGKALEWL AHIWWDDDKY YNPSLKSRLT ISKDTSKNQV VLTMTNMDPV DTATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449
SEQ ID NO:146 humanized 6C8 heavy chain variant	QVTLRESGPA LVKPTQTLTL TCTFSGFSLS TSGMGVGWIR QPPGKALEWL AHIWWDDDKY YQPSLKSRLT ISKDTSKNQV VLTMTNMDPV DTATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449
SEQ ID NO:147	QVTLRESGPA LVKPTQTLTL TCTFSGFSLS TSGMGVGWIR QPPGKALEWL AHIWWDDDKY YQPSLKSRLT ISKDTSKNQV VLTMTNMDPV DTATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG	60 120 180

Identifier	Sequence (One-Letter Amino Acid Symbols)	
humanized 6C8 heavy chain variant	LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	240 300 360 420 449
SEQ ID NO:148 humanized 6C8 light chain	EIVMTQSPAT LSVSPGERAT LSCKASQNVG TNVAWYQQKP GQAPRLLIYS ASYRYSGIPA RFSGSGSGTE FTLTISSLQS EDFAVYYCQQ YNTDPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:149 6C8 heavy chain leader	MDRLTFSFLL LIVPAYVLS	19
SEQ ID NO:150 6C8 light chain leader	METQSQVFVY MLLWLSGVDG	20
SEQ ID NO:151 humanized 6C8 heavy chain variable region variant	MDRLTFSFLL LIVPAYVLSQ VTLKESGPGI LKPSQTLSLT CSFSGFSLST SGMGVGWIRQ PSGKGLEWLA HIWWDDDKYY NPSLKSQLTI SKDTSRNQVF LKITSVDTAD AATYYCARTR RYFPFAYWGQ GTLVTVSS	60 120 138
SEQ ID NO:152 humanized 6C8 heavy chain variable region variant	MDRLTFSFLL LIVPAYVLSQ VTLKESGPGI LKPSQTLSLT CSFSGFSLST SGMGVGWIRQ PSGKGLEWLA HIWWDDDKYY QPSLKSQLTI SKDTSRNQVF LKITSVDTAD AATYYCARTR RYFPFAYWGQ GTLVTVSS	60 120 138
SEQ ID NO:153 humanized 6C8 light chain variable region	METQSQVFVY MLLWLSGVDG DIVMTQSQKF MSTSVGDRVS VTCKASQNVG TNVAWYQQKP GQSPKALIYS ASYRYSGVPD RFTGSGSGTD FTLTINNVHS EDLAEYFCQQ YNTDPLTFGA GTKLEIK	60 120 127
SEQ ID NO:154 6C8 heavy chain CDR1	GFSLSTSGMG VG	12
SEQ ID NO:155 6C8 heavy chain CDR2 variant	HIWWDDDKYY NPSLKS	16
SEQ ID NO:156 6C8 heavy chain CDR2 variant	HIWWDDDKYY QPSLKS	16
SEQ ID NO:157 6C8 heavy chain CDR3	TRRYFPFAY	9
SEQ ID NO:158 6C8 light chain CDR1	KASQNVGTNV A	11
SEQ ID NO:159 6C8 light chain CDR2	SASYRYS	7
SEQ ID NO:160 6C8 light chain CDR3	QQYNTDPLT	9
SEQ ID NO:161 chimeric 6C8 heavy chain variant	QVTLKESGPG ILKPSQTLSL TCSFSGFSLS TSGMGVGWIR QPSGKGLEWL AHIWWDDDKY YNPSLKSQLT ISKDTSRNQV FLKITSVDTA DAATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449
SEQ ID NO:162 chimeric 6C8 heavy chain variant	QVTLKESGPG ILKPSQTLSL TCSFSGFSLS TSGMGVGWIR QPSGKGLEWL AHIWWDDDKY YNPSLKSQLT ISKDTSRNQV FLKITSVDTA DAATYYCART RRYFPFAYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:163 chimeric 6C8 light chain variant	DIVMTQSQKF MSTSVGDRVS VTCKASQNVG TNVAWYQQKP GQSPKALIYS ASYRYSGVPD RFTGSGSGTD FTLTINNVHS EDLAEYFCQQ YNTDPLTFGA GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214

[00894] In an embodiment, the GITR agonist is an agonistic anti-GITR monoclonal antibody with described in U.S. Patent No. 8,709,424; U.S. Patent Application Publication Nos. US 2012/0189639 A1 and US 2014/0348841 A1, and International Patent Application Publication No. WO 2011/028683 A1 (Merck Sharp & Dohme Corp.), the disclosures of which are incorporated by reference herein. In an embodiment, the GITR agonist is an agonistic, anti-GITR monoclonal antibody selected from the group consisting of 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6, and fragments, variants, derivatives, or biosimilars thereof. The structure, properties, and preparation of these antibodies are described in U.S. Patent No. 8,709,424; U.S. Patent Application Publication Nos. US 2012/0189639 A1 and US 2014/0348841 A1, the disclosures of which are incorporated herein by reference.

[00895] In some embodiments, the agonistic, anti-GITR monoclonal antibody comprises a humanized heavy chain variable domain (V_H) comprising a sequence selected from the group consisting of SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, or a variant, fragment, or biosimilar thereof, and a humanized heavy chain variable domain (V_H) comprising a sequence selected from the group consisting of SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:181, SEQ ID NO:183, SEQ ID NO:185, SEQ ID NO:187, SEQ ID NO:189, SEQ ID NO:191, SEQ ID NO:193, SEQ ID NO:195, SEQ ID NO:197, SEQ ID NO:199, SEQ ID NO:201, SEQ ID NO:203, SEQ ID NO:205, SEQ ID NO:207, or a variant, fragment, or biosimilar thereof (Table 21). In some embodiments, the agonistic, anti-GITR monoclonal antibody further comprises a heavy chain constant region, wherein the heavy chain constant region comprises a γ1, γ2, γ3, or γ4 human heavy chain constant region or a variant thereof. In some embodiments, the light chain constant region comprises a lambda or a kappa human light chain constant region.

[00896] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, and 31H6.

TABLE 21. Amino acid sequences for GITR agonist antibodies related to the GITR agonists described in International Patent Application Publication No. WO 2011/028683 A1.

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:164 36E5 heavy chain variable region	EVNLVESGGG LVKPGGSLKV SCAASGFTFS SYAMSWVRQT PEKRLEWVAS ISSGGTTYYP 60 DSVKGRFTIS RDNARNILYL QMSSLRSEDT AMYYCARVGG YYDSMDYWGQ GISVTDSS 118

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:165 36E5 light chain variable region	DIVLTQSPAS LAVSLGQRAT ISCRASESVD NYGVSFMNWF QQKPGQPPKL LIYAASNQGS GVPARFSGSG SGTDFSLNIH PMEEDDTAMY FCQQTKEVTW TFGGGTKLEI KRA	60 113
SEQ ID NO:166 3D6 heavy chain variable region	EVQLVESGGG LVQPGRSLKL SCAASGFTFS DYYMAWVRQA PTKGLEWVAY IHANGGSTYY RDSVRGRFSI SRDNGKSTLY LQMDSLRSED TATYYCTTGS FMYAADYYIM DAWGQGASVT VSS	60 120 123
SEQ ID NO:167 3D6 light chain variable region	DVVMTQTPVS LSVSLGNQAS ISCRSSQSLL HSDGNTFLSW YFQKPGQSPQ LLIYLASNRF SGVSNRFSGS GSGTDFTLKI SRVEPEDLGV YYCFQHTHLP LTFGSGTKLE IKR	60 113
SEQ ID NO:168 61G6 heavy chain variable region	DVQLQESGPG LVKPSQSLSL TCTVTGYSIT SDYAWNWIRQ FPGNKLEWMG YISYSGSTRY NPSLKSRISI TRDTSKNQFF LQLNSVTSED TATYYCARQL GLRFFDYWGQ GTTLTVSS	60 118
SEQ ID NO:169 61G6 light chain variable region	QIVLTQSPAL MSASPGEKVT MTCSANSTVN YMYWYQQKPR SSPKPCIYLT SNLASGVPAR FSGSGSGTSY SLTISSMEAE DAATYYCQQW NSNPPTFGAG TKLELRRA	60 108
SEQ ID NO:170 6H6 heavy chain variable region	QVQLQQSGAE LMKPGASVKI SCKATGYTFS RYWIEWIKQR PGHGLEWIGE ILPGSGSSNY NEKFKDKATF TADTSSNTAY MQFSSLTSED SAVYYCARKV YYYAMDFWGQ GTSVTVSS	60 118
SEQ ID NO:171 6H6 light chain variable region	QIVLTQSPAI MSVSLGERVT VTCTASSSVS SSYFHWYQQK PGSSPKLWIY STSNLASGVP ARFSGSGSGT SYSLTISTME AEDAATYYCH QYHRSPRTFG GGTKLEIKRA	60 110
SEQ ID NO:172 61F6 heavy chain variable region	QVQLQQSGAE LARPGASVKM SCKASGYTFT SYTMHWVKQR PGQGLEWIGY INPRSVYTNY NQKFKDKATL TADKSSSTAY MQLSSLTSED SAVYYCARLG GYYDTMDYWG QGTSVTVSS	60 119
SEQ ID NO:173 61F6 light chain variable region	DIVVTQSPAS LAVSLGQRAT ISCRASESVD NYGISFMNWF QQKPGQPPKL LIYAASNQGS GVPARFSGSG SGTDFSLNIH PMEEDDTAVY FCQQSKEVPF TFGSGTKLEI KRA	60 113
SEQ ID NO:174 1D8 heavy chain variable region	QVTLKESGPG ILKPSQTLSL TCSFSGFSLS TSGMGVGWIR QPSGKGLEWL AHIWWDDDKY YSPSLKSQLT ISKDTSRNQV FLKITSLDTA DTATYYCVRS YYYGSSGAMD YWGQGTSVTV SS	60 120 122
SEQ ID NO:175 1D8 light chain variable region	DIVMTQTPLS LPVSLGDQAS ISCRSSQSLV HSDGNTYLHW YLQKPGQSPK LLIYKVSKRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVP PTFGGGTKLE IKRADAAP	60 118
SEQ ID NO:176 17F10 heavy chain variable region	EVKLVESGGG FVKPGGSLKL SCAASGFTVR NYAMSWVRQT PEKRLEWVAS ISTGDRSYLP DSMKGRFTIS RDNARNILYL QMSSLRSEDT AIYYCQRYFD FDSFAFWGQG TLVTVSA	60 117
SEQ ID NO:177 17F10 light chain variable region	DIQMTQTPSS LSASLGDRVT ISCRASQDIN NFLNWYQQKP DGSLKLLIYY TSKLHSGVPS RFSGSGSGTD FSLTISNLDQ EDVATYFCQQ GHTLPPTFGG GTKLEVKRAD AAP	60 113
SEQ ID NO:178 35D8 heavy chain variable region	EVQLQESGPS LVKPSQTLSL TCSVTGDSIT SGYWNWIRKF PGNKLEYMGY ISYSGSTYYN PSLRGRISIT RDTSKSQYYL QLSSVTTEDT ATYYCSRRHL GSGYGWFAYW GQGTLVTVSA	60 120
SEQ ID NO:179 35D8 light chain variable region	DIVMTQSHKF MSTSVGDRVS ITCKASQDVN TAVAWYQQKP GQSPKLLIYW ASTRHTGVPD RFTGSGSGTD YALTINSVQA EDLALYYCQQ HSYTPPWTFG GGTKLEIRRA DAAP	60 114
SEQ ID NO:180 49A1 heavy chain variable region	EVQLQESGPS LVKPSQTLSL TCSVTGDSIT SGYWNWIRKF PGNKFEYMGF ISYSGNTYYN PSLRSRISIT RDTSKNQYFL HLNSVTTEDT ATYYCSRRHL ISGYGWFAYW GQGTLVTVSA	60 120
SEQ ID NO:181 49A1 light chain variable region	VIVMTQSHKF MSTSIGDRVN ITCKASQDVI SAVAWYQQKP GQSPKLLIYW ASTRHTGVPD RFTGSGSGTD FTLTINSVQA EDRALYYCQQ HSYTPPWTFG GGTNLEIKRA DAAP	60 114
SEQ ID NO:182 9E5 heavy chain variable region	QVTLKESGPG ILQPSQTLSL TCTFSGFSLS TYGVGVGWIR QPSGKGLEWL ANIWWDDDNY YNPSLIHRLT VSKDTSNNQA FLKITNVDTA ETATYYCAQI KEPRDWFFEF WGPGTMVSVS S	60 120 121
SEQ ID NO:183 9E5 light chain variable region	DIQMTQTPSS MPASLGERVT IFCRASQGVN NFLTWYQQKP DGTIKPLIFY TSNLQSGVPS RFSGSGSGTD YSLSISSLEP EDFAMYYCQQ YHGFPNTFGA GTKLELKRAD AAP	60 113
SEQ ID NO:184 31H6 heavy chain variable region	QVTLKESGPG ILQPSQTLSL TCTFSGFSLS TYGVGVGWIR QPSGKGLEWL ANIWWDDDKY YNPSLKNRLT ISKDTSNNQA FLKITNVDTA ETATYYCAQI KEPRDWFFEF WGPGTMVSVS S	60 120 121
SEQ ID NO:185 31H6 light chain variable region	DIQMTQTPSS MPASLGERVT IFCRASQGVN NYLTWYQQKP DGTIKPLIFY TSNLQSGVPS RFSGSGSGTD YSLSISSLEP EDFAMYYCQQ YHGFPNTFGA GTKLELKRAD AAP	60 113

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:186 humanized 36E5 heavy chain variable region	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAS ISSGGTTYYP DSVKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARVGG YYDSMDYWGQ GTLVTVSS	60 118
SEQ ID NO:187 humanized 36E5 light chain variable region	EIVLTQSPGT LSLSPGERAT LSCRASESVD XYGVSFMNWY QQKPGQAPRL LIYAASXQGS GIPDRFSGSG SGTDFTLTIS RLEPEDFAVY YCQQTKEVTW TFGQGTKVEI KR	60 112
SEQ ID NO:188 humanized 3D6 heavy chain variable region	QVQLVESGGG VVQPGRSLRL SCAASGFTFS DYYMAWVRQA PGKGLEWVAY IHANGGSTYY RDSVRGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCXXGS FMYAADYYIM DAWGQGTLVT VSS	60 120 123
SEQ ID NO:189 humanized 3D6 light chain variable region	DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSDGNTFLSW YLQKPGQSPQ LLIYLASNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQHTHLP LTFGQGTKVE IKR	60 113
SEQ ID NO:190 humanized 61G6 heavy chain variable region	QVQLQESGPG LVKPSETLSL TCTVSGYSIT SDYAWNWIRQ PPGKGLEWXG YISYSGSTRY NPSLKSRXTI SXDTSKNQFS LKLSSVTAAD TAVYYCARQL GLRFFDYWGQ GTLVTVSS	60 118
SEQ ID NO:191 humanized 61G6 light chain variable region	EIVLTQSPGT LSLSPGERAT LSCSANSTVN YMYWYQQKPG QAPRXXIYLT SNLASGIPDR FSGSGSGTDF TLTISRLEPE DFAVYYCQQW NSNPPTFGQG TKVEIKR	60 107
SEQ ID NO:192 humanized 6H6 heavy chain variable region	QVQLVQSGAE VKKPGASVKV SCKASGYTFS RYWIEWVRQA PGQGLEWXGE ILPGSGSSNY NEKFKDRXTX TXDTSTSTAY MELRSLRSDD TAVYYCARKV YYYAMDFWGQ GTLVTVSS	60 118
SEQ ID NO:193 humanized 6H6 light chain variable region	EIVLTQSPGT LSLSPGERAT LSCTASSSVS SSYFHWYQQK PGQAPRLXIY STSNLASGIP DRFSGSGSGT DXTLTISRLE PEDFAVYYCH QYHRSPRTFG QGTKVEIKR	60 109
SEQ ID NO:194 humanized 61F6 heavy chain variable region	QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYTMHWVRQA PGQGLEWXGY INPRSVYTNY NQKFKDRXTX TXDXSTSTAY MELRSLRSDD TAVYYCARLG GYYDTMDYWG QGTLVTVSS	60 119
SEQ ID NO:195 humanized 61F6 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRASESVD NYGISFMNWY QQKPGKAPKL LIYAASNQGS GVPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQQSKEVPF TFGQGTKVEI KR	60 112
SEQ ID NO:196 humanized 1D8 heavy chain variable region	QVQLVESGGG VVQPGRSLRL SCAXSGFSLS TSGMGVGWVR QAPGKGLEWV AHIWWDDDKY YSPSLKSRXT ISXDXSKNTX YLQMNSLRAE DTAVYYCXRS YYYGSSGAMD YWGQGTLVTV SS	60 120 122
SEQ ID NO:197 humanized 1D8 light chain variable region	DIVMTQSPLS LPVTPGEPAS ISCRSSQSLV HSDGNTYLHW YLQKPGQSPQ LLIYKVSKRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP PTFGQGTKVE IKR	60 113
SEQ ID NO:198 humanized 17F10 heavy chain variable region	QVQLVESGGG VVQPGRSLRL SCAASGFTVR NYAMSWVRQA PGKGLEWVAS ISTGDRSYLP DSMKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCXRYFD FDSFAFWGQG TLVTVSS	60 117
SEQ ID NO:199 humanized 17F10 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRASQDIN NFLNWYQQKP GKAPKLLIYY TSKLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GHTLPPTFGQ GTKVEIKR	60 108
SEQ ID NO:200 humanized 35D8 heavy chain variable region	QVQLQESGPG LVKPSETLSL TCTVSGDSIT SGYWNWIRQP PGKGLEXXGY ISYSGSTYYN PSLRGRVTIS XDTSKNQFSL KLSSVTAADT AVYYCXRRHL GSGYGWFAYW GQGTLVTVSS	60 120
SEQ ID NO:201 humanized 35D8 light chain variable region	DIVMTQSPDS LAVSLGERAT INCKASQDVN TAVAWYQQKP GQPPKLLIYW ASTRHTGVPD RFSGSGSGTD XTLTISSLQA EDVAVYYCQQ HSYTPPWTFG QGTKVEIKR	60 109
SEQ ID NO:202	QVQLQESGPG LVKPSETLSL TCTVSGDSIT SGYWNWIRQP PGKGLEXXGF ISYSGNTYYN PSLRSRXTIS XDTSKNQXSL KLSSVTAADT AVYYCXRRHL ISGYGWFAYW GQGTLVTVSS	60 120

Identifier	Sequence (One-Letter Amino Acid Symbols)	
humanized 49A1 heavy chain variable region		
SEQ ID NO:203 humanized 49A1 light chain variable region	XIVMTQSPDS LAVSLGERAT INCKASQDVI SAVAWYQQKP GQPPKLLIYW ASTRHTGVPD RFSGSGSGTD FTLTISSLQA EDVAVYYCQQ HSYTPPWTFG QGTKVEIKR	60 109
SEQ ID NO:204 humanized 9E5 heavy chain variable region	QVQLQESGPG LVKPSETLSL TCTXSGFSLS TYGVGVGWIR QPPGKGLEWX XNIWWDDDNY YNPSLIHRXT XSXDTSKNQX SLKLSSVTAA DTAVYYCAXI KEPRDWFFEF WGQGTLVTVS S	60 120 121
SEQ ID NO:205 humanized 9E5 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRASQGVN NFLTWYQQKP GKAPKXLIXY TSNLQSGVPS RFSGSGSGTD XTLTISSLQP EDFATYYCQQ YHGFPNTFGQ GTKVEIKR	60 108
SEQ ID NO:206 humanized 31H6 heavy chain variable region	QVQLQESGPG LVKPSETLSL TCTXSGFSLS TYGVGVGWIR QPPGKGLEWX XNIWWDDDKY YNPSLKNRXT ISXDTSKNQX SLKLSSVTAA DTAVYYCAXI KEPRDWFFEF WGQGTLVTVS S	60 120 121
SEQ ID NO:207 humanized 31H6 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRASQGVN NYLTWYQQKP GKAPKXLIXY TSNLQSGVPS RFSGSGSGTD XTLTISSLQP EDFATYYCQQ YHGFPNTFGQ GTKVEIKR	60 108

[00897] In an embodiment, the GITR agonist is an agonistic, anti-GITR monoclonal antibody described in U.S. Patent Application Publication No. US 2013/0108641 A1 (Sanofi SA) and International Patent Application Publication No. WO 2011/028683 A1 (Sanofi SA), the disclosures of which are incorporated by reference herein. In an embodiment, a GITR binding molecule includes monoclonal antibodies and variants and fragments thereof, including humanized and chimeric recombinant antibodies, that bind human GITR, comprising a heavy chain variable domain (V_H) selected from the group consisting of SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:219, SEQ ID NO:221, SEQ ID NO:223, and SEQ ID NO:225, and a light chain variable domain (V_L) selected from the group consisting of SEQ ID NO:209, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, and SEQ ID NO:226 (Table 22). In an embodiment, the GITR binding molecule is an agonistic, anti-GITR monoclonal antibody comprising (a) one, two, or three heavy chain CDRs selected from the group consisting of SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:249, and conservative amino acid substitutions thereof, and (b) one, two, or three light chain CDRs selected from the group consisting of SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ

ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, and conservative amino acid substitutions thereof (Table 22). In an embodiment, the GITR agonist is an agonistic, anti-GITR monoclonal antibody selected from the group consisting of 2155, 698, 706, 827, 1649, and 1718, and and fragments, derivatives, variants, biosimilars, and combinations thereof.

[00898] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 2155, 698, 706, 827, 1649, and 1718. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 2155, 698, 706, 827, 1649, and 1718. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 2155, 698, 706, 827, 1649, and 1718. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 2155, 698, 706, 827, 1649, and 1718. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 2155, 698, 706, 827, 1649, and 1718.

TABLE 22. Amino acid sequences for GITR agonist antibodies related to the GITR agonists described in International Patent Application Publication No. WO 2011/028683 A1.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:208 2155 variable heavy chain	EVKLVESGGG LVKPGGSLKL SCGASGFTIS SYAMSWVRQS PEKRLEWVAI ISTGGSTYYP DSVRGRFTIS RDNARNSLYL QMSSLRSEDT AMYYCARVGG YYDSMDHWGQ GTSVTVSS	60 118
SEQ ID NO:209 2155 variable light chain	DIVLTQSPAS LAVSLGQRAT ISCRASETVD NYGISFMNWF QQKPGQSPKL LIYAASNQGS GVPARFSGSG SGTDFSLNIH PMEEDDTAMY FCQQSKEVPW TFGGGTKLEI K	60 111
SEQ ID NO:210 2155 humanized (HC1) heavy chain	QVTLVESGGG LVKPGGSLTL SCGASGFTIS SYAMSWVRQS PGKALEWVAI ISTGGSTYYP DSVRGRFTIS RDNAKNSLYL TMSSLDSVDT AMYYCARVGG YYDSMDHWGQ GTSVT	60 115
SEQ ID NO:211 2155 humanized (HC2) heavy chain	QVTLVESGGG LVKPGGSLTL SCGASGFTIS SYAMSWVRQS PGKALEWVAI ISTGGSTYYP DSVRGRFTIS RDNAKNSLYL TMSSLDSVDT ATYYCARVGG YYDSMDHWGQ GTSVT	60 115
SEQ ID NO:212 2155 humanized (HC3a) heavy chain	QVTLVESGGG LVKPGGSLTL SCGASGFTIS SYAMSWVRQS PGKALEWVAI ISTGGSTYYP DKFRGRFTIS RDNAKNSLYL TMSSLRSEDT ATYYCARVGG YYDSMDHWGQ GTSVT	60 115
SEQ ID NO:213 humanized (HC3b) heavy chain	QVTLKESGGG LVKPGGSLTL SCGASGFTIS SYAMSWVRQS PGKALEWVAI ISTGGSTYYP DKFRGRFTIS RDNAKNSLYL TMSSLRSEDT ATYYCARVGG YYDSMDHWGQ GTSVT	60 115
SEQ ID NO:214 humanized (HC4) heavy chain	EVQLVESGGG LIQPGGSLKL SCAASGFTIS SYAMSWVRQA PGKGLEWVAI ISTGGSTYYA DSVKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARVGG YYDSMDHWGQ GTSVT	60 115
SEQ ID NO:215 2155 humanized (LC1) light chain	DIVLTQSPAS LAASVGDRAT ISCRASETVD NYGISFMNWF QQKPGKSPKL LIYAASNQGS GVPARFSGSG SGTDFSLNIH PMQPDDTATY FCQQSKEVPW TFGGGTKLE	60 109
SEQ ID NO:216 2155 humanized (LC2a) light chain	DIVLTQSPAS LSASVGDRAT ISCRASETVD NYGISFMNWF QQKPGQSPKL LIYAASNQGS GVPARFSGSG SGTDFSLTIS PMQPDDTATY YCQQSKEVPW TFGGGTKLE	60 109
SEQ ID NO:217 2155 humanized (LC2b) light chain	DIVLTQSPAS LSASVGDRAT ISCRASETVD NYGISYMNWF QQKPGQSPKL LIYAASNQGS GVPARFSGSG SGTDFSLTIS PMQPDDTATY YCQQSKEVPW TFGGGTKLE	60 109
SEQ ID NO:218 2155 humanized (LC3) light chain	DIVLTQSPAS LAVSPGQRAT ITCRASETVD NYGISFMNWF QQKPGQPPKL LIYAASNQGS GVPARFSGSG SGTDFTLTIN PVEADDTANY YCQQSKEVPW TFGQGTKVE	60 109
SEQ ID NO:219 698 variable heavy chain	EVQLQQSGTV LARPGASVKM SCEASGYSFT TYWMHWIKQR PGQGLEWIGA IYPGNSDTGY NQKFKGKAKL TAVTSATTAY MELSSLTDED SAVYYCTRTS TYPHFDYWGQ GTTLTVSS	60 118
SEQ ID NO:220 698 variable light chain	DILLTQSPAI LSVSPGERVS FSCRASQSIG TSIHWYQQRT NGSPRLLIKY ASESISGIPS RFSGSGSGTD FTLNINSVES EDIADYYCQQ SNNWPLTFGA GTKLELK	60 107
SEQ ID NO:221 706 variable heavy chain	EVQLQQSGTV LARPGASVKM SCEASGYSFT TYWMHWIKQR PGQGLEWIGA IYPGNSDTGY NQKFKGKAKL TAVTSASTAY MELSSLTNED SAVYYCTRTS TYPHFDYWGQ GTTLTVSS	60 118
SEQ ID NO:222 706 variable light chain	DILLTQSPAI LSVSPGERVS FSCRASQSIG TSIHWYQQRT NGSPRLLIKY ASESISGIPS RFSGSGSGTD FTLNINSVES EDIADYYCQQ TNNWPLTFGA GTKLELK	60 107
SEQ ID NO:223 827 variable heavy chain	EVQLQQSGTV LARPGASVKM SCETSGYSFT TYWIHWIKQR PGQGLEWIAT IYPGNSDAGY NQKFRGKAKL TAVTSASTAY MELSSLTNED SAVYYCTRSS TYPHFDYWGQ GTTLTVSS	60 118
SEQ ID NO:224 827 variable light chain	DILLTQSPAI LSVSPGERVS FSCRASQSIG TSIHWYQQRT NDSPRLLIKY ASESISGIPS RFSGSGSGTD FTLNINSVES EDIADYYCQQ TNNWPLTFGA GTKLELK	60 107
SEQ ID NO:225 1718 variable heavy chain	QVQVQQSGPE LVKPGASVRI SCKASDYTFT NYYIHWVRQR PGQGLEWLGW IYPGKGYTNY NEKFKGKATL TADKSSSTAY MQFSSLTSED SAVYFCASGY GNYYFPYWGQ GTLVTVSA	60 118

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:226 1718 variable light chain	IQMTQSSSYL SVSLGGRVTI TCKASDHIKN WLAWYQQKPG NVPRLLMSAA TSLETGFPSR FSGSGSGKDF TLTITSLQTE DVATYYCQQY WSTPWTFGGG TKLEIK	60 106
SEQ ID NO:227 2155 heavy chain CDR3	VGGYYDSMDH	10
SEQ ID NO:228 2155 heavy chain CDR2	IISTGGSTY	9
SEQ ID NO:229 2155 heavy chain CDR1	GFTISSYAMS	10
SEQ ID NO:230 2155 light chain CDR3	QQSKEVPWT	9
SEQ ID NO:231 2155 light chain CDR2	AASNQGS	7
SEQ ID NO:232 2155 light chain CDR1	RASETVDNYG ISFMN	15
SEQ ID NO:233 698 and 706 heavy chain CDR3	TSTYPHFDY	9
SEQ ID NO:234 698 and 706 heavy chain CDR2	AIYPGNSDTG	10
SEQ ID NO:235 698 and 706 heavy chain CDR1	GYSFTTYWMH	10
SEQ ID NO:236 698 light chain CDR3	QQSNNWPLT	9
SEQ ID NO:237 698, 706, 827, and 1649 light chain CDR2	KYASESIS	8
SEQ ID NO:238 698, 706, 827, and 1649 light chain CDR1	RASQSIGTSI H	11
SEQ ID NO:239 706, 827, and 1649 light chain CDR3	QQTNNWPLT	9
SEQ ID NO:240 827 and 1649 heavy chain CDR3	SSTYPHFDY	9
SEQ ID NO:241 827 heavy chain CDR2	TIYPGNSDAG	10
SEQ ID NO:242 1649 heavy chain CDR2	AIYPGNSDAG	10
SEQ ID NO:243 1718 heavy chain CDR3	GYGNYYFPY	9
SEQ ID NO:244 1718 heavy chain CDR2	WIYPGKGYTN	10
SEQ ID NO:245 1718 heavy chain CDR1	DYTFTNYYI	9
SEQ ID NO:246	QQTWSTPWT	9

Identifier	Sequence (One-Letter Amino Acid Symbols)	
1718 light chain CDR3		
SEQ ID NO:247 1718 light chain CDR2	AATSLET	7
SEQ ID NO:248 1718 light chain CDR1	KASDHIKNWL A	11
SEQ ID NO:249 827 and 1649 heavy chain CDR1	GYSFTTYWIH	10

[00899] In a preferred embodiment, the GITR agonist is the monoclonal antibody 1D7, or a fragment, derivative, variant, or biosimilar thereof. 1D7 is available from Amgen, Inc. The preparation and properties of 1D7 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 1D7 are set forth in Table 23.

[00900] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:250 and a light chain given by SEQ ID NO:251. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:250 and SEQ ID NO:251, respectively.

[00901] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 1D7. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:252, and the GITR agonist light chain

variable region (V_L) comprises the sequence shown in SEQ ID NO:253, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:252 and SEQ ID NO:253, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:252 and SEQ ID NO:253, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:252 and SEQ ID NO:253, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:252 and SEQ ID NO:253, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:252 and SEQ ID NO:253, respectively.

[00902] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:254, SEQ ID NO:255, and SEQ ID NO:256, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:257, SEQ ID NO:258, and SEQ ID NO:259, respectively, and conservative amino acid substitutions thereof.

[00903] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 1D7. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 1D7. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 1D7. The GITR agonist antibody may be authorized by a drug regulatory authority such as the

U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 1D7. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 1D7.

TABLE 23. Amino acid sequences for GITR agonist antibodies related to 1D7.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:250 1D7 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVTV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGKYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:251 1D7 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:252 1D7 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVTV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGKYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:253 1D7 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:254 1D7 heavy chain CDR1	SYGMH	5
SEQ ID NO:255 1D7 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:256 1D7 heavy chain CDR3	GGQLGKYYYY GMDV	14
SEQ ID NO:257 1D7 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:258 1D7 light chain CDR2	DASSLQS	7
SEQ ID NO:259 1D7 light chain CDR3	LQHNNYPWT	9

[00904] In a preferred embodiment, the GITR agonist is the monoclonal antibody 33C9, or a fragment, derivative, variant, or biosimilar thereof. 33C9 is available from Amgen, Inc. The preparation and properties of 33C9 are described in U.S. Patent Application Publication No. US

2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 33C9 are set forth in Table 24.

[00905] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:260 and a light chain given by SEQ ID NO:261. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:260 and SEQ ID NO:261, respectively.

[00906] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 1D7. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:262, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:263, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:262 and SEQ ID NO:263, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:262 and SEQ ID NO:263, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:262 and SEQ ID NO:263, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:262 and SEQ ID NO:263, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:262 and SEQ ID NO:263,

respectively.

[00907] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:264, SEQ ID NO:265, and SEQ ID NO:266, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:267, SEQ ID NO:268, and SEQ ID NO:269, respectively, and conservative amino acid substitutions thereof.

[00908] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 33C9. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33C9. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33C9. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33C9. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33C9.

TABLE 24. Amino acid sequences for GITR agonist antibodies related to 33C9.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:260 33C9 heavy chain	QVQVVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVSV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG LLGYYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:261 33C9 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HHSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:262 33C9 variable heavy chain	QVQVVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVSV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG LLGYYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:263 33C9 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HHSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:264 33C9 heavy chain CDR1	SYGMH	5
SEQ ID NO:265 33C9 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:266 33C9 heavy chain CDR3	GGLLGYYYYY GMDV	14
SEQ ID NO:267 33C9 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:268 33C9 light chain CDR2	DASSLQS	7
SEQ ID NO:269 33C9 light chain CDR3	LQHHSYPWT	9

[00909] In a preferred embodiment, the GITR agonist is the monoclonal antibody 33F6, or a fragment, derivative, variant, or biosimilar thereof. 33F6 is available from Amgen, Inc. The preparation and properties of 33F6 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 33F6 are set forth in Table 25.

[00910] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:270 and a light chain given by SEQ ID NO:271. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:270 and SEQ ID NO:271, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID

NO:270 and SEQ ID NO:271, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:270 and SEQ ID NO:271, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:270 and SEQ ID NO:271, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:270 and SEQ ID NO:271, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:270 and SEQ ID NO:271, respectively.

[00911] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 33F6. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:272, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:273, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:272 and SEQ ID NO:273, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:272 and SEQ ID NO:273, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:272 and SEQ ID NO:273, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:272 and SEQ ID NO:273, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:272 and SEQ ID NO:273, respectively.

[00912] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:274, SEQ ID NO:275, and SEQ ID NO:276, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:277, SEQ ID NO:278, and SEQ ID NO:279, respectively, and conservative amino acid substitutions thereof.

[00913] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal

antibody approved by drug regulatory authorities with reference to 33F6. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33F6. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33F6. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33F6. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 33F6.

TABLE 25. Amino acid sequences for GITR agonist antibodies related to 33F6.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:270 33F6 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS NYGMHWVRQA PGKGLEWVAV IWYVGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELRLYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:271 33F6 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTVSSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:272 33F6 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS NYGMHWVRQA PGKGLEWVAV IWYVGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELRLYYYYGM DVWGQGTTVT VSS	60 120 123

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:273 33F6 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTVSSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:274 33F6 heavy chain CDR1	NYGMH	5
SEQ ID NO:275 33F6 heavy chain CDR2	VIWYVGSNKY YADSVKG	17
SEQ ID NO:276 33F6 heavy chain CDR3	GGELRLYYYY GMDV	14
SEQ ID NO:277 33F6 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:278 33F6 light chain CDR2	AASSLQS	7
SEQ ID NO:279 33F6 light chain CDR3	LQLNSYPWT	9

[00914] In a preferred embodiment, the GITR agonist is the monoclonal antibody 34G4, or a fragment, derivative, variant, or biosimilar thereof. 34G4 is available from Amgen, Inc. The preparation and properties of 34G4 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 34G4 are set forth in Table 26.

[00915] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:280 and a light chain given by SEQ ID NO:281. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:280 and SEQ ID NO:281, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:280 and SEQ ID NO:281, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:280 and SEQ ID NO:281, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:280 and SEQ ID NO:281, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:280 and SEQ ID NO:281, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:280 and SEQ ID

NO:281, respectively.

[00916] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 34G4. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:282, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:283, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:282 and SEQ ID NO:283, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:282 and SEQ ID NO:283, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:282 and SEQ ID NO:283, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:282 and SEQ ID NO:283, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:282 and SEQ ID NO:283, respectively.

[00917] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:284, SEQ ID NO:285, and SEQ ID NO:286, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:287, SEQ ID NO:288, and SEQ ID NO:289, respectively, and conservative amino acid substitutions thereof.

[00918] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 34G4. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 34G4. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation,

deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 34G4. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 34G4. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 34G4.

TABLE 26. Amino acid sequences for GITR agonist antibodies related to 34G4.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:280 34G4 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGYYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:281 34G4 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:282 34G4 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGYYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:283 34G4 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:284 34G4 heavy chain CDR1	SYGMH	5
SEQ ID NO:285 34G4 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:286 34G4 heavy chain CDR3	GGQLGYYYYY GMDV	14
SEQ ID NO:287 34G4 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:288 34G4 light chain CDR2	DASSLQS	7

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:289 34G4 light chain CDR3	LQLNSYPWT	9

[00919] In a preferred embodiment, the GITR agonist is the monoclonal antibody 35B10, or a fragment, derivative, variant, or biosimilar thereof. 35B10 is available from Amgen, Inc. The preparation and properties of 35B10 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 35B10 are set forth in Table 27.

[00920] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:290 and a light chain given by SEQ ID NO:291. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:290 and SEQ ID NO:291, respectively.

[00921] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 35B10. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:292, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:293, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:292 and SEQ ID NO:293, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at

least 98% identical to the sequences shown in SEQ ID NO:292 and SEQ ID NO:293, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:292 and SEQ ID NO:293, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:292 and SEQ ID NO:293, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:292 and SEQ ID NO:293, respectively.

[00922] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:294, SEQ ID NO:295, and SEQ ID NO:296, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:297, SEQ ID NO:298, and SEQ ID NO:299, respectively, and conservative amino acid substitutions thereof.

[00923] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 35B10. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 35B10. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 35B10. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological

product is 35B10. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 35B10.

TABLE 27. Amino acid sequences for GITR agonist antibodies related to 35B10.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:290 35B10 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELSFYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:291 35B10 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASTLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:292 35B10 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELSFYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:293 35B10 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASTLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:294 35B10 heavy chain CDR1	SYGMH	5
SEQ ID NO:295 35B10 heavy chain CDR2	VIWYAGSNKY YADSVKG	17
SEQ ID NO:296 35B10 heavy chain CDR3	GGELSFYYYY GMDV	14
SEQ ID NO:297 35B10 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:298 35B10 light chain CDR2	AASTLQS	7
SEQ ID NO:299 35B10 light chain CDR3	LQHNNYPWT	9

[00924] In a preferred embodiment, the GITR agonist is the monoclonal antibody 41E11, or a fragment, derivative, variant, or biosimilar thereof. 41E11 is available from Amgen, Inc. The preparation and properties of 41E11 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 41E11 are set forth in Table 28.

[00925] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:300 and a light chain given by SEQ ID NO:301. In an embodiment, a GITR agonist

comprises heavy and light chains having the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:300 and SEQ ID NO:301, respectively.

[00926] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 41E11. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:302, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:303, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:302 and SEQ ID NO:303, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:302 and SEQ ID NO:303, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:302 and SEQ ID NO:303, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:302 and SEQ ID NO:303, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:302 and SEQ ID NO:303, respectively.

[00927] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:304, SEQ ID NO:305, and SEQ ID NO:306, respectively, and conservative amino acid substitutions thereof, and light chain CDR1,

CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:307, SEQ ID NO:308, and SEQ ID NO:309, respectively, and conservative amino acid substitutions thereof.

[00928] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 41E11. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41E11. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41E11. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41E11. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41E11.

TABLE 28. Amino acid sequences for GITR agonist antibodies related to 41E11.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:300 41E11 heavy chain	QVQVVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYEGSNKYY ADSVRGRFTI SRDNSKNTLY LQMNSLRAED TALYYCARGG QLGKDYYSGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:301 41E11 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQVIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:302 41E11 variable heavy chain	QVQVVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYEGSNKYY ADSVRGRFTI SRDNSKNTLY LQMNSLRAED TALYYCARGG QLGKDYYSGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:303 41E11 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQVIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPLTFGG GTKVEIKR	60 108
SEQ ID NO:304 41E11 heavy chain CDR1	SYGMY	5
SEQ ID NO:305 41E11 heavy chain CDR2	VIWYEGSNKY YADSVRG	17
SEQ ID NO:306 41E11 heavy chain CDR3	GGQLGKDYYS GMDV	14
SEQ ID NO:307 41E11 light chain CDR1	RASQVIRNDL G	11
SEQ ID NO:308 41E11 light chain CDR2	AASSLQS	7
SEQ ID NO:309 41E11 light chain CDR3	LQHNSYPLT	9

[00929] In a preferred embodiment, the GITR agonist is the monoclonal antibody 41G5, or a fragment, derivative, variant, or biosimilar thereof. 41G5 is available from Amgen, Inc. The preparation and properties of 41G5 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 41G5 are set forth in Table 29.

[00930] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:310 and a light chain given by SEQ ID NO:311. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively. In an embodiment, a GITR agonist comprises heavy and light

chains that are each at least 96% identical to the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:310 and SEQ ID NO:311, respectively.

[00931] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 41G5. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:312, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:313, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:312 and SEQ ID NO:313, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:312 and SEQ ID NO:313, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:312 and SEQ ID NO:313, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:312 and SEQ ID NO:313, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:312 and SEQ ID NO:313, respectively.

[00932] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:314, SEQ ID NO:315, and SEQ ID NO:316, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:317, SEQ ID NO:318, and SEQ ID NO:319, respectively, and conservative amino acid substitutions thereof.

[00933] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 41G5. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the

reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41G5. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41G5. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41G5. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 41G5.

TABLE 29. Amino acid sequences for GITR agonist antibodies related to 41G5.

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:310 41G5 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYPGSNKYY 60 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELGRYYYYGM DVWGQGTTVT 120 VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL 180 QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL 240 LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300 QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS 360 REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK 420 SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK 453
SEQ ID NO:311 41G5 light chain	DIQMTQSPSS LSASVGDRVT VTCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS 60 RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVDIKRTV AAPSVFIFPP 120 SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT 180 LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214
SEQ ID NO:312 41G5 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYPGSNKYY 60 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG ELGRYYYYGM DVWGQGTTVT 120 VSS 123
SEQ ID NO:313 41G5 variable light chain	DIQMTQSPSS LSASVGDRVT VTCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS 60 RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVDIKR 108
SEQ ID NO:314 41G5 heavy chain CDR1	SYGMH 5
SEQ ID NO:315 41G5 heavy chain CDR2	VIWYPGSNKY YADSVKG 17
SEQ ID NO:316 41G5 heavy chain CDR3	GGELGRYYYY GMDV 14

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:317 41G5 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:318 41G5 light chain CDR2	AASSLQS	7
SEQ ID NO:319 41G5 light chain CDR3	LQHNNYPWT	9

[00934] In a preferred embodiment, the GITR agonist is the monoclonal antibody 42A11, or a fragment, derivative, variant, or biosimilar thereof. 42A11 is available from Amgen, Inc. The preparation and properties of 42A11 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 42A11 are set forth in Table 30.

[00935] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:320 and a light chain given by SEQ ID NO:321. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:320 and SEQ ID NO:321, respectively.

[00936] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 42A11. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:322, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:323, and conservative amino

acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:322 and SEQ ID NO:323, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:322 and SEQ ID NO:323, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:322 and SEQ ID NO:323, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:322 and SEQ ID NO:323, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:322 and SEQ ID NO:323, respectively.

[00937] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:324, SEQ ID NO:325, and SEQ ID NO:326, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:327, SEQ ID NO:328, and SEQ ID NO:329, respectively, and conservative amino acid substitutions thereof.

[00938] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 42A11. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 42A11. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 42A11. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is

provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 42A11. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 42A11.

TABLE 30. Amino acid sequences for GITR agonist antibodies related to 42A11.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:320 42A11 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGYYYYSGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:321 42A11 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EEFATYYCLQ HNNYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:322 42A11 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG QLGYYYYSGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:323 42A11 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYD ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EEFATYYCLQ HNNYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:324 42A11 heavy chain CDR1	SYGMH	5
SEQ ID NO:325 42A11 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:326 42A11 heavy chain CDR3	GGQLGYYYYS GMDV	14
SEQ ID NO:327 42A11 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:328 42A11 light chain CDR2	DASSLQS	7
SEQ ID NO:329 42A11 light chain CDR3	LQHNNYPWT	9

[00939] In a preferred embodiment, the GITR agonist is the monoclonal antibody 44C1, or a fragment, derivative, variant, or biosimilar thereof. 44C1 is available from Amgen, Inc. The preparation and properties of 44C1 are described in U.S. Patent Application Publication No. US

2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 44C1 are set forth in Table 31.

[00940] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:330 and a light chain given by SEQ ID NO:331. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:330 and SEQ ID NO:331, respectively.

[00941] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 44C1. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:332, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:333, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:332 and SEQ ID NO:333, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:332 and SEQ ID NO:333, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:332 and SEQ ID NO:333, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:332 and SEQ ID NO:333, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:332 and SEQ ID NO:333,

respectively.

[00942] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:334, SEQ ID NO:335, and SEQ ID NO:336, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:337, SEQ ID NO:338, and SEQ ID NO:339, respectively, and conservative amino acid substitutions thereof.

[00943] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 44C1. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 44C1. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 44C1. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 44C1. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 44C1.

TABLE 31. Amino acid sequences for GITR agonist antibodies related to 44C1.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:330 44C1 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTLS SYGMHWVRQA PGKGLEWVAV IWYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARRG TVTTPDFDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 240 300 360 420 450
SEQ ID NO:331 44C1 light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG TYNLVSWYQQ HPGKAPKLMI YEVSKRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGFSTWV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	60 120 180 216
SEQ ID NO:332 44C1 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTLS SYGMHWVRQA PGKGLEWVAV IWYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARRG TVTTPDFDYW GQGTLVTVSS	60 120
SEQ ID NO:333 44C1 variable light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG TYNLVSWYQQ HPGKAPKLMI YEVSKRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGFSTWV FGGGTKLTVL G	60 111
SEQ ID NO:334 44C1 heavy chain CDR1	SYGMH	5
SEQ ID NO:335 44C1 heavy chain CDR2	VIWYDGSNKY YADSVKG	17
SEQ ID NO:336 44C1 heavy chain CDR3	RGTVTTPDFD Y	11
SEQ ID NO:337 44C1 light chain CDR1	TGTSSDVGTY NLVS	14
SEQ ID NO:338 44C1 light chain CDR2	EVSKRPS	7
SEQ ID NO:339 44C1 light chain CDR3	CSYAGFSTWV	10

[00944] In a preferred embodiment, the GITR agonist is the monoclonal antibody 45A8, or a fragment, derivative, variant, or biosimilar thereof. 45A8 is available from Amgen, Inc. The preparation and properties of 45A8 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 45A8 are set forth in Table 32.

[00945] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:340 and a light chain given by SEQ ID NO:341. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:340 and SEQ ID NO:341, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID

NO:340 and SEQ ID NO:341, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:340 and SEQ ID NO:341, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:340 and SEQ ID NO:341, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:340 and SEQ ID NO:341, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:340 and SEQ ID NO:341, respectively.

[00946] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 45A8. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:342, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:343, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:342 and SEQ ID NO:343, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:342 and SEQ ID NO:343, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:342 and SEQ ID NO:343, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:342 and SEQ ID NO:343, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:342 and SEQ ID NO:343, respectively.

[00947] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:344, SEQ ID NO:345, and SEQ ID NO:346, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:347, SEQ ID NO:348, and SEQ ID NO:349, respectively, and conservative amino acid substitutions thereof.

[00948] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal

antibody approved by drug regulatory authorities with reference to 45A8. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 45A8. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 45A8. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 45A8. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 45A8.

TABLE 32. Amino acid sequences for GITR agonist antibodies related to 45A8.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:340 45A8 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWHDGSNKYY ADSVKGRFTI SKDNSKNTLY LQMNSLRAED TAVYYCAREY GGNFDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	60 120 180 240 300 360 420 447
SEQ ID NO:341 45A8 light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG TYNLVSWYQQ HPGKAPKLMI YEVSKRPSGI SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGYSTWV FGGGTKLTVL RQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	60 120 180 216
SEQ ID NO:342 45A8 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWHDGSNKYY ADSVKGRFTI SKDNSKNTLY LQMNSLRAED TAVYYCAREY GGNFDYWGQG TLVTVSS	60 117

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:343 45A8 variable light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG TYNLVSWYQQ HPGKAPKLMI YEVSKRPSGI SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGYSTWV FGGGTKLTVL R	60 111
SEQ ID NO:344 45A8 heavy chain CDR1	SYGMH	5
SEQ ID NO:345 45A8 heavy chain CDR2	VIWHDGSNKY YADSVKG	17
SEQ ID NO:346 45A8 heavy chain CDR3	EYGGNFDY	8
SEQ ID NO:347 45A8 light chain CDR1	TGTSSDVGTY NLVS	14
SEQ ID NO:348 45A8 light chain CDR2	EVSKRPS	7
SEQ ID NO:349 45A8 light chain CDR3	CSYAGYSTWV	10

[00949] In a preferred embodiment, the GITR agonist is the monoclonal antibody 46E11, or a fragment, derivative, variant, or biosimilar thereof. 46E11 is available from Amgen, Inc. The preparation and properties of 46E11 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 46E11 are set forth in Table 33.

[00950] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:350 and a light chain given by SEQ ID NO:351. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:350 and SEQ ID NO:351, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:350 and SEQ ID NO:351, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:350 and SEQ ID NO:351, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:350 and SEQ ID NO:351, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:350 and SEQ ID NO:351, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:350 and SEQ ID

NO:351, respectively.

[00951] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 46E11. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:352, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:353, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:352 and SEQ ID NO:353, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:352 and SEQ ID NO:353, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:352 and SEQ ID NO:353, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:352 and SEQ ID NO:353, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:352 and SEQ ID NO:353, respectively.

[00952] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:354, SEQ ID NO:355, and SEQ ID NO:356, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:357, SEQ ID NO:358, and SEQ ID NO:359, respectively, and conservative amino acid substitutions thereof.

[00953] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 46E11. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 46E11. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation,

deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 46E11. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 46E11. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 46E11.

TABLE 33. Amino acid sequences for GITR agonist antibodies related to 46E11.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:350 46E11 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGD ILTGYSLYYG MDVWGQGTTV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK	60 120 180 240 300 360 420 454
SEQ ID NO:351 46E11 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGAE FTLTISSLQP EDFATYYCLQ HNSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:352 46E11 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGD ILTGYSLYYG MDVWGQGTTV TVSS	60 120 124
SEQ ID NO:353 46E11 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGAE FTLTISSLQP EDFATYYCLQ HNSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:354 46E11 heavy chain CDR1	SYGMH	5
SEQ ID NO:355 46E11 heavy chain CDR2	VIWYAGSNKY YADSVKG	17
SEQ ID NO:356 46E11 heavy chain CDR3	GDILTGYSLY YGMDV	15
SEQ ID NO:357 46E11 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:358 46E11 light chain CDR2	AASSLQS	7

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:359 46E11 light chain CDR3	LQHNSYPWT	9

[00954] In a preferred embodiment, the GITR agonist is the monoclonal antibody 48H12, or a fragment, derivative, variant, or biosimilar thereof. 48H12 is available from Amgen, Inc. The preparation and properties of 48H12 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 48H12 are set forth in Table 34.

[00955] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:360 and a light chain given by SEQ ID NO:361. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:360 and SEQ ID NO:361, respectively.

[00956] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 48H12. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:362, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:363, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:362 and SEQ ID NO:363, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at

least 98% identical to the sequences shown in SEQ ID NO:362 and SEQ ID NO:363, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:362 and SEQ ID NO:363, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:362 and SEQ ID NO:363, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:362 and SEQ ID NO:363, respectively.

[00957] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:364, SEQ ID NO:365, and SEQ ID NO:366, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369, respectively, and conservative amino acid substitutions thereof.

[00958] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 48H12. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H12. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H12. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference

biological product is 48H12. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H12.

TABLE 34. Amino acid sequences for GITR agonist antibodies related to 48H12.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:360 48H12 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTVY LQMNSLRAED TAVYYCARGG QLALYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:361 48H12 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:362 48H12 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTVY LQMNSLRAED TAVYYCARGG QLALYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:363 48H12 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNNYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:364 48H12 heavy chain CDR1	SYGMH	5
SEQ ID NO:365 48H12 heavy chain CDR2	VIWYAGSNKY YADSVKG	17
SEQ ID NO:366 48H12 heavy chain CDR3	GGQLALYYYY GMDV	14
SEQ ID NO:367 48H12 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:368 48H12 light chain CDR2	AASSLQS	7
SEQ ID NO:369 48H12 light chain CDR3	LQHNNYPWT	9

[00959] In a preferred embodiment, the GITR agonist is the monoclonal antibody 48H7, or a fragment, derivative, variant, or biosimilar thereof. 48H7 is available from Amgen, Inc. The preparation and properties of 48H7 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 48H7 are set forth in Table 35.

[00960] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:370 and a light chain given by SEQ ID NO:371. In an embodiment, a GITR agonist

comprises heavy and light chains having the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:370 and SEQ ID NO:371, respectively.

[00961] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 48H7. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:372, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:373, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:372 and SEQ ID NO:373, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:372 and SEQ ID NO:373, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:372 and SEQ ID NO:373, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:372 and SEQ ID NO:373, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:372 and SEQ ID NO:373, respectively.

[00962] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:374, SEQ ID NO:375, and SEQ ID NO:376, respectively, and conservative amino acid substitutions thereof, and light chain CDR1,

CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:377, SEQ ID NO:378, and SEQ ID NO:379, respectively, and conservative amino acid substitutions thereof.

[00963] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 48H7. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H7. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H7. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H7. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48H7.

TABLE 35. Amino acid sequences for GITR agonist antibodies related to 48H7.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:370 48H7 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYFCARGG ELGRDYYSGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:371 48H7 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQVIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPITFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:372 48H7 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYFCARGG ELGRDYYSGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:373 48H7 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQVIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPITFGG GTKVEIKR	60 108
SEQ ID NO:374 48H7 heavy chain CDR1	SYGMY	5
SEQ ID NO:375 48H7 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:376 48H7 heavy chain CDR3	GGELGRDYYS GMDV	14
SEQ ID NO:377 48H7 light chain CDR1	RASQVIRNDL G	11
SEQ ID NO:378 48H7 light chain CDR2	AASSLQS	7
SEQ ID NO:379 48H7 light chain CDR3	LQHNSYPIT	9

[00964] In a preferred embodiment, the GITR agonist is the monoclonal antibody 49D9, or a fragment, derivative, variant, or biosimilar thereof. 49D9 is available from Amgen, Inc. The preparation and properties of 49D9 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 49D9 are set forth in Table 36.

[00965] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:380 and a light chain given by SEQ ID NO:381. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively. In an embodiment, a GITR agonist comprises heavy and light

chains that are each at least 96% identical to the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:380 and SEQ ID NO:381, respectively.

[00966] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 49D9. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:382, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:383, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:382 and SEQ ID NO:383, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:382 and SEQ ID NO:383, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:382 and SEQ ID NO:383, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:382 and SEQ ID NO:383, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:382 and SEQ ID NO:383, respectively.

[00967] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:384, SEQ ID NO:385, and SEQ ID NO:386, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:387, SEQ ID NO:388, and SEQ ID NO:389, respectively, and conservative amino acid substitutions thereof.

[00968] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 49D9. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the

reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49D9. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49D9. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49D9. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49D9.

TABLE 36. Amino acid sequences for GITR agonist antibodies related to 49D9.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:380 49D9 heavy chain	QMQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG RLGFYYYYGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:381 49D9 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:382 49D9 variable heavy chain	QMQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYAGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG RLGFYYYYGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:383 49D9 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ LNSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:384 49D9 heavy chain CDR1	SYGMH	5
SEQ ID NO:385 49D9 heavy chain CDR2	VIWYAGSNKY YADSVKG	17
SEQ ID NO:386 49D9 heavy chain CDR3	GGRLGFYYYY GMDV	14

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:387 49D9 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:388 49D9 light chain CDR2	AASSLQS	7
SEQ ID NO:389 49D9 light chain CDR3	LQLNSYPWT	9

[00969] In a preferred embodiment, the GITR agonist is the monoclonal antibody 49E2, or a fragment, derivative, variant, or biosimilar thereof. 49E2 is available from Amgen, Inc. The preparation and properties of 49E2 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 49E2 are set forth in Table 37.

[00970] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:390 and a light chain given by SEQ ID NO:391. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:390 and SEQ ID NO:391, respectively.

[00971] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 49E2. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:392, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:393, and conservative amino

acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:392 and SEQ ID NO:393, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:392 and SEQ ID NO:393, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:392 and SEQ ID NO:393, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:392 and SEQ ID NO:393, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:392 and SEQ ID NO:393, respectively.

[00972] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:394, SEQ ID NO:395, and SEQ ID NO:396, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:397, SEQ ID NO:398, and SEQ ID NO:399, respectively, and conservative amino acid substitutions thereof.

[00973] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 49E2. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49E2. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49E2. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided

as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49E2. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 49E2.

TABLE 37. Amino acid sequences for GITR agonist antibodies related to 49E2.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:390 49E2 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWSDGNNKYY EDSVKGRFTI SRDSSKNTLF LQMNSLRAED TAVYYCARDT ATPFDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	60 120 180 240 300 360 420 447
SEQ ID NO:391 49E2 light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG IYNLVSWYQQ HPGKAPKLMI HEVSKRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGISTWV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	60 120 180 216
SEQ ID NO:392 49E2 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWSDGNNKYY EDSVKGRFTI SRDSSKNTLF LQMNSLRAED TAVYYCARDT ATPFDYWGQG TLVTVSS	60 117
SEQ ID NO:393 49E2 variable light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG IYNLVSWYQQ HPGKAPKLMI HEVSKRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC CSYAGISTWV FGGGTKLTVL G	60 111
SEQ ID NO:394 49E2 heavy chain CDR1	SYGMH	5
SEQ ID NO:395 49E2 heavy chain CDR2	VIWSDGNNKY YEDSVKG	17
SEQ ID NO:396 49E2 heavy chain CDR3	DTATPFDY	8
SEQ ID NO:397 49E2 light chain CDR1	TGTSSDVGIY NLVS	14
SEQ ID NO:398 49E2 light chain CDR2	EVSKRPS	7
SEQ ID NO:399 49E2 light chain CDR3	CSYAGISTWV	10

[00974] In a preferred embodiment, the GITR agonist is the monoclonal antibody 48A9, or a fragment, derivative, variant, or biosimilar thereof. 48A9 is available from Amgen, Inc. The preparation and properties of 48A9 are described in U.S. Patent Application Publication No. US

2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 48A9 are set forth in Table 38.

[00975] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:400 and a light chain given by SEQ ID NO:401. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:400 and SEQ ID NO:401, respectively.

[00976] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 48A9. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:402, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:403, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:402 and SEQ ID NO:403, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:402 and SEQ ID NO:403, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:402 and SEQ ID NO:403, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:402 and SEQ ID NO:403, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:402 and SEQ ID NO:403,

respectively.

[00977] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:404, SEQ ID NO:405, and SEQ ID NO:406, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:407, SEQ ID NO:408, and SEQ ID NO:409, respectively, and conservative amino acid substitutions thereof.

[00978] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 48A9. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48A9. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48A9. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48A9. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 48A9.

TABLE 38. Amino acid sequences for GITR agonist antibodies related to 48A9.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:400 48A9 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SCGMHWVRQA PGKGLEWVAV ISYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDL RYNWNDGGVD YWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK	60 120 180 240 300 360 420 452
SEQ ID NO:401 48A9 light chain	DIQMTQSPSS LSASVGDRVI ITCRASQSIS SYLHWYKQKP GKAPKLLIYG ASRLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SSSTPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:402 48A9 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SCGMHWVRQA PGKGLEWVAV ISYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDL RYNWNDGGVD YWGQGTLVTV SS	60 120 122
SEQ ID NO:403 48A9 variable light chain	DIQMTQSPSS LSASVGDRVI ITCRASQSIS SYLHWYKQKP GKAPKLLIYG ASRLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SSSTPLTFGG GTKVEIKR	60 108
SEQ ID NO:404 48A9 heavy chain CDR1	SCGMH	5
SEQ ID NO:405 48A9 heavy chain CDR2	VISYDGSNKY YADSVKG	17
SEQ ID NO:406 48A9 heavy chain CDR3	DLRYNWNDGG VDY	13
SEQ ID NO:407 48A9 light chain CDR1	RASQSISSYL H	11
SEQ ID NO:408 48A9 light chain CDR2	GASRLQS	7
SEQ ID NO:409 48A9 light chain CDR3	QQSSSTPLT	9

[00979] In a preferred embodiment, the GITR agonist is the monoclonal antibody 5H7, or a fragment, derivative, variant, or biosimilar thereof. 5H7 is available from Amgen, Inc. The preparation and properties of 5H7 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 5H7 are set forth in Table 39.

[00980] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:410 and a light chain given by SEQ ID NO:411. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:410 and SEQ ID NO:411, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID

NO:410 and SEQ ID NO:411, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:410 and SEQ ID NO:411, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:410 and SEQ ID NO:411, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:410 and SEQ ID NO:411, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:410 and SEQ ID NO:411, respectively.

[00981] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 5H7. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:412, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:413, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:412 and SEQ ID NO:413, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:412 and SEQ ID NO:413, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:412 and SEQ ID NO:413, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:412 and SEQ ID NO:413, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:412 and SEQ ID NO:413, respectively.

[00982] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:414, SEQ ID NO:415, and SEQ ID NO:416, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:417, SEQ ID NO:418, and SEQ ID NO:419, respectively, and conservative amino acid substitutions thereof.

[00983] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal

antibody approved by drug regulatory authorities with reference to 5H7. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 5H7. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 5H7. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 5H7. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 5H7.

TABLE 39. Amino acid sequences for GITR agonist antibodies related to 5H7.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:410 5H7 heavy chain	QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYFWSWIR QHPGKGLEWI GYIYYSGTTY YNPSLKSRVT ISIDTSKNHF SLKLSSVTAA DTAVYYCARD LFYYDSSGPR GFDPWGQGTL VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK	60 120 180 240 300 360 420 455
SEQ ID NO:411 5H7 light chain	EIVLTQSPGT LSLSPGERAT LSCRASQTVS SNYLAWYQQK PGQAPRLLIY GSSTRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYDSSPWTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC	60 120 180 215
SEQ ID NO:412 5H7 variable heavy chain	QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYFWSWIR QHPGKGLEWI GYIYYSGTTY YNPSLKSRVT ISIDTSKNHF SLKLSSVTAA DTAVYYCARD LFYYDSSGPR GFDPWGQGTL VTVSS	60 120 125

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:413 5H7 variable light chain	EIVLTQSPGT LSLSPGERAT LSCRASQTVS SNYLAWYQQK PGQAPRLLIY GSSTRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYDSSPWTFG QGTKVEIKR	60 109
SEQ ID NO:414 5H7 heavy chain CDR1	SGGYFWS	7
SEQ ID NO:415 5H7 heavy chain CDR2	YIYYSGTTYY NPSLKS	16
SEQ ID NO:416 5H7 heavy chain CDR3	DLFYYDSSGP RGFDP	15
SEQ ID NO:417 5H7 light chain CDR1	RASQTVSSNY LA	12
SEQ ID NO:418 5H7 light chain CDR2	GSSTRAT	7
SEQ ID NO:419 5H7 light chain CDR3	QQYDSSPWT	9

[00984] In a preferred embodiment, the GITR agonist is the monoclonal antibody 7A10, or a fragment, derivative, variant, or biosimilar thereof. 7A10 is available from Amgen, Inc. The preparation and properties of 7A10 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 7A10 are set forth in Table 40.

[00985] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:420 and a light chain given by SEQ ID NO:421. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:420 and SEQ ID NO:421, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:420 and SEQ ID NO:421, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:420 and SEQ ID NO:421, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:420 and SEQ ID NO:421, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:420 and SEQ ID NO:421, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:420 and SEQ ID

NO:421, respectively.

[00986] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 7A10. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:422, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:423, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:422 and SEQ ID NO:423, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:422 and SEQ ID NO:423, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:422 and SEQ ID NO:423, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:422 and SEQ ID NO:423, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:422 and SEQ ID NO:423, respectively.

[00987] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:424, SEQ ID NO:425, and SEQ ID NO:426, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:427, SEQ ID NO:428, and SEQ ID NO:429, respectively, and conservative amino acid substitutions thereof.

[00988] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 7A10. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 7A10. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation,

deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 7A10. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 7A10. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 7A10.

TABLE 40. Amino acid sequences for GITR agonist antibodies related to 7A10.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:420 7A10 heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWMAV IWYVGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLSAED TAVYYCARGG ELGRDYYSGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:421 7A10 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HNSYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:422 7A10 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWMAV IWYVGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLSAED TAVYYCARGG ELGRDYYSGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:423 7A10 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HNSYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:424 7A10 heavy chain CDR1	SYGMH	5
SEQ ID NO:425 7A10 heavy chain CDR2	VIWYVGSNKY YADSVKG	17
SEQ ID NO:426 7A10 heavy chain CDR3	GGELGRDYYS GMDV	14
SEQ ID NO:427 7A10 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:428 7A10 light chain CDR2	AASSLQS	7

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:429 7A10 light chain CDR3	QQHNSYPWT	9

[00989] In a preferred embodiment, the GITR agonist is the monoclonal antibody 9H6, or a fragment, derivative, variant, or biosimilar thereof. 9H6 is available from Amgen, Inc. The preparation and properties of 9H6 are described in U.S. Patent Application Publication No. US 2015/0064204 A1, the disclosures of which are incorporated by reference herein. The amino acid sequences of 9H6 are set forth in Table 41.

[00990] In an embodiment, a GITR agonist comprises a heavy chain given by SEQ ID NO:430 and a light chain given by SEQ ID NO:431. In an embodiment, a GITR agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively. In an embodiment, a GITR agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:430 and SEQ ID NO:431, respectively.

[00991] In an embodiment, the GITR agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 9H6. In an embodiment, the GITR agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:432, and the GITR agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:433, and conservative amino acid substitutions thereof. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:432 and SEQ ID NO:433, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at

least 98% identical to the sequences shown in SEQ ID NO:432 and SEQ ID NO:433, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:432 and SEQ ID NO:433, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:432 and SEQ ID NO:433, respectively. In an embodiment, a GITR agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:432 and SEQ ID NO:433, respectively.

[00992] In an embodiment, a GITR agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:434, SEQ ID NO:435, and SEQ ID NO:436, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:437, SEQ ID NO:438, and SEQ ID NO:439, respectively, and conservative amino acid substitutions thereof.

[00993] In an embodiment, the GITR agonist is a GITR agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 9H6. In an embodiment, the biosimilar monoclonal antibody comprises an GITR antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 9H6. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a GITR agonist antibody authorized or submitted for authorization, wherein the GITR agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 9H6. The GITR agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological

product is 9H6. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 9H6.

TABLE 41. Amino acid sequences for GITR agonist antibodies related to 9H6.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:430 9H6 heavy chain	QVQLVESGGG VVQPGRSLRL SCVASGFTFS SYGMHWIRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG RLGKDYYSGM DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK	60 120 180 240 300 360 420 453
SEQ ID NO:431 9H6 light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPNRLIYA TSSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNTYPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:432 9H6 variable heavy chain	QVQLVESGGG VVQPGRSLRL SCVASGFTFS SYGMHWIRQA PGKGLEWVAV IWYEGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGG RLGKDYYSGM DVWGQGTTVT VSS	60 120 123
SEQ ID NO:433 9H6 variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPNRLIYA TSSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNTYPWTFGQ GTKVEIKR	60 108
SEQ ID NO:434 9H6 heavy chain CDR1	SYGMH	5
SEQ ID NO:435 9H6 heavy chain CDR2	VIWYEGSNKY YADSVKG	17
SEQ ID NO:436 9H6 heavy chain CDR3	GGRLGKDYYS GMDV	14
SEQ ID NO:437 9H6 light chain CDR1	RASQGIRNDL G	11
SEQ ID NO:438 9H6 light chain CDR2	ATSSLQS	7
SEQ ID NO:439 9H6 light chain CDR3	LQHNTYPWT	9

[00994] In an embodiment, the GITR agonist is a GITR agonist described in International Patent Application Publication Nos. WO 2013/039954 A1 and WO 2011/028683 A1; U.S. Patent Application Publication Nos. US 2013/0108641 A1, US 2012/0189639 A1, and US 2014/0348841 A1; and U.S. Patent Nos. 7,812,135; 8,388,967; and 9,028,823, the disclosures of which are incorporated by reference herein. In an embodiment, the GITR agonist is an agonistic, anti-GITR monoclonal antibody with a structure and preparation described in US Patent Application Publication No. US 2015/0064204 and International Patent Application Publication

No. WO 2015/031667 A1 (Amgen, Inc.), the disclosures of which are incorporated by reference herein. In an embodiment, the GITR agonist is a fully-human, agonistic, anti-GITR monoclonal antibody selected from the group consisting of 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, and 9H6. In an embodiment, the GITR agonist is a fully-human, agonistic, anti-GITR monoclonal antibody with an amino acid sequence identity of greater than 99% to the sequence of an antibody selected from the group consisting of 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, and 9H6. In an embodiment, the GITR agonist is a fully-human, agonistic, anti-GITR monoclonal antibody with an amino acid sequence identity of greater than 98% to the sequence of an antibody selected from the group consisting of 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, and 9H6. In an embodiment, the GITR agonist is a fully-human, agonistic, anti-GITR monoclonal antibody selected from the group consisting of 9H6v3, 5H7v2, 33C9v2, 41G5v2, and 7A10v1, as described in US Patent Application Publication No. US 2015/0064204 A1, the disclosure of which is incorporated by reference herein. In an embodiment, the GITR agonist is a fully-human, agonistic, anti-GITR monoclonal antibody selected from the group consisting of 44C1v1, 45A8v1, 49D9v1, 49E2v1, 48A9v1, 5H7v1, 5H7v2, 5H7v3, 5H7v5, 5H7v7, 5H7v9, 5H7v10, 5H7v11, 5H7v13, 5H7v14, 5H7v17, 5H7v18, 5H7v19, 5H7v22, 7A10v1, 7A10v2, 7A10v3, 7A10v4, 7A10v5, 9H6v1, 9H6v2, 9H6v3, 9H6v4, 9H6v5, 9H6v6, 33C9v1, 33C9v2, 33C9v3, 33C9v4, 33C9v5, 41G5v1, 41G5v2, 41G5v3, 41G5v4, and 41G5v5, as described in US Patent Application Publication No. US 2015/0064204 A1, the disclosure of which is incorporated by reference herein.

[00995] In an embodiment, the GITR agonist is an GITR agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for

connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[00996] In an embodiment, an GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains selected from the group consisting of a variable heavy chain and variable light chain of TRX518, 6C8, 36E5, 3D6, 61G6, 6H6, 61F6, 1D8, 17F10, 35D8, 49A1, 9E5, 31H6, 2155, 698, 706, 827, 1649, 1718, 1D7, 33C9, 33F6, 34G4, 35B10, 41E11, 41G5, 42A11, 44C1, 45A8, 46E11, 48H12, 48H7, 49D9, 49E2, 48A9, 5H7, 7A10, 9H6, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00997] In an embodiment, a GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains comprising an GITRL sequence (Table 42). In an embodiment, an GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains comprising a sequence according to SEQ ID NO:440. In an embodiment, an GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains comprising a soluble GITRL sequence. In an embodiment, a GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains comprising a sequence according to SEQ ID NO:441.

[00998] In an embodiment, an GITR agonist fusion protein according to structures I-A or I-B comprises one or more GITR binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L GITR sequences shown above in Tables 18 to 39, wherein the V_H and V_L domains are connected by a linker.

TABLE 42. Additional polypeptide domains useful as GITR binding domains in fusion proteins (*e.g.*, structures I-A and I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:440 GITRL	MCLSHLENMP LSHSRTQGAQ RSSWKLWLFC SIVMLLFLCS FSWLIFIFLQ LETAKEPCMA KFGPLPSKWQ MASSEPPCVN KVSDWKLEIL QNGLYLIYGQ VAPNANYNDV APFEVRLYKN KDMIQTLTNK SKIQNVGGTY ELHVGDTIDL IFNSEHQVLK NNTYWGIILL ANPQFIS	60 120 177

SEQ ID NO:441 GITRL soluble domain	TAKEPCMAKF GPLPSKWQMA SSEPPCVNKV SDWKLEILQN GLYLIYGQVA PNANYNDVAP FEVRLYKNKD MIQTLTNKSK IQNVGGTYEL HVGDTIDLIF NSEHQVLKNN TYWGIILLAN PQFIS	60 120 125

[00999] In an embodiment, the GITR agonist is a GITR agonistic single-chain fusion polypeptide comprising (i) a first soluble GITR binding domain, (ii) a first peptide linker, (iii) a second soluble GITR binding domain, (iv) a second peptide linker, and (v) a third soluble GITR binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the GITR agonist is a GITR agonistic single-chain fusion polypeptide comprising (i) a first soluble GITR binding domain, (ii) a first peptide linker, (iii) a second soluble GITR binding domain, (iv) a second peptide linker, and (v) a third soluble GITR binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble GITR binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the GITR binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[001000] In an embodiment, the GITR agonist is an GITR agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an GITR binding domain.

[001001] In an embodiment, the GITR agonist is a GITR agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

HVEM (CD270) Agonists

[001002] In an embodiment, the TNFRSF agonist is a HVEM agonist. HVEM is also known as CD270 and TNFRSF14. Any HVEM agonist known in the art may be used. The HVEM binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian HVEM. The HVEM agonists or HVEM binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*,

IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The HVEM agonist or HVEM binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab′) fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to HVEM. In an embodiment, the HVEM agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the HVEM agonist is an antigen binding protein that is a humanized antibody. In some embodiments, HVEM agonists for use in the presently disclosed methods and compositions include anti-HVEM antibodies, human anti-HVEM antibodies, mouse anti-HVEM antibodies, mammalian anti-HVEM antibodies, monoclonal anti-HVEM antibodies, polyclonal anti-HVEM antibodies, chimeric anti-HVEM antibodies, anti-HVEM adnectins, anti-HVEM domain antibodies, single chain anti-HVEM fragments, heavy chain anti-HVEM fragments, light chain anti-HVEM fragments, anti-HVEM fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the HVEM agonist is an agonistic, anti-HVEM humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[001003] In a preferred embodiment, the HVEM agonist or HVEM binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric HVEM agonist, such as a trimeric or hexameric HVEM agonist (with three or six ligand binding domains), may induce superior receptor (HVEML) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[001004] Agonistic HVEM antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the HVEM agonist is a monoclonal antibody or fusion protein that binds specifically to HVEM antigen in a manner sufficient to reduce toxicity. In some embodiments, the HVEM agonist is an agonistic HVEM monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell

cytotoxicity. In some embodiments, the HVEM agonist is an agonistic HVEM monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the HVEM agonist is an agonistic HVEM monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the HVEM agonist is an agonistic HVEM monoclonal antibody or fusion protein which abrogates Fc region functionality.

[001005] In some embodiments, the HVEM agonists are characterized by binding to human HVEM (SEQ ID NO:442) with high affinity and agonistic activity. In an embodiment, the HVEM agonist is a binding molecule that binds to human HVEM (SEQ ID NO:442). The amino acid sequence of HVEM antigen to which a HVEM agonist or binding molecule may bind is summarized in Table 43.

TABLE 43. Amino acid sequence of HVEM (CD270) antigen.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:442 human CD270, Tumor necrosis factor receptor superfamily, member 14 (Homo sapiens)	MEPPGDWGPP PWRSTPRTDV LRLVLYLTFL GAPCYAPALP SCKEDEYPVG SECCPKCSPG YRVKEACGEL TGTVCEPCPP GTYIAHLNGL SKCLQCQMCD PAMGLRASRN CSRTENAVCG CSPGHFCIVQ DGDHCAACRA YATSSPGQRV QKGGTESQDT LCQNCPPGTF SPNGTLEECQ HQTKCSWLVT KAGAGTSSSH WVWWFLSGSL VIVIVCSTVG LIICVKRRKP RGDVVKVIVS VQRKRQEAEG EATVIEALQA PPDVTTVAVE ETIPSFTGRS PNH	60 120 180 240 283

[001006] In some embodiments, the compositions, processes and methods described include a HVEM agonist that binds human or murine HVEM with a K_D of about 100 pM or lower, binds human or murine HVEM with a K_D of about 90 pM or lower, binds human or murine HVEM with a K_D of about 80 pM or lower, binds human or murine HVEM with a K_D of about 70 pM or lower, binds human or murine HVEM with a K_D of about 60 pM or lower, binds human or murine HVEM with a K_D of about 50 pM or lower, binds human or murine HVEM with a K_D of about 40 pM or lower, or binds human or murine HVEM with a K_D of about 30 pM or lower.

[001007] In some embodiments, the compositions, processes and methods described include a HVEM agonist that binds to human or murine HVEM with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine HVEM with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine HVEM with a k_{assoc} of about 8×10^5 l/M·s or faster, binds to human or murine HVEM with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine HVEM with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine HVEM with a k_{assoc} of about 9.5

$\times 10^5$ 1/M·s or faster, or binds to human or murine HVEM with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001008] In some embodiments, the compositions, processes and methods described include a HVEM agonist that binds to human or murine HVEM with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine HVEM with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine HVEM with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine HVEM with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine HVEM with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[001009] In some embodiments, the compositions, processes and methods described include a HVEM agonist that binds to human or murine HVEM with an IC_{50} of about 10 nM or lower, binds to human or murine HVEM with an IC_{50} of about 9 nM or lower, binds to human or murine HVEM with an IC_{50} of about 8 nM or lower, binds to human or murine HVEM with an IC_{50} of about 7 nM or lower, binds to human or murine HVEM with an IC_{50} of about 6 nM or lower, binds to human or murine HVEM with an IC_{50} of about 5 nM or lower, binds to human or murine HVEM with an IC_{50} of about 4 nM or lower, binds to human or murine HVEM with an IC_{50} of about 3 nM or lower, binds to human or murine HVEM with an IC_{50} of about 2 nM or lower, or binds to human or murine HVEM with an IC_{50} of about 1 nM or lower.

[001010] In an embodiment, the HVEM agonist is an HVEM agonist described in International Patent Application Publication No. WO 2009/007120 A2 and U.S. Patent Application Publication No. US 2016/0176941 A1, the disclosure of each of which is incorporated by reference herein.

[001011] In an embodiment, the HVEM agonist is the HVEM agonist clone REA247, which is commercially available from Miltenyi Biotech, Inc. (San Diego, CA 92121).

[001012] In an embodiment, the HVEM agonist is an HVEM agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-

terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[001013] In an embodiment, an HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising an LIGHT (HVEM ligand) sequence (Table 44). In an embodiment, an HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising a sequence according to SEQ ID NO:443. In an embodiment, an HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising a soluble LIGHT sequence. In an embodiment, a HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising a sequence according to SEQ ID NO:444. In an embodiment, a HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising a sequence according to SEQ ID NO:445. In an embodiment, a HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains comprising a sequence according to SEQ ID NO:446.

[001014] In an embodiment, an HVEM agonist fusion protein according to structures I-A or I-B comprises one or more HVEM binding domains that is a scFv domain comprising V_H and V_L regions, wherein the V_H and V_L domains are connected by a linker.

TABLE 44. Additional polypeptide domains useful as HVEM binding domains in fusion proteins (*e.g.*, structures I-A and I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:443 LIGHT (HVEM ligand)	MEESVVRPSV FVVDGQTDIP FTRLGRSHRR QSCSVARVGL GLLLLLMGAG LAVQGWFLLQ LHWRLGEMVT RLPDGPAGSW EQLIQERRSH EVNPAAHLTG ANSSLTGSGG PLLWETQLGL AFLRGLSYHD GALVVTKAGY YYIYSKVQLG GVGCPLGLAS TITHGLYKRT PRYPEELELL VSQQSPCGRA TSSSRVWWDS SFLGGVVHLE AGEKVVVRVL DERLVRLRDG TRSYFGAFMV	60 120 180 240
SEQ ID NO:444 LIGHT soluble domain	PAAHLTGANS SLTGSGGPLL WETQLGLAFL RGLSYHDGAL VVTKAGYYYI YSKVQLGGVG CPLGLASTIT HGLYKRTPRY PEELELLVSQ QSPCGRATSS SRVWWDSSFL GGVVHLEAGE KVVVRVLDER LVRLRDGTRS YFGAFMV	60 120 147
SEQ ID NO:445 LIGHT soluble domain (alternative)	AAHLTGANSS LTGSGGPLLW ETQLGLAFLR GLSYHDGALV VTKAGYYYIY SKVQLGGVGC PLGLASTITH GLYKRTPRYP EELELLVSQQ SPCGRATSSS RVWWDSSFLG GVVHLEAGEK VVVRVLDERL VRLRDGTRSY FGAFMV	60 120 146
SEQ ID NO:446 LIGHT soluble domain (alternative)	AHLTGANSSL TGSGGPLLWE TQLGLAFLRG LSYHDGALVV TKAGYYYIYS KVQLGGVGCP LGLASTITHG LYKRTPRYPE ELELLVSQQS PCGRATSSSR VWWDSSFLGG VVHLEAGEKV VVRVLDERLV RLRDGTRSYF GAFMV	60 120 145

[001015] In an embodiment, the HVEM agonist is a HVEM agonistic single-chain fusion polypeptide comprising (i) a first soluble HVEM binding domain, (ii) a first peptide linker, (iii) a second soluble HVEM binding domain, (iv) a second peptide linker, and (v) a third soluble HVEM binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the HVEM agonist is a HVEM agonistic single-chain fusion polypeptide comprising (i) a first soluble HVEM binding domain, (ii) a first peptide linker, (iii) a second soluble HVEM binding domain, (iv) a second peptide linker, and (v) a third soluble HVEM binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble HVEM binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the HVEM binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[001016] In an embodiment, the HVEM agonist is an HVEM agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an HVEM binding domain.

[001017] In an embodiment, the HVEM agonist is a HVEM agonist described in U.S. Patent No. 7,118,742, the disclosure of which is incorporated by reference herein.

CD95 Agonists

[001018] In an embodiment, the TNFRSF agonist is a CD95 agonist or CD95 binding molecule. CD95 is also known as TNFRSF6, Fas receptor (FasR), and APO-1. Any CD95 agonist or binding molecule known in the art may be used. The CD95 binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian CD95, and may be used at a concentration appropriate for T cell agonistic activity rather than T cell apoptotic activity, as described elsewhere herein. The CD95 agonists or CD95 binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The CD95 agonist or CD95 binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab′) fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to CD95. In an embodiment, the CD95 agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the CD95 agonist is an antigen binding protein that is a humanized antibody. In some embodiments, CD95 agonists for use in the presently disclosed methods and compositions include anti-CD95 antibodies, human anti-CD95 antibodies, mouse anti-CD95 antibodies, mammalian anti-CD95 antibodies, monoclonal anti-CD95 antibodies, polyclonal anti-CD95 antibodies, chimeric anti-CD95 antibodies, anti-CD95 adnectins, anti-CD95 domain antibodies, single chain anti-CD95 fragments, heavy chain anti-CD95 fragments, light chain anti-CD95 fragments, anti-CD95 fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the CD95 agonist is an agonistic, anti-CD95 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[001019] In a preferred embodiment, the CD95 agonist or CD95 binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric CD95 agonist, such as a trimeric or

hexameric CD95 agonist (with three or six ligand binding domains), may induce superior receptor (CD95L) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* **2013,** *12,* 2735-47.

[001020] Agonistic CD95 antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the CD95 agonist is a monoclonal antibody or fusion protein that binds specifically to CD95 antigen in a manner sufficient to reduce toxicity. In some embodiments, the CD95 agonist is an agonistic CD95 monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the CD95 agonist is an agonistic CD95 monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the CD95 agonist is an agonistic CD95 monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the CD95 agonist is an agonistic CD95 monoclonal antibody or fusion protein which abrogates Fc region functionality.

[001021] In some embodiments, the CD95 agonists are characterized by binding to human CD95 (SEQ ID NO:447) with high affinity and agonistic activity. In an embodiment, the CD95 agonist is a binding molecule that binds to human CD95 (SEQ ID NO:447). In an embodiment, the CD95 agonist is a binding molecule that binds to human CD95 (SEQ ID NO:448). In an embodiment, the CD95 agonist is a binding molecule that binds to human CD95 (SEQ ID NO:449). In an embodiment, the CD95 agonist is a binding molecule that binds to human CD95 (SEQ ID NO:450). The amino acid sequence of CD95 antigens to which a CD95 agonist or binding molecule may bind is summarized in Table 45.

TABLE 45. Amino acid sequence of CD95 antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:447 human CD95, Tumor necrosis factor receptor superfamily, member 6 (Homo sapiens), isoform 1	MLGIWTLLPL VLTSVARLSS KSVNAQVTDI NSKGLELRKT VTTVETQNLE GLHHDGQFCH KPCPPGERKA RDCTVNGDEP DCVPCQEGKE YTDKAHFSSK CRRCRLCDEG HGLEVEINCT RTQNTKCRCK PNFFCNSTVC EHCDPCTKCE HGIIKECTLT SNTKCKEEGS RSNLGWLCLL LLPIPLIVWV KRKEVQKTCR KHRKENQGSH ESPTLNPETV AINLSDVDLS KYITTIAGVM TLSQVKGFVR KNGVNEAKID EIKNDNVQDT AEQKVQLLRN WHQLHGKKEA YDTLIKDLKK ANLCTLAEKI QTIILKDITS DSENSNFRNE IQSLV	60 120 180 240 300 335

SEQ ID NO:448 human CD95, Tumor necrosis factor receptor superfamily, member 6 (Homo sapiens), isoform 2	MLGIWTLLPL VLTSVARLSS KSVNAQVTDI NSKGLELRKT VTTVETQNLE GLHHDGQFCH KPCPPGERKA RDCTVNGDEP DCVPCQEGKE YTDKAHFSSK CRRCRLCDEG HGLEVEINCT RTQNTKCRCK PNFFCNSTVC EHCDPCTKCE HGIIKECTLT SNTKCKEEVK RKEVQKTCRK HRKENQGSHE SPTLNPETVA INLSDVDLSK YITTIAGVMT LSQVKGFVRK NGVNEAKIDE IKNDNVQDTA EQKVQLLRNW HQLHGKKEAY DTLIKDLKKA NLCTLAEKIQ TIILKDITSD SENSNFRNEI QSLV	60 120 180 240 300 314
SEQ ID NO:449 human CD95, Tumor necrosis factor receptor superfamily, member 6 (Homo sapiens), isoform 3	MLGIWTLLPL VLTSVARLSS KSVNAQVTDI NSKGLELRKT VTTVETQNLE GLHHDGQFCH KPCPPGERKA RDCTVNGDEP DCVPCQEGKE YTDKAHFSSK CRRCRLCDEG HGLEVEINCT RTQNTKCRCK PNFFCNSTVC EHCDPCTKCE HGIIKECTLT SNTKCKEEGS RSNLGWLCLL LLPIPLIVWV KRKEVQKTCR KHRKENQGSH ESPTLNPMLT	60 120 180 220
SEQ ID NO:450 human CD95, Tumor necrosis factor receptor superfamily, member 6 (Homo sapiens), isoform 4	MLGIWTLLPL VLTSVARLSS KSVNAQVTDI NSKGLELRKT VTTVETQNLE GLHHDGQFCH KPCPPGERKA RDCTVNGDEP DCVPCQEGKE YTDKAHFSSK CRRCRLCDEG HGLEVEINCT RTQNTKCRCK PNFFCNSTVC EHCDPCTKCE HGIIKECTLT SNTKCKEEGS RSNLGWLCLL LLPIPLIVWG NSGNKFI	60 120 180 197

[001022] In some embodiments, the compositions, processes and methods described include a CD95 agonist that binds human or murine CD95 with a K_D of about 100 pM or lower, binds human or murine CD95 with a K_D of about 90 pM or lower, binds human or murine CD95 with a K_D of about 80 pM or lower, binds human or murine CD95 with a K_D of about 70 pM or lower, binds human or murine CD95 with a K_D of about 60 pM or lower, binds human or murine CD95 with a K_D of about 50 pM or lower, binds human or murine CD95 with a K_D of about 40 pM or lower, or binds human or murine CD95 with a K_D of about 30 pM or lower.

[001023] In some embodiments, the compositions, processes and methods described include a CD95 agonist that binds to human or murine CD95 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine CD95 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine CD95 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine CD95 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine CD95 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine CD95 with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine CD95 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001024] In some embodiments, the compositions, processes and methods described include a CD95 agonist that binds to human or murine CD95 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human or murine CD95 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine CD95

with a k_{dissoc} of about 2.3 × 10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.4 × 10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.5 × 10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.6 × 10^{-5} 1/s or slower or binds to human or murine CD95 with a k_{dissoc} of about 2.7 × 10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.8 × 10^{-5} 1/s or slower, binds to human or murine CD95 with a k_{dissoc} of about 2.9 × 10^{-5} 1/s or slower, or binds to human or murine CD95 with a k_{dissoc} of about 3 × 10^{-5} 1/s or slower.

[001025] In some embodiments, the compositions, processes and methods described include a CD95 agonist that binds to human or murine CD95 with an IC_{50} of about 10 nM or lower, binds to human or murine CD95 with an IC_{50} of about 9 nM or lower, binds to human or murine CD95 with an IC_{50} of about 8 nM or lower, binds to human or murine CD95 with an IC_{50} of about 7 nM or lower, binds to human or murine CD95 with an IC_{50} of about 6 nM or lower, binds to human or murine CD95 with an IC_{50} of about 5 nM or lower, binds to human or murine CD95 with an IC_{50} of about 4 nM or lower, binds to human or murine CD95 with an IC_{50} of about 3 nM or lower, binds to human or murine CD95 with an IC_{50} of about 2 nM or lower, or binds to human or murine CD95 with an IC_{50} of about 1 nM or lower.

[001026] In a preferred embodiment, the CD95 agonist is the monoclonal antibody E09, or a fragment, derivative, variant, or biosimilar thereof. The preparation and properties of E09 are described in Chodorge, *et al., Cell Death & Differ.* **2012,** *19,* 1187-95. The amino acid sequences of E09 are set forth in Table 46.

[001027] In an embodiment, the CD95 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of E09. In an embodiment, the CD95 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:451, and the CD95 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:452, and conservative amino acid substitutions thereof. In an embodiment, a CD95 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:451 and SEQ ID NO:452, respectively. In an embodiment, a CD95 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:451 and SEQ ID NO:452, respectively. In an embodiment, a CD95 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:451 and SEQ ID NO:452,

respectively. In an embodiment, a CD95 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:451 and SEQ ID NO:452, respectively. In an embodiment, a CD95 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:451 and SEQ ID NO:452, respectively.

[001028] In an embodiment, a CD95 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:453, SEQ ID NO:454, and SEQ ID NO:455, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:456, SEQ ID NO:457, and SEQ ID NO:458, respectively, and conservative amino acid substitutions thereof.

[001029] In an embodiment, the CD95 agonist is a CD95 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to E09. In an embodiment, the biosimilar monoclonal antibody comprises an CD95 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is E09. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a CD95 agonist antibody authorized or submitted for authorization, wherein the CD95 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is E09. The CD95 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is E09. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product,

wherein the reference medicinal product or reference biological product is E09.

TABLE 46. Amino acid sequences for CD95 agonist antibody E09.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:451 heavy chain variable region for E09	QLQLQESGPG LVKPSETLSL TCTVSGASIS ANSYYGVWVR QSPGKGLEWV GSIAYRGNSN SGSTYYNPSL KSRATVSVDT SKNQVSLRLT SVTAADTALY YCARRQLLDD GTGYQWAAFD VWGQGTMVTV SS	60 120 132
SEQ ID NO:452 light chain variable region for E09	QSVLTQPPSV SEAPRQTVTI SCSGNSFNIG RYPVNWYQQL PGKAPKLLIY YNNLRFSGVS DRFSGSKSGT SASLAIRDLL SEDEADYYCS TWDDTLKGWV FGGGTKVTVL	60 110
SEQ ID NO:453 heavy chain CDRl for E09	ANSYYGV	7
SEQ ID NO:454 heavy chain CDR2 for E09	GSIAYRGNSN SGSTYYNPSL KS	22
SEQ ID NO:455 heavy chain CDR3 for E09	RQLLDDGTGY QWAAFDV	17
SEQ ID NO:456 light chain CDR1 for E09	SGNSFNIGRY PVN	13
SEQ ID NO:457 light chain CDR2 for E09	YNNLRFS	7
SEQ ID NO:458 light chain CDR3 for E09	STWDDTLKGW V	11

[001030] In an embodiment, the CD95 agonist is an CD95 agonist described in International Patent Application Publication No. WO 2009/007120 A2 and U.S. Patent Application Publication No. US 2016/0176941 A1, the disclosure of each of which is incorporated by reference herein.

[001031] In an embodiment, the CD95 agonist is an CD95 agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 6. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID

NO:33 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 7. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[001032] In an embodiment, an CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a CD95 ligand sequence (Table 47). In an embodiment, an CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a sequence according to SEQ ID NO:459. In an embodiment, an CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a soluble LIGHT sequence. In an embodiment, a CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a sequence according to SEQ ID NO:460. In an embodiment, a CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a sequence according to SEQ ID NO:461. In an embodiment, a CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains comprising a sequence according to SEQ ID NO:462.

[001033] In an embodiment, an CD95 agonist fusion protein according to structures I-A or I-B comprises one or more CD95 binding domains that is a scFv domain comprising V_H and V_L regions, wherein the V_H and V_L domains are connected by a linker.

TABLE 47. Additional polypeptide domains useful as CD95 binding domains in fusion proteins (*e.g.*, structures I-A and I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)
SEQ ID NO:459 CD95L (CD95 ligand)	MQQPFNYPYP QIYWVDSSAS SPWAPPGTVL PCPTSVPRRP GQRRPPPPPP PPPLPPPPPP 60 PPLPPLPLPP LKKRGNHSTG LCLLVMFFMV LVALVGLGLG MFQLFHLQKE LAELRESTSQ 120 MHTASSLEKQ IGHPSPPPEK KELRKVAHLT GKSNSRSMPL EWEDTYGIVL LSGVKYKKGG 180 LVINETGLYF VYSKVYFRGQ SCNNLPLSHK VYMRNSKYPQ DLVMMEGKMM SYCTTGQMWA 240 RSSYLGAVFN LTSADHLYVN VSELSLVNFE ESQTFFGLYK L 281
SEQ ID NO:460 CD95L soluble domain	VAHLTGKSNS RSMPLEWEDT YGIVLLSGVK YKKGGLVINE TGLYFVYSKV YFRGQSCNNL 60 PLSHKVYMRN SKYPQDLVMM EGKMMSYCTT GQMWARSSYL GAVFNLTSAD HLYVNVSELS 120 LVNFEESQTF FGLYKL 136
SEQ ID NO:461 CD95L soluble domain (alternative)	AHLTGKSNSR SMPLEWEDTY GIVLLSGVKY KKGGLVINET GLYFVYSKVY FRGQSCNNLP 60 LSHKVYMRNS KYPQDLVMME GKMMSYCTTG QMWARSSYLG AVFNLTSADH LYVNVSELSL 120 VNFEESQTFF GLYKL 135

SEQ ID NO:462 CD95L soluble domain (alternative)	HLTGKSNSRS MPLEWEDTYG IVLLSGVKYK KGGLVINETG LYFVYSKVYF RGQSCNNLPL SHKVYMRNSK YPQDLVMMEG KMMSYCTTGQ MWARSSYLGA VFNLTSADHL YVNVSELSLV NFEESQTFFG LYKL	60 120 134

[001034] In an embodiment, the CD95 agonist is a CD95 agonistic single-chain fusion polypeptide comprising (i) a first soluble CD95 binding domain, (ii) a first peptide linker, (iii) a second soluble CD95 binding domain, (iv) a second peptide linker, and (v) a third soluble CD95 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the CD95 agonist is a CD95 agonistic single-chain fusion polypeptide comprising (i) a first soluble CD95 binding domain, (ii) a first peptide linker, (iii) a second soluble CD95 binding domain, (iv) a second peptide linker, and (v) a third soluble CD95 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble CD95 binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the CD95 binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[001035] In an embodiment, the CD95 agonist is an CD95 agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an CD95 binding domain.

[001036] In an embodiment, the CD95 agonist is a CD95 agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

Methods of Expanding Tumor Infilitrating Lymphocytes

[001037] In an embodiment, the invention provides a method of expanding a population of TILs using any of the TNFRSF agonists of the present disclosure, the method comprising the steps as described in Jin, *et al.*, *J. Immunotherapy* **2012,** *35,* 283-292, the disclosure of which is incorporated by reference herein. For example, the tumor may be placed in enzyme media and mechanically dissociated for approximately 1 minute. The mixture may then be incubated for 30

minutes at 37 °C in 5% CO_2 and then mechanically disrupted again for approximately 1 minute. After incubation for 30 minutes at 37 °C in 5% CO_2, the tumor may be mechanically disrupted a third time for approximately 1 minute. If after the third mechanical disruption, large pieces of tissue are present, 1 or 2 additional mechanical dissociations may be applied to the sample, with or without 30 additional minutes of incubation at 37 °C in 5% CO_2. At the end of the final incubation, if the cell suspension contains a large number of red blood cells or dead cells, a density gradient separation using Ficoll may be performed to remove these cells. TIL cultures were initiated in 24-well plates (Costar 24-well cell culture cluster, flat bottom; Corning Incorporated, Corning, NY), each well may be seeded with 1×10^6 tumor digest cells or one tumor fragment approximately 1 to 8 mm^3 in size in 2 mL of complete medium (CM) with IL-2 (6000 IU/mL; Chiron Corp., Emeryville, CA). CM comprises Roswell Park Memorial Institute (RPMI) 1640 buffer with GlutaMAX, supplemented with 10% human AB serum, 25mM Hepes, and 10 mg/mL gentamicin. Cultures may be initiated in gas-permeable flasks with a 40 mL capacity and a 10 cm^2 gas-permeable silicon bottom (G-Rex 10; Wilson Wolf Manufacturing, New Brighton, each flask may be loaded with $10\text{-}40\times10^6$ viable tumor digest cells or 5–30 tumor fragments in 10–40 mL of CM with IL-2. G-Rex 10 and 24-well plates may be incubated in a humidified incubator at 37 °C in 5% CO_2 and 5 days after culture initiation, half the media may be removed and replaced with fresh CM and IL-2 and after day 5, half the media may be changed every 2–3 days. Rapid expansion protocol (REP) of TILs may be performed using T-175 flasks and gas-permeable bags or gas-permeable G-Rex flasks, as described elsewhere herein, using the TNFRSF agonists of the present disclosure. For REP in T-175 flasks, 1×10^6 TILs may be suspended in 150 mL of media in each flask. The TIL may be cultured with TNFRSF agonists of the present disclosure at a ratio described herein, in a 1 to 1 mixture of CM and AIM-V medium (50/50 medium), supplemented with 3000 IU/mL of IL-2 and 30 ng/mL of anti-CD3 antibody (OKT-3). The T-175 flasks may be incubated at 37 °C in 5% CO_2. Half the media may be changed on day 5 using 50/50 medium with 3000 IU/mL of IL-2. On day 7, cells from 2 T-175 flasks may be combined in a 3L bag and 300mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 may be added to the 300mL of TIL suspension. The number of cells in each bag may be counted every day or two days, and fresh media may be added to keep the cell count between 0.5 and 2.0×10^6 cells/mL. For REP in 500 mL capacity flasks with 100 cm^2 gas-permeable silicon bottoms (*e.g.*, G-Rex 100, Wilson Wolf Manufacturing, as described

elsewhere herein), 5×10^6 or 10×10^6 TILs may be cultured with TNFRSF agonists at a ratio described herein (*e.g.*, 1 to 100) in 400 mL of 50/50 medium, supplemented with 3000 IU/mL of IL-2 and 30 ng/mL of anti-CD3 antibody (OKT-3). The G-Rex100 flasks may be incubated at 37 °C in 5% CO_2. On day five, 250 mL of supernatant may be removed and placed into centrifuge bottles and centrifuged at 1500 rpm (491 g) for 10 minutes. The obtained TIL pellets may be resuspended with 150 mL of fresh 50/50 medium with 3000 IU/mL of IL-2 and added back to the G-Rex 100 flasks. When TIL are expanded serially in G-Rex 100 flasks, on day seven the TIL in each G-Rex100 are suspended in the 300 mL of media present in each flask and the cell suspension may be divided into three 100 mL aliquots that may be used to seed 3 G-Rex100 flasks. About 150 mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 may then be added to each flask. G-Rex100 flasks may then be incubated at 37 °C in 5% CO_2, and after four days, 150 mL of AIM-V with 3000 IU/mL of IL-2 may be added to each G-Rex100 flask. After this, the REP may be completed by harvesting cells on day 14 of culture.

[001038] In an embodiment, a method or process of expanding or treating a cancer includes a step wherein TILs are obtained from a patient tumor sample. A patient tumor sample may be obtained using methods known in the art. For example, TILs may be cultured from enzymatic tumor digests and tumor fragments (about 1 to about 8 mm^3 in size) from sharp dissection. Such tumor digests may be produced by incubation in enzymatic media (*e.g.*, Roswell Park Memorial Institute (RPMI) 1640 buffer, 2 mM glutamate, 10 mcg/mL gentamicine, 30 units/mL of DNase and 1.0 mg/mL of collagenase) followed by mechanical dissociation (*e.g.*, using a tissue dissociator). Tumor digests may be produced by placing the tumor in enzymatic media and mechanically dissociating the tumor for approximately 1 minute, followed by incubation for 30 minutes at 37 °C in 5% CO_2, followed by repeated cycles of mechanical dissociation and incubation under the foregoing conditions until only small tissue pieces are present. At the end of this process, if the cell suspension contains a large number of red blood cells or dead cells, a density gradient separation using FICOLL branched hydrophilic polysaccharide may be performed to remove these cells. Alternative methods known in the art may be used, such as those described in U.S. Patent Application Publication No. 2012/0244133 A1, the disclosure of which is incorporated by reference herein. Any of the foregoing methods may be used in any of the embodiments described herein for methods or processes of expanding TILs or methods treating a cancer.

[001039] In an embodiment, a rapid expansion process for TILs may be performed using T-175 flasks and gas permeable bags as previously described (Tran, *et al.*, *J. Immunother.* **2008,** *31,* 742-51; Dudley, *et al.*, *J. Immunother.* **2003,** *26,* 332-42) or gas permeable cultureware (G-Rex flasks, commercially available from Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). For TIL rapid expansion in T-175 flasks, 1 x 10^6 TILs suspended in 150 mL of media may be added to each T-175 flask. The TILs may be cultured with TNFRSF agonists at a ratio of 1 TIL to 100 TNFRSF agonists and the cells were cultured in a 1 to 1 mixture of CM and AIM-V medium, supplemented with 3000 IU (international units) per mL of IL-2 and 30 ng per ml of anti-CD3 antibody (*e.g.*, OKT-3). The T-175 flasks may be incubated at 37° C in 5% CO_2. Half the media may be exchanged on day 5 using 50/50 medium with 3000 IU per mL of IL-2. On day 7 cells from two T-175 flasks may be combined in a 3 L bag and 300 mL of AIM V with 5% human AB serum and 3000 IU per mL of IL-2 was added to the 300 ml of TIL suspension. The number of cells in each bag was counted every day or two and fresh media was added to keep the cell count between 0.5 and 2.0 x 10^6 cells/mL.

[001040] In an embodiment, for TIL rapid expansions in 500 mL capacity gas permeable flasks with 100 cm^2 gas-permeable silicon bottoms (G-Rex 100, commercially available from Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA), 5 × 10^6 or 10 × 10^6 TIL may be cultured with TNFRSF agonists in 400 mL of 50/50 medium, supplemented with 5% human AB serum, 3000 IU per mL of IL-2 and 30 ng per mL of anti-CD3 (OKT-3). The G-Rex 100 flasks may be incubated at 37°C in 5% CO_2. On day 5, 250 mL of supernatant may be removed and placed into centrifuge bottles and centrifuged at 1500 rpm (revolutions per minute; 491 × g) for 10 minutes. The TIL pellets may be re-suspended with 150 mL of fresh medium with 5% human AB serum, 3000 IU per mL of IL-2, and added back to the original G-Rex 100 flasks. When TIL are expanded serially in G-Rex 100 flasks, on day 7 the TIL in each G-Rex 100 may be suspended in the 300 mL of media present in each flask and the cell suspension may be divided into 3 100 mL aliquots that may be used to seed 3 G-Rex 100 flasks. Then 150 mL of AIM-V with 5% human AB serum and 3000 IU per mL of IL-2 may be added to each flask. The G-Rex 100 flasks may be incubated at 37° C in 5% CO_2 and after 4 days 150 mL of AIM-V with 3000 IU per mL of IL-2 may be added to each G-Rex 100 flask. The cells may be harvested on day 14 of culture.

[001041] In an embodiment, TILs may be prepared as follows. 2 mm^3 tumor fragments are cultured in complete media (CM) comprised of AIM-V medium (Invitrogen Life Technologies, Carlsbad, CA) supplemented with 2 mM glutamine (Mediatech, Inc. Manassas, VA), 100 U/mL penicillin (Invitrogen Life Technologies), 100 μg/mL streptomycin (Invitrogen Life Technologies), 5% heat-inactivated human AB serum (Valley Biomedical, Inc. Winchester, VA) and 600 IU/mL rhIL-2 (Chiron, Emeryville, CA). For enzymatic digestion of solid tumors, tumor specimens are diced into RPMI-1640, washed and centrifuged at 800 rpm for 5 minutes at 15-22°C, and resuspended in enzymatic digestion buffer (0.2 mg/mL Collagenase and 30 units/ml of DNase in RPMI-1640) followed by overnight rotation at room temperature. TILs established from fragments may be grown for 3-4 weeks in CM and expanded fresh or cryopreserved in heat-inactivated HAB serum with 10% dimethylsulfoxide (DMSO) and stored at -180 °C until the time of study. Tumor associated lymphocytes (TAL) obtained from ascites collections were seeded at 3×10^6 cells/well of a 24 well plate in CM. TIL growth was inspected about every other day using a low-power inverted microscope.

[001042] In an embodiment, the invention includes a method of expanding tumor infiltrating lymphocytes (TILs), the method comprising contacting a population of TILs comprising at least one TIL with a TNFRSF agonist described herein, wherein said TNFRSF agonist comprises at least one co-stimulatory ligand that specifically binds with a co-stimulatory molecule expressed on the cellular surface of the TILs, wherein binding of said co-stimulatory molecule with said co-stimulatory ligand induces proliferation of the TILs, thereby specifically expanding TILs.

[001043] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium.

[001044] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the concentrations of the one or more TNFRSF agonists in the cell culture medium are independently selected from the group consisting of 50 ng/mL, 100 ng/mL, 500 ng/mL, 1 μg/mL, 5 μg/mL, 10 μg/mL, 20 μg/mL, 30 μg/mL, 40 μg/mL, 50 μg/mL, 60 μg/mL, 70 μg/mL, 80 μg/mL, 90 μg/mL, and 100 μg/mL.

[001045] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL.

[001046] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist.

[001047] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises an OX40 agonist.

[001048] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB and an OX40 agonist.

[001049] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a CD27 agonist.

[001050] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a GITR agonist.

[001051] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a HVEM agonist.

[001052] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a CD95 agonist.

[001053] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the the population of TILs by at least 50-fold over a period of 7 days in the cell culture medium.

[001054] In an embodiment, the invention provides a method of expanding a population of tumor infiltrating lymphocytes (TILs), the method comprising the steps of contacting the population of TILs with one or more TNFRSF agonists in a cell culture medium, wherein the the population of TILs by at least 50-fold over a period of 7 days in the cell culture medium, and wherein the expansion is performed using a gas permeable container.

[001055] In an embodiment, REP can be performed in a gas permeable container using the TNFRSF agonists of the present disclosure by any suitable method. For example, TILs can be rapidly expanded using non-specific T-cell receptor stimulation in the presence of interleukin-2

(IL-2) or interleukin-15 (IL-15). The non-specific T-cell receptor stimulus can include, for example, an anti-CD3 antibody, such as about 30 ng/mL of OKT-3, a monoclonal anti-CD3 antibody (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA) or UHCT-1 (commercially available from BioLegend, San Diego, CA, USA). TILs can be rapidly expanded by further stimulation of the TILs *in vitro* with one or more antigens, including antigenic portions thereof, such as epitope(s), of the cancer, which can be optionally expressed from a vector, such as a human leukocyte antigen A2 (HLA-A2) binding peptide, *e.g.*, 0.3 μM MART-1 :26-35 (27 L) or gpl 00:209-217 (210M), optionally in the presence of a T-cell growth factor, such as 300 IU/mL IL-2 or IL-15. Other suitable antigens may include, *e.g.*, NY-ESO-1, TRP-1, TRP-2, tyrosinase cancer antigen, MAGE-A3, SSX-2, and VEGFR2, or antigenic portions thereof. TIL may also be rapidly expanded by re-stimulation with the same antigen(s) of the cancer pulsed onto HLA-A2-expressing antigen-presenting cells. Alternatively, the TILs can be further re-stimulated with, *e.g.*, example, irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2.

[001056] In an embodiment, a method for expanding TILs may include using about 5000 mL to about 25000 mL of cell culture medium, about 5000 mL to about 10000 mL of cell culture medium, or about 5800 mL to about 8700 mL of cell culture medium. In an embodiment, a method for expanding TILs may include using about 1000 mL to about 2000 mL of cell medium, about 2000 mL to about 3000 mL of cell culture medium, about 3000 mL to about 4000 mL of cell culture medium, about 4000 mL to about 5000 mL of cell culture medium, about 5000 mL to about 6000 mL of cell culture medium, about 6000 mL to about 7000 mL of cell culture medium, about 7000 mL to about 8000 mL of cell culture medium, about 8000 mL to about 9000 mL of cell culture medium, about 9000 mL to about 10000 mL of cell culture medium, about 10000 mL to about 15000 mL of cell culture medium, about 15000 mL to about 20000 mL of cell culture medium, or about 20000 mL to about 25000 mL of cell culture medium. In an embodiment, expanding the number of TILs uses no more than one type of cell culture medium. Any suitable cell culture medium may be used, *e.g.*, AIM-V cell medium (L-glutamine, 50 μM streptomycin sulfate, and 10 μM gentamicin sulfate) cell culture medium (Invitrogen, Carlsbad CA). In this regard, the inventive methods advantageously reduce the amount of medium and the number of types of medium required to expand the number of TIL. In an embodiment, expanding the number of TIL may comprise feeding the cells no more frequently than every

third or fourth day. Expanding the number of cells in a gas permeable container simplifies the procedures necessary to expand the number of cells by reducing the feeding frequency necessary to expand the cells.

[001057] In an embodiment, the rapid expansion is performed using a gas permeable container. Such embodiments allow for cell populations to expand from about 5×10^5 cells/cm^2 to between 10×10^6 and 30×10^6 cells/cm^2. In an embodiment, this expansion occurs without feeding. In an embodiment, this expansion occurs without feeding so long as medium resides at a height of about 10 cm in a gas-permeable flask. In an embodiment this is without feeding but with the addition of one or more cytokines. In an embodiment, the cytokine can be added as a bolus without any need to mix the cytokine with the medium. Such containers, devices, and methods are known in the art and have been used to expand TILs, and include those described in U.S. Patent Application Publication No. US 2014/0377739 A1, International Patent Application Publication No. WO 2014/210036 A1, U.S. Patent Application Publication No. US 2013/0115617 A1, International Publication No. WO 2013/188427 A1, U.S. Patent Application Publication No. US 2011/0136228 A1, U.S. Patent No. 8,809,050, International Patent Application Publication No. WO 2011/072088 A2, U.S. Patent Application Publication No. US 2016/0208216 A1, U.S. Patent Application Publication No. US 2012/0244133 A1, International Patent Application Publication No. WO 2012/129201 A1, U.S. Patent Application Publication No. US 2013/0102075 A1, U.S. Patent No. 8,956,860, International Patent Application Publication No. WO 2013/173835 A1, and U.S. Patent Application Publication No. US 2015/0175966 A1, the disclosures of which are incorporated herein by reference. Such processes are also described in Jin, *et al.*, *J. Immunotherapy* **2012**, *35,* 283-292, the disclosure of which is incorporated by reference herein.

[001058] In an embodiment, the gas permeable container is a G-Rex 10 flask (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable container includes a 10 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a 40 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 100 to 300 million TILs after 2 medium exchanges.

[001059] In an embodiment, the gas permeable container is a G-Rex 100 flask (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable

container includes a 100 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a 450 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 1 to 3 billion TILs after 2 medium exchanges.

[001060] In an embodiment, the gas permeable container is a G-Rex 100M flask (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable container includes a 100 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a 1000 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 1 to 3 billion TILs without medium exchange.

[001061] In an embodiment, the gas permeable container is a G-Rex 100L flask (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable container includes a 100 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a 2000 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 1 to 3 billion TILs without medium exchange.

[001062] In an embodiment, the gas permeable container is a G-Rex 24 well plate (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable container includes a plate with wells, wherein each well includes a 2 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a plate with wells, wherein each well includes an 8 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 20 to 60 million cells per well after 2 medium exchanges.

[001063] In an embodiment, the gas permeable container is a G-Rex 6 well plate (Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA). In an embodiment, the gas permeable container includes a plate with wells, wherein each well includes a 10 cm^2 gas permeable culture surface. In an embodiment, the gas permeable container includes a plate with wells, wherein each well includes a 40 mL cell culture medium capacity. In an embodiment, the gas permeable container provides 100 to 300 million cells per well after 2 medium exchanges.

[001064] In an embodiment, the cell medium in the first and/or second gas permeable container is unfiltered. The use of unfiltered cell medium may simplify the procedures necessary to expand the number of cells. In an embodiment, the cell medium in the first and/or second gas permeable container lacks beta-mercaptoethanol (BME).

[001065] In an embodiment, the duration of the method comprising obtaining a tumor tissue sample from the mammal; culturing the tumor tissue sample in a first gas permeable container containing cell medium therein; obtaining TILs from the tumor tissue sample; expanding the number of TILs in a second gas permeable container containing cell medium therein using TNFRSF agonists for a duration of about 14 to about 42 days, *e.g.*, about 28 days.

[001066] In an embodiment, the ratio of TILs to TNFRSF agonists (cells to moles) in the rapid expansion is about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 500, about 1 to 1000, or about 1 to 10000. In an embodiment, the ratio of TILs to TNFRSF agonists in the rapid expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to TNFRSF agonists in the rapid expansion is between 1 to 100 and 1 to 200.

[001067] In an embodiment, the ratio of TILs to TNFRSF agonist (TIL:TNFRSF agonist, cells to moles) is selected from the group consisting of 1:5, 1:10, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, 1:50, 1:55, 1:60, 1:65, 1:70, 1:75, 1:80, 1:85, 1:90, 1:95, 1:100, 1:105, 1:110, 1:115, 1:120, 1:125, 1:130, 1:135, 1:140, 1:145, 1:150, 1:155, 1:160, 1:165, 1:170, 1:175, 1:180, 1:185, 1:190, 1:195, 1:200, 1:225, 1:250, 1:275, 1:300, 1:350, 1:400, 1:450, 1:500, 1:1000, 1:5000, 1:10000, and 1:50000.

[001068] In an embodiment, TILs are expanded in gas-permeable containers. Gas-permeable containers have been used to expand TILs using PBMCs using methods, compositions, and devices known in the art, including those described in U.S. Patent Application Publication No. U.S. Patent Application Publication No. 2005/0106717 A1, the disclosures of which are incorporated herein by reference. In an embodiment, TILs are expanded in gas-permeable bags. In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the Xuri Cell Expansion System W25 (GE Healthcare). In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the WAVE Bioreactor System, also known as the Xuri Cell Expansion System W5 (GE Healthcare). In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume selected from the group consisting of about 100 mL, about 200 mL, about 300 mL, about 400 mL, about 500 mL, about 600 mL, about 700 mL, about 800 mL,

about 900 mL, about 1 L, about 2 L, about 3 L, about 4 L, about 5 L, about 6 L, about 7 L, about 8 L, about 9 L, about 10 L, about 11 L, about 12 L, about 13 L, about 14 L, about 15 L, about 16 L, about 17 L, about 18 L, about 19 L, about 20 L, about 25 L, and about 30 L. In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume range selected from the group consisting of between 50 and 150 mL, between 150 and 250 mL, between 250 and 350 mL, between 350 and 450 mL, between 450 and 550 mL, between 550 and 650 mL, between 650 and 750 mL, between 750 and 850 mL, between 850 and 950 mL, and between 950 and 1050 mL. In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume range selected from the group consisting of between 1 L and 2 L, between 2 L and 3 L, between 3 L and 4 L, between 4 L and 5 L, between 5 L and 6 L, between 6 L and 7 L, between 7 L and 8 L, between 8 L and 9 L, between 9 L and 10 L, between 10 L and 11 L, between 11 L and 12 L, between 12 L and 13 L, between 13 L and 14 L, between 14 L and 15 L, between 15 L and 16 L, between 16 L and 17 L, between 17 L and 18 L, between 18 L and 19 L, and between 19 L and 20 L. In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume range selected from the group consisting of between 0.5 L and 5 L, between 5 L and 10 L, between 10 L and 15 L, between 15 L and 20 L, between 20 L and 25 L, and between 25 L and 30 L. In an embodiment, the cell expansion system utilizes a rocking time of about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, and about 28 days. In an embodiment, the cell expansion system utilizes a rocking time of between 30 minutes and 1 hour, between 1 hour and 12 hours, between 12 hours and 1 day, between 1 day and 7 days, between 7 days and 14 days, between 14 days and 21 days, and between 21 days and 28 days. In an embodiment, the cell expansion system utilizes a rocking rate of about 2 rocks/minute, about 5 rocks/minute, about 10 rocks/minute, about 20 rocks/minute, about 30 rocks/minute, and about 40 rocks/minute. In an embodiment, the cell expansion system utilizes a rocking rate of between 2 rocks/minute and 5 rocks/minute, 5 rocks/minute and 10 rocks/minute, 10

rocks/minute and 20 rocks/minute, 20 rocks/minute and 30 rocks/minute, and 30 rocks/minute and 40 rocks/minute. In an embodiment, the cell expansion system utilizes a rocking angle of about 2°, about 3°, about 4°, about 5°, about 6°, about 7°, about 8°, about 9°, about 10°, about 11°, and about 12°. In an embodiment, the cell expansion system utilizes a rocking angle of between 2° and 3°, between 3° and 4°, between 4° and 5°, between 5° and 6°, between 6° and 7°, between 7° and 8°, between 8° and 9°, between 9° and 10°, between 10° and 11°, and between 11° and 12°.

[001069] In an embodiment, a method of expanding TILs using TNFRSF agonists further comprises a step wherein TILs are selected for superior tumor reactivity. Any selection method known in the art may be used. For example, the methods described in U.S. Patent Application Publication No. 2016/0010058 A1, the disclosures of which are incorporated herein by reference, may be used for selection of TILs for superior tumor reactivity.

[001070] In an embodiment, the cell culture medium further comprises OKT-3 antibody. In a preferred embodiment, the cell culture medium comprises about 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL, between 5 ng/mL and 10 ng/mL, between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, or between 50 ng/mL and 100 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 10 ng/mL and 60 ng/mL of OKT-3 antibody.

[001071] In an embodiment, the cell culture medium further comprises IL-2. In a preferred embodiment, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 500 IU/mL, about 700 IU/mL, about 800 IU/mL, about 1000 IU/mL, about 1100 IU/mL, about 1200 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about

7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 500 and 1000 IU/mL, 800 and 1200 IU/mL, 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or between 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 10 and 6000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 500 and 2000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 800 and 1100 IU/mL of IL-2.

[001072] In an embodiment, the cell culture medium further comprises IL-15, as described, *e.g.*, in International Patent Application Publication Nos. WO 2015/189356 A1 and WO 2015/189356 A1, the disclosures of each of which are incorporated by reference herein. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, or about 1 μg/mL of IL-15. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 100 ng/mL, between 2 ng/mL and 50 ng/mL, or between 5 ng/mL and 25 ng/mL of IL-15. In an embodiment, the cell culture medium comprises between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, between 50 ng/mL and 60 ng/mL, between 60 ng/mL and 70 ng/mL, between 70 ng/mL and 80 ng/mL, between 80 ng/mL and 90, ir between 90 ng/mL and 100 ng/mL of IL-15.

[001073] In an embodiment, the cell culture medium further comprises IL-21, as described, *e.g.*, in International Patent Application Publication Nos. WO 2015/189356 A1 and WO 2015/189356 A1, the disclosures of each of which are incorporated by reference herein. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, or about 1 μg/mL of IL-21. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 100 ng/mL, between 2 ng/mL and 50 ng/mL,

or between 5 ng/mL and 25 ng/mL of IL-21. In an embodiment, the cell culture medium comprises between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, between 50 ng/mL and 60 ng/mL, between 60 ng/mL and 70 ng/mL, between 70 ng/mL and 80 ng/mL, between 80 ng/mL and 90, ir between 90 ng/mL and 100 ng/mL of IL-21.

[001074] In an embodiment, the cell culture medium further comprises IL-4 and/or IL-7.

[001075] In an embodiment, the TNFRSF agonists of the present invention may be used to expand T cells. Any of the foregoing embodiments of the present invention described for the expansion of TILs may also be applied to the expansion of T cells. In an embodiment, the TNFRSF agonists of the present invention may be used to expand $CD8^+$ T cells. In an embodiment, the TNFRSF agonists of the present invention may be used to expand $CD4^+$ T cells. In an embodiment, the TNFRSF agonists of the present invention may be used to expand T cells transduced with a chimeric antigen receptor (CAR-T). In an embodiment, the TNFRSF agonists of the present invention may be used to expand T cells comprising a modified T cell receptor (TCR). The CAR-T cells may be targeted against any suitable antigen, including CD19, as described in the art, *e.g.*, in U.S. Patent Nos. 7,070,995; 7,446,190; 8,399,645; 8,916,381; and 9,328,156; the disclosures of which are incorporated by reference herein. The modified TCR cells may be targeted against any suitable antigen, including NY-ESO-1, TRP-1, TRP-2, tyrosinase cancer antigen, MAGE-A3, SSX-2, and VEGFR2, or antigenic portions thereof, as described in the art, *e.g.*, in U.S. Patent Nos. 8,367,804 and 7,569,664, the disclosures of which are incorporated by reference herein.

[001076] In another embodiment, an exemplary TIL manufacturing/expansion process known as process 2A is schematically illustrated in FIG. 13. In certain aspects, the present methods produce TILs which are capable of increased replication cycles upon administration to a subject/patient and as such may provide additional therapeutic benefits over older TILs (*i.e.*, TILs which have further undergone more rounds of replication prior to administration to a subject/patient). Features of younger TILs have been described in the literature, for example Donia, at al., *Scandinavian Journal of Immunology,* 75:157–167 (2012); Dudley et al., *Clin Cancer Res,* 16:6122-6131 (2010); Huang et al., *J Immunother*, 28(3):258–267 (2005); Besser et al., *Clin Cancer Res*, 19(17):OF1-OF9 (2013); Besser et al., *J Immunother* 32:415–423 (2009);

Robbins, et al., *J Immunol* 2004; 173:7125-7130; Shen et al., J Immunother, 30:123–129 (2007); Zhou, et al., *J Immunother*, 28:53–62 (2005); and Tran, et al., J Immunother, 31:742–751 (2008), all of which are incorporated herein by reference in their entireties.

[001077] As discussed herein, the present invention can include a step relating to the restimulation of cyropreserved TILs to increase their metabolic activity and thus relative health prior to transplant into a patient, and methods of testing said metabolic health. As generally outlined herein, TILs are generally taken from a patient sample and manipulated to expand their number prior to transplant into a patient. In some embodiments, the TILs may be optionally genetically manipulated as discussed below.

[001078] In some embodiments, the TILs may be cryopreserved. Once thawed, they may also be restimulated to increase their metabolism prior to infusion into a patient.

[001079] In some embodiments, the first expansion (including processes referred to as the preREP) is shortened in comparison to conventional expansion methods to 7-14 days and the second expansion (including processes referred to as the REP) is shortened to 7-14 days, as discussed in detail below as well as in the examples and figures.

[001080] FIG. 14 illustrates an exemplary 2A process. As illustrated in FIG. 14 and further explained in detail below, in some embodiments, the first expansion (Step B) is shortened to 11 days and the second expansion (Step D) is shortened to 11 days. In some embodiments, the combination of the first and second expansions (Step B and Step D) is shortened to 22 days, as discussed in detail below and in the examples and figures. As will be appreciated, the process illustrated in FIG. 14 and described below is exemplary and the methods described herein encompass alterations and additions to the described steps as well as any combinations.

[001081] In general, TILs are initially obtained from a patient tumor sample ("primary TILs") and then expanded into a larger population for further manipulation as described herein, optionally cyropreserved, restimulated as outlined herein and optionally evaluated for phenotype and metabolic parameters as an indication of TIL health.

[001082] A patient tumor sample may be obtained using methods known in the art, generally via surgical resection, needle biopsy or other means for obtaining a sample that contains a mixture of tumor and TIL cells. In general, the tumor sample may be from any solid tumor,

including primary tumors, invasive tumors or metastatic tumors. The tumor sample may also be a liquid tumor, such as a tumor obtained from a hematological malignancy. The solid tumor may be of any cancer type, including, but not limited to, breast, pancreatic, prostate, colorectal, lung, brain, renal, stomach, and skin (including but not limited to squamous cell carcinoma, basal cell carcinoma, and melanoma). In some embodiments, useful TILs are obtained from malignant melanoma tumors, as these have been reported to have particularly high levels of TILs. In some embodiments, the tumor is greater than about 1.5 cm but less than about 4 cm. In some embodiments, the tumor is less than 4 cm.

[001083] Once obtained, the tumor sample is generally fragmented using sharp dissection into small pieces of between 1 to about 8 mm^3, with from about 2-3 mm^3 being particularly useful. The TILs are cultured from these fragments using enzymatic tumor digests. Such tumor digests may be produced by incubation in enzymatic media (*e.g.*, Roswell Park Memorial Institute (RPMI) 1640 buffer, 2 mM glutamate, 10 mcg/mL gentamicine, 30 units/mL of DNase and 1.0 mg/mL of collagenase) followed by mechanical dissociation (*e.g.*, using a tissue dissociator). Tumor digests may be produced by placing the tumor in enzymatic media and mechanically dissociating the tumor for approximately 1 minute, followed by incubation for 30 minutes at 37 °C in 5% CO_2, followed by repeated cycles of mechanical dissociation and incubation under the foregoing conditions until only small tissue pieces are present. At the end of this process, if the cell suspension contains a large number of red blood cells or dead cells, a density gradient separation using FICOLL branched hydrophilic polysaccharide may be performed to remove these cells. Alternative methods known in the art may be used, such as those described in U.S. Patent Application Publication No. 2012/0244133 A1, the disclosure of which is incorporated by reference herein. Any of the foregoing methods may be used in any of the embodiments described herein for methods and processes of expanding TILs or methods treating a cancer.

[001084] In general, the harvested cell suspension is called a "primary cell population" or a "freshly harvested" cell population.

[001085] In an embodiment, TILs can be initially cultured from enzymatic tumor digests and tumor fragments obtained from patients.

[001086] In some embodiments, the TILs, are obtained from tumor fragments. In some embodiments, the tumor fragment is obtained sharp dissection. In some embodiments, the tumor

fragment is between about 1 mm^3 and 10 mm^3. In some embodiments, the tumor fragment is between about 1 mm^3 and 8 mm^3. In some embodiments, the tumor fragment is about 1 mm^3. In some embodiments, the tumor fragment is about 2 mm^3. In some embodiments, the tumor fragment is about 3 mm^3. In some embodiments, the tumor fragment is about 4 mm^3. In some embodiments, the tumor fragment is about 5 mm^3. In some embodiments, the tumor fragment is about 6 mm^3. In some embodiments, the tumor fragment is about 7 mm^3. In some embodiments, the tumor fragment is about 8 mm^3. In some embodiments, the tumor fragment is about 9 mm^3. In some embodiments, the tumor fragment is about 10 mm^3. In some embodiments, about the tumor fragment is about 8-27 mm^3. In some embodiments, about the tumor fragment is about 10-25 mm^3. In some embodiments, about the tumor fragment is about 15-25 mm^3. In some embodiments, the tumor fragment is about 8-20 mm^3. In some embodiments, the tumor fragment is about 15-20 mm^3. In some embodiments, the tumor fragment is about 8-15 mm^3. In some embodiments, the tumor fragment is about 8-10 mm^3.

[001087] In some embodiments, the number of tumor fragments is about 40 to about 50 tumor fragments. In some embodiments, the number of tumor fragments is about 40 tumor fragments. In some embodiments, the number of tumor fragments is about 50 tumor fragments. In some embodiments, the tumor fragment size is about 8-27 mm^3 and there are less than about 50 tumor fragments.

[001088] In some embodiments, the TILs, are obtained from tumor digests. In some embodiments, tumor digests were generated by incubation in enzyme media, for example but not limited to RPMI 1640, 2mM GlutaMAX, 10 mg/mL gentamicin, 30 U/mL DNase, and 1.0 mg/mL collagenase, followed by mechanical dissociation (GentleMACS, Miltenyi Biotec, Auburn, CA). After placing the tumor in enzyme media, the tumor can be mechanically dissociated for approximately 1 minute. The solution can then be incubated for 30 minutes at 37 °C in 5% CO_2 and it then mechanically disrupted again for approximately 1 minute. After being incubated again for 30 minutes at 37 °C in 5% CO_2, the tumor can be mechanically disrupted a third time for approximately 1 minute. In some embodiments, after the third mechanical disruption if large pieces of tissue were present, 1 or 2 additional mechanical dissociations were applied to the sample, with or without 30 additional minutes of incubation at 37 °C in 5% CO_2. In some embodiments, at the end of the final incubation if the cell

suspension contained a large number of red blood cells or dead cells, a density gradient separation using Ficoll can be performed to remove these cells.

[001089] After dissection or digestion of tumor fragments in Step A, the resulting cells are cultured in serum containing IL-2 under conditions that favor the growth of TILs over tumor and other cells. In some embodiments, the tumor digests are incubated in 2 mL wells in media comprising inactivated human AB serum with 6000 IU/mL of IL-2. This primary cell population is cultured for a period of days, generally from 3 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of 7 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of 10 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of about 11 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of about 11 days, resulting in a bulk TIL population, generally less than or equal to about $200x10^6$ bulk TIL cells.

[001090] In a preferred embodiment, expansion of TILs may be performed using an initial bulk TIL expansion step (Step B as pictured in FIG. 14, which can include processes referred to as pre-REP) as described below and herein, followed by a second expansion (Step D, including processes referred to as rapid expansion protocol (REP) steps) as described below under Step D and herein, followed by optional cryopreservation, and followed by a second Step D (including processes referred to as restimulation REP steps) as described below and herein. The TILs obtained from this process may be optionally characterized for phenotypic characteristics and metabolic parameters as described herein.

[001091] In embodiments where TIL cultures are initiated in 24-well plates, for example, using Costar 24-well cell culture cluster, flat bottom (Corning Incorporated, Corning, NY, each well can be seeded with 1×10^6 tumor digest cells or one tumor fragment in 2mL of complete medium (CM) with IL-2 (6000 IU/mL; Chiron Corp., Emeryville, CA). In some embodiments, the tumor fragment is between about 1 mm^3 and 10 mm^3.

[001092] In some embodiments, CM for Step B consists of RPMI 1640 with GlutaMAX, supplemented with 10% human AB serum, 25mM HEPES, and 10 mg/mL gentamicin. In

embodiments where cultures are initiated in gas-permeable flasks with a 40 mL capacity and a 10cm^2 gas-permeable silicon bottom (for example, G-Rex10; Wilson Wolf Manufacturing, New Brighton, MN) (Fig. 1), each flask was loaded with 10–40 × 10^6 viable tumor digest cells or 5–30 tumor fragments in 10–40 mL of CM with IL-2. Both the G-Rex10 and 24-well plates were incubated in a humidified incubator at 37°C in 5% CO_2 and 5 days after culture initiation, half the media was removed and replaced with fresh CM and IL-2 and after day 5, half the media was changed every 2–3 days.

[001093] In an embodiment, the cell culture medium further comprises IL-2. In a preferred embodiment, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or between 8000 IU/mL of IL-2.

[001094] In some embodiments, the first expansion (including processes referred to as the pre-REP; Step B) process is shortened to 3-14 days, as discussed in the examples and figures. In some embodiments, the first expansion of Step B is shortened to 7-14 days, as discussed in the Examples and shown in Figures 4 and 5. In some embodiments, the first expansion of Step B is shortened to 10-14 days, as discussed in the Examples and shown in Figures 4 and 5. In some embodiments, the first expansion of Step B is shortened to 11 days, as discussed in the Examples and shown in Figures 4 and 5.

[001095] In some embodiments, IL-2, IL-7, IL-15, and IL-21 as well as combinations thereof can be included during Step B processes as described herein.

[001096] In some embodiments, Step B is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a single bioreactor is employed. In some embodiments, the single bioreactor employed is for example a GREX-10 or a GREX-100.

[001097] In some embodiments, the bulk TIL population from Step B can be cryopreserved immediately, using methods known in the art and described herein. Alternatively, the bulk TIL population can be subjected to a second expansion (REP) and then cryopreserved as discussed below.

[001098] In some embodiments, the Step B TILs are not stored and the Step B TILs proceed directly to Step D. In some embodiments, the transition occurs in a closed system, as further described herein.

[001099] In some embodiments, the TIL cell population is expanded in number after harvest and initial bulk processing (i.e., after Step A and Step B). This is referred to herein as the second expansion, which can include expansion processes generally referred to in the art as a rapid expansion process (REP). The second expansion is generally accomplished using culture media comprising a number of components, including feeder cells, a cytokine source, and an anti-CD3 antibody, in a gas-permeable container. In some embodiments, the second expansion can include scaling-up in order to increase the number of TILs obtained in the second expansion.

[001100] In an embodiment, REP and/or the second expansion can be performed in a gas permeable container using the methods of the present disclosure. For example, TILs can be rapidly expanded using non-specific T-cell receptor stimulation in the presence of interleukin-2 (IL-2) or interleukin-15 (IL-15). The non-specific T-cell receptor stimulus can include, for example, about 30 ng/ml of OKT3, a mouse monoclonal anti-CD3 antibody (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA). TILs can be rapidly expanded further stimulation of the TILs *in vitro* with one or more antigens, including antigenic portions thereof, such as epitope(s), of the cancer, which can be optionally expressed from a vector, such as a human leukocyte antigen A2 (HLA-A2) binding peptide, *e.g.*, 0.3 μM MART-1 :26-35 (27 L) or gpl 00:209-217 (210M), optionally in the presence of a T-cell growth factor, such as 300 IU/mL IL-2 or IL-15. Other suitable antigens may include, *e.g.*, NY-ESO-1, TRP-1, TRP-2, tyrosinase cancer antigen, MAGE-A3, SSX-2, and VEGFR2, or antigenic portions thereof. TIL may also be rapidly expanded by re-stimulation with the same antigen(s) of the cancer pulsed onto HLA-A2-expressing antigen-presenting cells. Alternatively, the TILs can be further re-stimulated with, *e.g.*, example, irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2.

[001101] In an embodiment, the cell culture medium further comprises IL-2. In a preferred embodiment, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or between 8000 IU/mL of IL-2.

[001102] In an embodiment, the cell culture medium comprises OKT3 antibody. In a preferred embodiment, the cell culture medium comprises about 30 ng/mL of OKT3 antibody. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL, between 5 ng/mL and 10 ng/mL, between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, and between 50 ng/mL and 100 ng/mL of OKT3 antibody.

[001103] In some embodiments, IL-2, IL-7, IL-15, and IL-21 as well as combinations thereof can be included during the second expansion in Step D processes as described herein.

[001104] In some embodiments, the second expansion can be conducted in a supplemented cell culture medium comprising IL-2, OKT-3, and antigen-presenting feeder cells.

[001105] In some embodiments the antigen-presenting feeder cells (APCs) are PBMCs. In an embodiment, the ratio of TILs to PBMCs and/or antigen-presenting cells in the rapid expansion and/or the second expansion is about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an

embodiment, the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 100 and 1 to 200.

[001106] In an embodiment, REP and/or the second expansion is performed in flasks with the bulk TILs being mixed with a 100- or 200-fold excess of inactivated feeder cells, 30 mg/mL OKT3 anti-CD3 antibody and 3000 IU/mL IL-2 in 150 ml media. Media replacement is done (generally 2/3 media replacement via respiration with fresh media) until the cells are transferred to an alternative growth chamber. Alternative growth chambers include GRex flasks and gas permeable containers as more fully discussed below.

[001107] In some embodiments, the second expansion (also referred to as the REP process) is shortened to 7-14 days, as discussed in the examples and figures. In some embodiments, the second expansion is shortened to 11 days.

[001108] In an embodiment, REP and/or the second expansion may be performed using T-175 flasks and gas permeable bags as previously described (Tran, *et al.*, *J. Immunother.* **2008,** *31,* 742-51; Dudley, *et al.*, *J. Immunother.* **2003,** *26,* 332-42) or gas permeable cultureware (G-Rex flasks). For TIL rapid expansion and/or second expansion in T-175 flasks, 1 x 10^6 TILs suspended in 150 mL of media may be added to each T-175 flask. The TILs may be cultured in a 1 to 1 mixture of CM and AIM-V medium, supplemented with 3000 IU per mL of IL-2 and 30 ng per ml of anti-CD3. The T-175 flasks may be incubated at 37° C in 5% CO_2. Half the media may be exchanged on day 5 using 50/50 medium with 3000 IU per mL of IL-2. On day 7 cells from two T-175 flasks may be combined in a 3 L bag and 300 mL of AIM V with 5% human AB serum and 3000 IU per mL of IL-2 was added to the 300 ml of TIL suspension. The number of cells in each bag was counted every day or two and fresh media was added to keep the cell count between 0.5 and 2.0 x 10^6 cells/mL.

[001109] In an embodiment, REP and/or the second expansion may be performed in 500 mL capacity gas permeable flasks with 100 cm gas-permeable silicon bottoms (G-Rex 100, commercially available from Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA), 5 × 10^6 or 10 × 10^6 TIL may be cultured with PBMCs in 400 mL of 50/50 medium, supplemented with 5% human AB serum, 3000 IU per mL of IL-2 and 30 ng per ml of anti-CD3 (OKT3). The G-Rex 100 flasks may be incubated at 37°C in 5% CO_2. On day 5, 250 mL of

supernatant may be removed and placed into centrifuge bottles and centrifuged at 1500 rpm (491 × g) for 10 minutes. The TIL pellets may be re-suspended with 150 mL of fresh medium with 5% human AB serum, 3000 IU per mL of IL-2, and added back to the original G-Rex 100 flasks. When TIL are expanded serially in G-Rex 100 flasks, on day 7 the TIL in each G-Rex 100 may be suspended in the 300 mL of media present in each flask and the cell suspension may be divided into 3 100 mL aliquots that may be used to seed 3 G-Rex 100 flasks. Then 150 mL of AIM-V with 5% human AB serum and 3000 IU per mL of IL-2 may be added to each flask. The G-Rex 100 flasks may be incubated at 37° C in 5% CO_2 and after 4 days 150 mL of AIM-V with 3000 IU per mL of IL-2 may be added to each G-Rexl OO flask. The cells may be harvested on day 14 of culture.

[001110] In an embodiment, REP and/or the second expansion is performed in flasks with the bulk TILs being mixed with a 100- or 200-fold excess of inactivated feeder cells, 30 mg/mL OKT3 anti-CD3 antibody and 3000 IU/mL IL-2 in 150 ml media. Media replacement is done (generally 2/3 media replacement via respiration with fresh media) until the cells are transferred to an alternative growth chamber. Alternative growth chambers include GRex flasks and gas permeable containers as more fully discussed below.

[001111] In an embodiment, REP and/or the second expansion is performed and further comprises a step wherein TILs are selected for superior tumor reactivity. Any selection method known in the art may be used. For example, the methods described in U.S. Patent Application Publication No. 2016/0010058 A1, the disclosures of which are incorporated herein by reference, may be used for selection of TILs for superior tumor reactivity.

[001112] REP and/or the second expansion of TIL can be performed using T-175 flasks and gas-permeable bags as previously described (Tran KQ, Zhou J, Durflinger KH, et al., **2008**, *J Immunother.*, 31:742–751, and Dudley ME, Wunderlich JR, Shelton TE, et al. 2003, *J Immunother.*, 26:332–342) or gas-permeable G-Rex flasks. In some embodiments, REP and/or the second expansion is performed using flasks. In some embodiments, REP is performed using gas-permeable G-Rex flasks. For TIL REP and/or the second expansion in T-175 flasks, about 1 x 10^6 TIL are suspended in about 150 mL of media and this is added to each T-175 flask. The TIL are cultured with irradiated (50 Gy) allogeneic PBMC as "feeder" cells at a ratio of 1 to 100 and the cells were cultured in a 1 to 1 mixture of CM and AIM-V medium (50/50 medium),

supplemented with 3000 IU/mL of IL-2 and 30 ng/mL of anti-CD3. The T-175 flasks are incubated at 37°C in 5% CO_2. In some embodiments, half the media is changed on day 5 using 50/50 medium with 3000 IU/mL of IL-2. In some embodiments, on day 7, cells from 2 T-175 flasks are combined in a 3 L bag and 300 mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 is added to the 300 mL of TIL suspension. The number of cells in each bag can be counted every day or two and fresh media can be added to keep the cell count between about 0.5 and about 2.0 x 10^6 cells/mL.

[001113] For TIL REP and/or the second expansion in 500 mL capacity flasks with 100 cm^2 gas-permeable silicon bottoms (G-Rex100,Wilson Wolf) (Fig. 1), about 5 x 10^6 or 10x 10^6 TIL are cultured with irradiated allogeneic PBMC at a ratio of 1 to 100 in 400 mL of 50/50 medium, supplemented with 3000 IU/mL of IL-2 and 30 ng/ mL of anti-CD3. The G-Rex100 flasks are incubated at 37°C in 5% CO_2. In some embodiments, on day 5, 250mL of supernatant is removed and placed into centrifuge bottles and centrifuged at 1500 rpm (491g) for 10 minutes. The TIL pellets can then be resuspended with 150 mL of fresh 50/50 medium with 3000 IU/ mL of IL-2 and added back to the original G-Rex100 flasks. In embodiments where TILs are expanded serially in G-Rex100 flasks, on day 7 the TIL in each G-Rex100 are suspended in the 300mL of media present in each flask and the cell suspension was divided into three 100mL aliquots that are used to seed 3 G-Rex100 flasks. Then 150 mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 is added to each flask. The G-Rex100 flasks are incubated at 37°C in 5% CO_2 and after 4 days 150 mL of AIM-V with 3000 IU/mL of IL-2 is added to each G-Rex100 flask. The cells are harvested on day 14 of culture.

[001114] In an embodiment, the second expansion procedures described herein (Step D, including REP) require an excess of feeder cells during REP TIL expansion and/or during the second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation.

[001115] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the REP procedures, as described in the examples, in particular example 14, which provides an exemplary protocol for evaluating the replication incompetence of irradiate allogeneic PBMCs.

[001116] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells on day 14 is less than the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion).

[001117] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 30ng/ml OKT3 antibody and 3000 IU/ml IL-2.

[001118] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 5-60 ng/ml OKT3 antibody and 1000-6000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 10-50 ng/ml OKT3 antibody and 2000-5000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 20-40 ng/ml OKT3 antibody and 2000-4000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 25-35 ng/ml OKT3 antibody and 2500-3500 IU/ml IL-2.

[001119] In an embodiment, artificial antigen presenting cells are used in the REP stage as a replacement for, or in combination with, PBMCs.

[001120] The expansion methods described herein generally use culture media with high doses of a cytokine, in particular IL-2, as is known in the art.

[001121] Alternatively, using combinations of cytokines for the rapid expansion and or second expansion of TILs is additionally possible, with combinations of two or more of IL-2, IL-15 and IL-21 as is generally outlined in International Publication No. WO 2015/189356 and W International Publication No. WO 2015/189357, hereby expressly incorporated by reference in their entirety. Thus, possible combinations include IL-2 and IL-15, IL-2 and IL-21, IL-15 and IL-21 and IL-2, IL-15 and IL-21, with the latter finding particular use in many embodiments.

The use of combinations of cytokines specifically favors the generation of lymphocytes, and in particular T-cells as described therein.

[001122] In some embodiments, the culture media used in expansion methods described herein (including REP) also includes an anti-CD3 antibody. An anti-CD3 antibody in combination with IL-2 induces T cell activation and cell division in the TIL population. This effect can be seen with full length antibodies as well as Fab and F(ab')2 fragments, with the former being generally preferred; see, *e.g.,* Tsoukas *et al.*, *J. Immunol.* **1985,** *135,* 1719, hereby incorporated by reference in its entirety.

[001123] As will be appreciated by those in the art, there are a number of suitable anti-human CD3 antibodies that find use in the invention, including anti-human CD3 polyclonal and monoclonal antibodies from various mammals, including, but not limited to, murine, human, primate, rat, and canine antibodies. In particular embodiments, the OKT3 anti-CD3 antibody is used (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA).

[001124] After the second expansion step, cells can be harvested. In some embodiments the TILs are harvested after one, two, three, four or more second expansion steps.

[001125] TILs can be harvested in any appropriate and sterile manner, including for example by centrifugation. Methods for TIL harvesting are well known in the art and any such know methods can be employed with the present process. In some embodiments, TILs are harvested using an automated system. In some embodiments, TILs are harvest using a semi-automated system. In some embodiments, the TILs from the second expansion are harvested using a semi-automated machine. In some embodiments, the LOVO system is employed (commercially available from Benchmark Electronics, for example). In some embodiments, the harvesting step includes wash the TILs, formulating the TILs, and/or aliquoting the TILs. In some embodiments, the cells are optionally frozen after harvesting or as part of harvesting.

[001126] After Steps A through E are complete, cells are transferred to a container for use in administration to a patient.

[001127] In an embodiment, TILs expanded using APCs of the present disclosure are administered to a patient as a pharmaceutical composition. In an embodiment, the

pharmaceutical composition is a suspension of TILs in a sterile buffer. TILs expanded using PBMCs of the present disclosure may be administered by any suitable route as known in the art. In some embodiments, the T-cells are administered as a single intra-arterial or intravenous infusion, which preferably lasts approximately 30 to 60 minutes. Other suitable routes of administration include intraperitoneal, intrathecal, and intralymphatic.

[001128] As will be appreciated, any of the steps A through F described above can be repeated any number of times and may in addition be conducted in different orders than described above.

[001129] In some embodiments, one or more of the expansion steps may be repeated prior to the Final Formulation Step F. Such additional expansion steps may include the elements of the first and/or second expansion steps described above (e.g., include the described components in the cell culture medium). The additional expansion steps may further include additional elements, including additional components in the cell culture medium that are supplemented into the cell culture medium before and/or during the additional expansion steps.

[001130] In further embodiments, any of the expansion steps described in FIG. 14 and in the above paragraphs may be preceded or followed by a cryopreservation step in which the cells produced during an expansion step are preserved using methods known in the art for storage until needed for the remaining steps of the manufacturing/expansion process.

[001131] In an embodiment, the invention includes a kit for expanding TILs according to any of the foregoing methods.

Pharmaceutical Compositions, Dosages, and Dosing Regimens for TILs

[001132] In an embodiment, TILs expanded using processes and methods of the present disclosure are administered to a patient as a pharmaceutical composition. In an embodiment, the pharmaceutical composition is a suspension of TILs in a sterile buffer. TILs expanded using processes and methods of the present disclosure may be administered by any suitable route as known in the art. Preferably, the TILs are administered as a single intra-arterial or intravenous infusion, which preferably lasts approximately 30 to 60 minutes. Other suitable routes of administration include intraperitoneal, intrathecal, and intralymphatic administration.

[001133] Any suitable dose of TILs can be administered. Preferably, from about 2.3×10^{10} to about 13.7×10^{10} TILs are administered, with an average of around 7.8×10^{10} TILs, particularly if

the cancer is melanoma. In an embodiment, about 1.2×10^{10} to about 4.3×10^{10} of TILs are administered.

[001134] In some embodiments, the number of the TILs provided in the pharmaceutical compositions of the invention is about 1×10^{6}, 2×10^{6}, 3×10^{6}, 4×10^{6}, 5×10^{6}, 6×10^{6}, 7×10^{6}, 8×10^{6}, 9×10^{6}, 1×10^{7}, 2×10^{7}, 3×10^{7}, 4×10^{7}, 5×10^{7}, 6×10^{7}, 7×10^{7}, 8×10^{7}, 9×10^{7}, 1×10^{8}, 2×10^{8}, 3×10^{8}, 4×10^{8}, 5×10^{8}, 6×10^{8}, 7×10^{8}, 8×10^{8}, 9×10^{8}, 1×10^{9}, 2×10^{9}, 3×10^{9}, 4×10^{9}, 5×10^{9}, 6×10^{9}, 7×10^{9}, 8×10^{9}, 9×10^{9}, 1×10^{10}, 2×10^{10}, 3×10^{10}, 4×10^{10}, 5×10^{10}, 6×10^{10}, 7×10^{10}, 8×10^{10}, 9×10^{10}, 1×10^{11}, 2×10^{11}, 3×10^{11}, 4×10^{11}, 5×10^{11}, 6×10^{11}, 7×10^{11}, 8×10^{11}, 9×10^{11}, 1×10^{12}, 2×10^{12}, 3×10^{12}, 4×10^{12}, 5×10^{12}, 6×10^{12}, 7×10^{12}, 8×10^{12}, 9×10^{12}, 1×10^{13}, 2×10^{13}, 3×10^{13}, 4×10^{13}, 5×10^{13}, 6×10^{13}, 7×10^{13}, 8×10^{13}, and 9×10^{13}. In an embodiment, the number of the TILs provided in the pharmaceutical compositions of the invention is in the range of 1×10^{6} to 5×10^{6}, 5×10^{6} to 1×10^{7}, 1×10^{7} to 5×10^{7}, 5×10^{7} to 1×10^{8}, 1×10^{8} to 5×10^{8}, 5×10^{8} to 1×10^{9}, 1×10^{9} to 5×10^{9}, 5×10^{9} to 1×10^{10}, 1×10^{10} to 5×10^{10}, 5×10^{10} to 1×10^{11}, 5×10^{11} to 1×10^{12}, 1×10^{12} to 5×10^{12}, and 5×10^{12} to 1×10^{13}.

[001135] In some embodiments, the concentration of the TILs provided in the pharmaceutical compositions of the invention is less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v of the pharmaceutical composition.

[001136] In some embodiments, the concentration of the TILs provided in the pharmaceutical compositions of the invention is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%,

0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v of the pharmaceutical composition.

[001137] In some embodiments, the concentration of the TILs provided in the pharmaceutical compositions of the invention is in the range from about 0.0001% to about 50%, about 0.001% to about 40%, about 0.01% to about 30%, about 0.02% to about 29%, about 0.03% to about 28%, about 0.04% to about 27%, about 0.05% to about 26%, about 0.06% to about 25%, about 0.07% to about 24%, about 0.08% to about 23%, about 0.09% to about 22%, about 0.1% to about 21%, about 0.2% to about 20%, about 0.3% to about 19%, about 0.4% to about 18%, about 0.5% to about 17%, about 0.6% to about 16%, about 0.7% to about 15%, about 0.8% to about 14%, about 0.9% to about 12% or about 1% to about 10% w/w, w/v or v/v of the pharmaceutical composition.

[001138] In some embodiments, the concentration of the TILs provided in the pharmaceutical compositions of the invention is in the range from about 0.001% to about 10%, about 0.01% to about 5%, about 0.02% to about 4.5%, about 0.03% to about 4%, about 0.04% to about 3.5%, about 0.05% to about 3%, about 0.06% to about 2.5%, about 0.07% to about 2%, about 0.08% to about 1.5%, about 0.09% to about 1%, about 0.1% to about 0.9% w/w, w/v or v/v of the pharmaceutical composition.

[001139] In some embodiments, the amount of the TILs provided in the pharmaceutical compositions of the invention is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[001140] In some embodiments, the amount of the TILs provided in the pharmaceutical compositions of the invention is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g,

0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[001141] The TILs provided in the pharmaceutical compositions of the invention are effective over a wide dosage range. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician. The clinically-established dosages of the TILs may also be used if appropriate. The amounts of the pharmaceutical compositions administered using the methods herein, such as the dosages of TILs, will be dependent on the human or mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the active pharmaceutical ingredients and the discretion of the prescribing physician.

[001142] In some embodiments, TILs may be administered in a single dose. Such administration may be by injection, *e.g.*, intravenous injection. In some embodiments, TILs may be administered in multiple doses. Dosing may be once, twice, three times, four times, five times, six times, or more than six times per year. Dosing may be once a month, once every two weeks, once a week, or once every other day. Administration of TILs may continue as long as necessary.

[001143] In some embodiments, an effective dosage of TILs is about 1×10^6, 2×10^6, 3×10^6, 4×10^6, 5×10^6, 6×10^6, 7×10^6, 8×10^6, 9×10^6, 1×10^7, 2×10^7, 3×10^7, 4×10^7, 5×10^7, 6×10^7, 7×10^7, 8×10^7, 9×10^7, 1×10^8, 2×10^8, 3×10^8, 4×10^8, 5×10^8, 6×10^8, 7×10^8, 8×10^8, 9×10^8, 1×10^9, 2×10^9, 3×10^9, 4×10^9, 5×10^9, 6×10^9, 7×10^9, 8×10^9, 9×10^9, 1×10^{10}, 2×10^{10}, 3×10^{10}, 4×10^{10}, 5×10^{10}, 6×10^{10}, 7×10^{10}, 8×10^{10}, 9×10^{10}, 1×10^{11}, 2×10^{11}, 3×10^{11}, 4×10^{11}, 5×10^{11}, 6×10^{11}, 7×10^{11}, 8×10^{11}, 9×10^{11}, 1×10^{12}, 2×10^{12}, 3×10^{12}, 4×10^{12}, 5×10^{12}, 6×10^{12}, 7×10^{12}, 8×10^{12}, 9×10^{12}, 1×10^{13}, 2×10^{13}, 3×10^{13}, 4×10^{13}, 5×10^{13}, 6×10^{13}, 7×10^{13}, 8×10^{13}, and 9×10^{13}. In some embodiments, an effective dosage of TILs is in the range of 1×10^6 to 5×10^6, 5×10^6 to 1×10^7, 1×10^7 to 5×10^7, 5×10^7 to 1×10^8, 1×10^8 to 5×10^8, 5×10^8 to 1×10^9, 1×10^9 to 5×10^9, 5×10^9 to 1×10^{10}, 1×10^{10} to 5×10^{10}, 5×10^{10} to 1×10^{11}, 5×10^{11} to 1×10^{12}, 1×10^{12} to 5×10^{12}, and 5×10^{12} to 1×10^{13}.

[001144] In some embodiments, an effective dosage of TILs is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2

mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg.

[001145] In some embodiments, an effective dosage of TILs is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 1 mg to about 50 mg, about 5 mg to about 45 mg, about 10 mg to about 40 mg, about 15 mg to about 35 mg, about 20 mg to about 30 mg, about 23 mg to about 28 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, or about 95 mg to about 105 mg, about 98 mg to about 102 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 207 mg.

[001146] An effective amount of the TILs may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, topically, by transplantation or direct injection into tumor, or by inhalation.

Pharmaceutical Compositions, Dosages, and Dosing Regimens for TNFRSF Agonists

[001147] In one embodiment, the invention provides a pharmaceutical composition for use in the treatment of the diseases and conditions described herein. In a preferred embodiment, the invention provides pharmaceutical compositions, including those described below, for use in the treatment of a hyperproliferative disease. In a preferred embodiment, the invention provides

pharmaceutical compositions, including those described below, for use in the treatment of cancer.

[001148] In some embodiments, a TNFRSF agonist antibody formulation comprises one or more excipients selected from tris-hydrochloride, sodium chloride, mannitol, pentetic acid, polysorbate 80, sodium hydroxide, and hydrochloric acid.

[001149] In an embodiment, a TNFRSF agonist is administered to a subject by infusing a dose selected from the group consisting of about 5 mg, about 8 mg, about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, and about 2000 mg. In an embodiment, a TNFRSF agonist is administered weekly. In an embodiment, a TNFRSF agonist is administered every two weeks. In an embodiment, a TNFRSF agonist is administered every three weeks. In an embodiment, a TNFRSF agonist is administered monthly. In an embodiment, a TNFRSF agonist is administered intravenously in a dose of 8 mg given every three weeks for 4 doses over a 12-week period. In an embodiment, a TNFRSF agonist is administered at a lower initial dose, which is escalated when administered at subsequent intervals administered monthly. For example, the first infusion can deliver 300 mg of a TNFRSF agonist, and subsequent weekly doses could deliver 2,000 mg of a TNFRSF agonist for eight weeks, followed by monthly doses of 2,000 mg of a TNFRSF agonist.

[001150] The amounts of TNFRSF agonists administered will be dependent on the human or mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage of each is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day. The dosage of the TNFRSF agonist(s) may be provided in units of mg/kg of body mass or in mg/m^2

of body surface area. In an embodiment, a TNFRSF agonist and a second TNFRSF agonist are delivered in mg/kg or in mg/m^2 in a ration selected from the group consisting of about 20:1, about 19:1, about 18:1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:11, about 1:12, about 1:13, about 1:14, about 1:15, about 1:16, about 1:17, about 1:18, about 1:19, and about 1:20.

[001151] In some embodiments, the combination of TILs and a TNFRSF agonist is administered in a single dose. Such administration may be by injection, *e.g.*, intravenous injection, in order to introduce the TNFRSF agonist.

[001152] In some embodiments, the combination of TILs and TNFRSF agonists is administered in multiple doses. In a preferred embodiment, the combination of TILs and TNFRSF agonists is administered in multiple doses. Dosing of the TNFRSF agonists may be once, twice, three times, four times, five times, six times, or more than six times per day. Dosing of TILs and TNFRSF agonists may be once a month, once every two weeks, once a week, or once every other day.

[001153] In selected embodiments, the TNFRSF agonists are administered for more than 1, 2, 3, 4, 5, 6, 7, 14, 28 days, 2 months, 3 months, 6 months, 12 months, or 24 months. In some cases, continuous dosing is achieved and maintained as long as necessary.

[001154] In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of a

TNFRSF agonist disclosed herein is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, or about 250 mg.

[001155] In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.

[001156] In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 1 mg to about 50 mg, about 5 mg to about 45 mg, about 10 mg to about 40 mg, about 15 mg to about 35 mg, about 20 mg to about 30 mg, about 23 mg to about 28 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, or about 95 mg to about 105 mg, about 98 mg to about 102 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 207 mg. In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, or about 250 mg.

[001157] In some embodiments, an effective dosage of a TNFRSF agonist disclosed herein is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.01 mg/kg to about 0.7 mg/kg, about 0.07 mg/kg to about 0.65 mg/kg, about 0.15 mg/kg to about 0.6 mg/kg, about 0.2 mg/kg to about 0.5 mg/kg, about 0.3 mg/kg to about 0.45 mg/kg, about 0.3 mg/kg to about 0.4 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 1.4 mg/kg to about 1.45 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, a TNFRSF agonist disclosed herein is about 0.4 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.

[001158] In some embodiments, a TNFRSF agonist is administered at a dosage of 10 to 1000 mg BID, including 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, or 200 mg BID.

[001159] In some embodiments, the concentration of the TNFRSF agonists, and combinations thereof provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v of the pharmaceutical composition.

[001160] In some embodiments, the concentration of the TNFRSF agonists, and combinations thereof provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%,

9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v of the pharmaceutical composition.

[001161] In some embodiments, the concentration of the TNFRSF agonists in pharmaceutical compositions is independently in the range from about 0.0001% to about 50%, about 0.001% to about 40%, about 0.01% to about 30%, about 0.02% to about 29%, about 0.03% to about 28%, about 0.04% to about 27%, about 0.05% to about 26%, about 0.06% to about 25%, about 0.07% to about 24%, about 0.08% to about 23%, about 0.09% to about 22%, about 0.1% to about 21%, about 0.2% to about 20%, about 0.3% to about 19%, about 0.4% to about 18%, about 0.5% to about 17%, about 0.6% to about 16%, about 0.7% to about 15%, about 0.8% to about 14%, about 0.9% to about 12% or about 1% to about 10% w/w, w/v or v/v of the pharmaceutical composition.

[001162] In some embodiments, the concentration of the TNFRSF agonists in pharmaceutical compositions is independently in the range from about 0.001% to about 10%, about 0.01% to about 5%, about 0.02% to about 4.5%, about 0.03% to about 4%, about 0.04% to about 3.5%, about 0.05% to about 3%, about 0.06% to about 2.5%, about 0.07% to about 2%, about 0.08% to about 1.5%, about 0.09% to about 1%, about 0.1% to about 0.9% w/w, w/v or v/v of the pharmaceutical composition.

[001163] In some embodiments, the concentration of the TNFRSF agonists in pharmaceutical compositions is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[001164] In some embodiments, the concentration of the TNFRSF agonists in pharmaceutical compositions is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g,

0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5 g, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[001165] Described below are non-limiting pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Injection

[001166] In preferred embodiments, the invention provides a pharmaceutical composition for injection containing the combination of a TIL and at least one TNFRSF agonist, and combinations thereof, and a pharmaceutical excipient suitable for injection, including intratumoral injection or intravenous infusion. Components and amounts of agents in the compositions are as described herein.

[001167] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[001168] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[001169] Sterile injectable solutions are prepared by incorporating the combination of the TNFRSF agonists and TILs in the required amounts in the appropriate media with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile

vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Other Pharmaceutical Compositions

[001170] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[001171] Administration of a combination of a TIL and a TNFRSF agonist can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[001172] The invention also provides kits. The kits include a combination of ready-to-administer TILs and a TNFRSF agonist, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another active pharmaceutical ingredient. In selected

embodiments, the TNFRSF agonists and TILs and another active pharmaceutical ingredient are provided as separate compositions in separate containers within the kit. In selected embodiments, the molecule selected from the group consisting of a TNFRSF agonist and the TILs are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer.

[001173] The kits described above are preferably for use in the treatment of the diseases and conditions described herein. In a preferred embodiment, the kits are for use in the treatment of cancer. In preferred embodiments, the kits are for use in treating solid tumor cancers, lymphomas and leukemias.

[001174] In a preferred embodiment, the kits of the present invention are for use in the treatment of cancer, including any of the cancers described herein.

Methods of Treating Cancers

[001175] The compositions and combinations of TILs and TNFRSF agonists described herein can be used in a method for treating hyperproliferative disorders. In a preferred embodiment, they are for use in treating cancers. In a preferred embodiment, the invention provides a method of treating a cancer and compositions and combinations of TILs and TNFRSF agonists for treating a cancer, wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, and sarcoma. In a preferred embodiment, the invention provides a method of treating a cancer and compositions and combinations of TILs and TNFRSF agonists for treating a cancer, wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC) or triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma. In a preferred embodiment, the invention provides a method of treating a cancer wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer (head and neck squamous cell cancer), renal cell carcinoma,

acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, and sarcoma with a combination of TILs and a TNFRSF agonist. In a preferred embodiment, the invention provides compositions and combinations of TILs and TNFRSF agonists for treating a cancer wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, and sarcoma. In a preferred embodiment, the invention provides a method of treating a cancer, wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC) or triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma with a combination of TILs and a TNFRSF agonist. In a preferred embodiment, the invention provides compositions and combinations of TILs and TNFRSF agonists for treating a cancer wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC) or triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma. In an embodiment, the TILs are expanded by a process described herein.

[001176] In some embodiments, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer;

wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, sarcoma, non-small cell lung cancer (NSCLC) or triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma.

[001177] In some embodiments, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer;

wherein the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, lung cancer, bladder cancer, breast cancer, head and neck cancer, renal cell

carcinoma, acute myeloid leukemia, colorectal cancer, cholangiocarcinoma, sarcoma, non-small cell lung cancer (NSCLC) or triple negative breast cancer, double-refractory melanoma, and uveal (ocular) melanoma.

[001178] In some embodiments, the invention provides a method of treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs; and

(f) administering a therapeutically effective portion of the third population of TILs to a patient with the cancer;

wherein the cancer is uveal (ocular) melanoma.

[001179] In an embodiment, the invention includes a kit for treating a cancer with a population of TILs according to any of the foregoing methods.

[001180] Efficacy of the methods, compounds, and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various animal models known in the art. Models for determining efficacy of treatments for pancreatic cancer are described in Herreros-Villanueva, *et al.*, *World J. Gastroenterol.* **2012,** *18,*

1286-1294. Models for determining efficacy of treatments for breast cancer are described, *e.g.*, in Fantozzi, *Breast Cancer Res.* **2006,** *8,* 212. Models for determining efficacy of treatments for ovarian cancer are described, *e.g.*, in Mullany, *et al.*, *Endocrinology* **2012,** *153,* 1585-92; and Fong, *et al.*, *J. Ovarian Res.* **2009,** *2,* 12. Models for determining efficacy of treatments for melanoma are described, *e.g.*, in Damsky, *et al.*, *Pigment Cell & Melanoma Res.* **2010,** *23,* 853–859. Models for determining efficacy of treatments for lung cancer are described, *e.g.*, in Meuwissen, *et al.*, *Genes & Development*, **2005,** *19,* 643-664. Models for determining efficacy of treatments for lung cancer are described, *e.g.*, in Kim, *Clin. Exp. Otorhinolaryngol.* **2009,** *2,* 55-60; and Sano, *Head Neck Oncol.* **2009,** *1,* 32. Models for determining efficacy of treatments for colorectal cancer, including the CT26 model, are described in Castle, *et al.*, *BMC Genomics,* **2013,** *15,* 190; Endo, *et al.*, *Cancer Gene Therapy*, **2002,** *9,* 142-148; Roth, *et al.*, *Adv. Immunol.* **1994,** *57,* 281-351; Fearon, *et al., Cancer Res.* **1988,** *48,* 2975-2980.

Co-Administration of IL-2

[001181] In an embodiment, the invention provides a method treating a cancer with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) resecting a tumor from a patient;

(b) obtaining a first population of TILs from the tumor;

(c) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2 and a tumor necrosis factor receptor superfamily (TNFRSF) agonist, and wherein the initial expansion is performed over a period of 21 days or less;

(d) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), and optionally the TNFRSF agonist, and wherein the rapid expansion is performed over a period of 14 days or less;

(e) harvesting the third population of TILs;

(f) administering a therapeutically effective portion of the third population of TILs to the patient with the cancer; and

(g) administering an IL-2 regimen to the patient.

[001182] In an embodiment, the IL-2 regimen comprises a high-dose IL-2 regimen, wherein the high-dose IL-2 regimen comprises aldesleukin, or a biosimilar or variant thereof, administered intraveneously starting on the day after administering a therapeutically effective portion of the third population of TILs, wherein the aldesleukin or a biosimilar or variant thereof is administered at a dose of 600,000 or 720,000 IU/kg (patient body mass) using 15-minute bolus intravenous infusions every eight hours until tolerance, for a maximum of 14 doses. Following 9 days of rest, this schedule may be repeated for another 14 doses, for a maximum of 28 doses in total.

[001183] In an embodiment, the IL-2 regimen comprises a high-dose IL-2 regimen, wherein the high-dose IL-2 regimen comprises aldesleukin, or a biosimilar or variant thereof, administered intraveneously starting on the day after administering a therapeutically effective portion of the third population of TILs, wherein the aldesleukin or a biosimilar or variant thereof is administered at a dose of 0.037 mg/kg or 0.044 mg/kg IU/kg (patient body mass) using 15-minute bolus intravenous infusions every eight hours until tolerance, for a maximum of 14 doses. Following 9 days of rest, this schedule may be repeated for another 14 doses, for a maximum of 28 doses in total.

[001184] In an embodiment, the IL-2 regimen comprises a decrescendo IL-2 regimen. Decrescendo IL-2 regimens have been described in O'Day, *et al.*, *J. Clin. Oncol.* **1999,** *17,* 2752-61 and Eton, *et al.*, *Cancer* **2000,** *88,* 1703-9, the disclosures of which are incorporated herein by reference. In an embodiment, a decrescendo IL-2 regimen comprises 18×10^6 IU/m^2 administered intraveneously over 6 hours, followed by 18×10^6 IU/m^2 administered intraveneously over 12 hours, followed by 18×10^6 IU/m^2 administered intraveneously over 24 hrs, followed by 4.5×10^6 IU/m^2 administered intraveneously over 72 hours. This treatment cycle may be repeated every 28 days for a maximum of four cycles. In an embodiment, a decrescendo IL-2 regimen comprises 18,000,000 IU/m^2 on day 1, 9,000,000 IU/m^2 on day 2, and 4,500,000 IU/m^2 on days 3 and 4.

[001185] In an embodiment, the IL-2 regimen comprises administration of pegylated IL-2 every 1, 2, 4, 6, 7, 14 or 21 days at a dose of 0.10 mg/day to 50 mg/day.

Non-Myeloablative Lymphodepletion with Chemotherapy

[001186] In an embodiment, the invention includes a method of treating a cancer with a population of TILs, wherein a patient is pre-treated with non-myeloablative chemotherapy prior to an infusion of TILs and prior to or concurrent with treatment with a TNFRSF agonist according to the present disclosure. In an embodiment, the non-myeloablative chemotherapy is cyclophosphamide 60 mg/kg/d for 2 days (days 27 and 26 prior to TIL infusion) and fludarabine 25 mg/m^2/d for 5 days (days 27 to 23 prior to TIL infusion). In an embodiment, after non-myeloablative chemotherapy and TIL infusion (at day 0) according to the present disclosure, the patient receives an intravenous infusion of IL-2 intravenously at 720,000 IU/kg every 8 hours to physiologic tolerance.

[001187] Experimental findings indicate that lymphodepletion prior to adoptive transfer of tumor-specific T lymphocytes plays a key role in enhancing treatment efficacy by eliminating regulatory T cells and competing elements of the immune system ("cytokine sinks"). Accordingly, some embodiments of the invention utilize a lymphodepletion step (sometimes also referred to as "immunosuppressive conditioning") on the patient prior to the introduction of the reREP TILs of the invention.

[001188] In general, lymphodepletion is achieved using administration of fludarabine or cyclophosphamide (the active form being referred to as mafosfamide) and combinations thereof. Such methods are described in Gassner, *et al., Cancer Immunol. Immunother.* **2011**, *60,* 75–85, Muranski, *et al.*, *Nat. Clin. Pract. Oncol.,* **2006,** *3,* 668–681, Dudley, *et al.*, *J. Clin. Oncol.* **2008**, *26,* 5233-5239, and Dudley, *et al.*, *J. Clin. Oncol.* **2005**, *23,* 2346–2357, all of which are incorporated by reference herein in their entireties.

[001189] In some embodiments, the fludarabine is administered at a concentration of 0.5 μg/ml -10 μg/ml fludarabine. In some embodiments, the fludarabine is administered at a concentration of 1μg/ml fludarabine. In some embodiments, the fludarabine treatment is administered for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days or more. In some embodiments, the fludarabine is administered at a dosage of 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, 40 mg/kg/day, or 45 mg/kg/day. In some

embodiments, the fludarabine treatment is administered for 2-7 days at 35 mg/kg/day. In some embodiments, the fludarabine treatment is administered for 4-5 days at 35 mg/kg/day. In some embodiments, the fludarabine treatment is administered for 4-5 days at 25 mg/kg/day.

[001190] In some embodiments, the mafosfamide, the active form of cyclophosphamide, is obtained at a concentration of 0.5 μg/mL -10 μg/mL by administration of cyclophosphamide. In some embodiments, mafosfamide, the active form of cyclophosphamide, is obtained at a concentration of 1 μg/mL by administration of cyclophosphamide. In some embodiments, the cyclophosphamide treatment is administered for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days or more. In some embodiments, the cyclophosphamide is administered at a dosage of 100 mg/m^2/day, 150 mg/m^2/day, 175 mg/m^2/day, 200 mg/m^2/day, 225 mg/m^2/day, 250 mg/m^2/day, 275 mg/m^2/day, or 300 mg/m^2/day. In some embodiments, the cyclophosphamide is administered intravenously *(i.e.*, i.v.) In some embodiments, the cyclophosphamide treatment is administered for 2-7 days at 35 mg/kg/day. In some embodiments, the cyclophosphamide treatment is administered for 4-5 days at 250 mg/m^2/day i.v. In some embodiments, the cyclophosphamide treatment is administered for 4 days at 250 mg/m^2/day i.v.

[001191] In some embodiments, lymphodepletion is performed by administering the fludarabine and the cyclophosphamide are together to a patient. In some embodiments, fludarabine is administered at 25 mg/m^2/day i.v. and cyclophosphamide is administered at 250 mg/m^2/day i.v. over 4 days.

[001192] In an embodiment, the lymphodepletion is performed by administration of cyclophosphamide at a dose of 60 mg/m^2/day for two days followed by administration of fludarabine at a dose of 25 mg/m^2/day for five days.

Combinations with PD-1 and PD-L1 Inhibitors

[001193] Programmed death 1 (PD-1) is a 288-amino acid transmembrane immunocheckpoint receptor protein expressed by T cells, B cells, natural killer (NK) T cells, activated monocytes, and dendritic cells. PD-1, which is also known as CD279, belongs to the CD28 family, and in humans is encoded by the *Pdcd1* gene on chromosome 2. PD-1 consists of one immunoglobulin (Ig) superfamily domain, a transmembrane region, and an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). PD-1 and its ligands (PD-L1 and PD-L2) are known to play a key role in

immune tolerance, as described in Keir, *et al.*, *Annu. Rev. Immunol.* **2008,** *26,* 677-704. PD-1 provides inhibitory signals that negatively regulate T cell immune responses. PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273) are expressed on tumor cells and stromal cells, which may be encountered by activated T cells expressing PD-1, leading to immunosuppression of the T cells. PD-L1 is a 290 amino acid transmembrane protein encoded by the *Cd274* gene on human chromosome 9. Blocking the interaction between PD-1 and its ligands PD-L1 and PD-L2 by use of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor can overcome immune resistance, as demonstrated in recent clinical studies, such as that described in Topalian, *et al.*, *N. Eng. J. Med.* **2012,** *366,* 2443-54. PD-L1 is expressed on many tumor cell lines, while PD-L2 is expressed is expressed mostly on dendritic cells and a few tumor lines. In addition to T cells (which inducibly express PD-1 after activation), PD-1 is also expressed on B cells, natural killer cells, macrophages, activated monocytes, and dendritic cells.

[001194] The methods, compositions, and combinations of TILs and TNFRSF agonists described herein may also be further combined with programmed death-1 (PD-1), programmed death ligand 1 (PD-L1), and/or programmed death ligand 2 (PD-L2) binding antibodies, antagonists, or inhibitors (*i.e.*, blockers). PD-1, PD-L1, and/or PD-L2 inhibitors may be used in cell culture in conjunction with the TNFRSF agonists described herein during the pre-REP or REP stages of TIL expansion. PD-1, PD-L1, and/or PD-L2 inhibitors may also be used in conjunction with TNFRSF agonists prior to surgical resection of tumor, or during or after infusion of TILs. For example, suitable methods of using PD-1/PD-L1 inhibitors in conjunction with agonistic GITR antibodies and compositions comprising PD-1/PD-L1 antagonists and GITR agonists are described in International Patent Application Publication No. WO 2015/026684 A1, the disclosures of which are incorporated by reference herein.

[001195] In an embodiment, the PD-1 inhibitor may be any PD-1 inhibitor or PD-1 blocker known in the art. In particular, it is one of the PD-1 inhibitors or blockers described in more detail in the following paragraphs. The terms "inhibitor," "antagonist," and "blocker" are used interchangeably herein in reference to PD-1 inhibitors. For avoidance of doubt, references herein to a PD-1 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to a PD-1 inhibitor may also refer to a small molecule compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

[001196] In some embodiments, the compositions and methods described herein include a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is a small molecule. In a preferred embodiment, the PD-1 inhibitor is an antibody (*i.e.*, an anti-PD-1 antibody), a fragment thereof, including Fab fragments, or a single-chain variable fragment (scFv) thereof. In some embodiments the PD-1 inhibitor is a polyclonal antibody. In a preferred embodiment, the PD-1 inhibitor is a monoclonal antibody. In some embodiments, the PD-1 inhibitor competes for binding with PD-1, and/or binds to an epitope on PD-1. In an embodiment, the antibody competes for binding with PD-1, and/or binds to an epitope on PD-1.

[001197] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds human PD-1 with a K_D of about 100 pM or lower, binds human PD-1 with a K_D of about 90 pM or lower, binds human PD-1 with a K_D of about 80 pM or lower, binds human PD-1 with a K_D of about 70 pM or lower, binds human PD-1 with a K_D of about 60 pM or lower, binds human PD-1 with a K_D of about 50 pM or lower, binds human PD-1 with a K_D of about 40 pM or lower, binds human PD-1 with a K_D of about 30 pM or lower, binds human PD-1 with a K_D of about 20 pM or lower, binds human PD-1 with a K_D of about 10 pM or lower, or binds human PD-1 with a K_D of about 1 pM or lower.

[001198] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a k_{assoc} of about 7.5×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human PD-1 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human PD-1 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human PD-1 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human PD-1 with a k_{assoc} of about 9.5×10^5 l/M·s or faster, or binds to human PD-1 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001199] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human PD-1 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human PD-1 with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human

PD-1 with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human PD-1 with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[001200] In some embodiments, the compositions and methods described include a PD-1 inhibitor that blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 10 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 9 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 8 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 7 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 6 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 5 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 4 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 3 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 2 nM or lower, or blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 1 nM or lower.

[001201] In an embodiment, the PD-1 inhibitor is nivolumab (commercially available as OPDIVO from Bristol-Myers Squibb Co.), or biosimilars, antigen-binding fragments, conjugates, or variants thereof. Nivolumab is a fully human IgG4 antibody blocking the PD-1 receptor. In an embodiment, the anti-PD-1 antibody is an immunoglobulin G4 kappa, anti-(human CD274) antibody. Nivolumab is assigned Chemical Abstracts Service (CAS) registry number 946414-94-4 and is also known as 5C4, BMS-936558, MDX-1106, and ONO-4538. The preparation and properties of nivolumab are described in U.S. Patent No. 8,008,449 and International Patent Publication No. WO 2006/121168, the disclosures of which are incorporated by reference herein. The clinical safety and efficacy of nivolumab in various forms of cancer has been described in Wang, *et al.*, *Cancer Immunol Res.* **2014,** 2, 846-56; Page, *et al.*, *Ann. Rev. Med.*, **2014,** *65,* 185-202; and Weber, *et al.*, *J. Clin. Oncology*, **2013,** *31,* 4311-4318, the disclosures of which are incorporated by reference herein. The amino acid sequences of nivolumab are set forth in Table 48. Nivolumab has intra-heavy chain disulfide linkages at 22-96,140-196, 254-314, 360-418, 22"-96", 140"-196", 254"-314", and 360"-418"; intra-light chain disulfide linkages at 23'-88', 134'-194', 23'"-88'", and 134'"-194'"; inter-heavy-light chain

disulfide linkages at 127-214', 127"-214"', inter-heavy-heavy chain disulfide linkages at 219-219" and 222-222"; and N-glycosylation sites (H CH_2 84.4) at 290, 290".

[001202] In an embodiment, a PD-1 inhibitor comprises a heavy chain given by SEQ ID NO:463 and a light chain given by SEQ ID NO:464. In an embodiment, a PD-1 inhibitor comprises heavy and light chains having the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:463 and SEQ ID NO:464, respectively.

[001203] In an embodiment, the PD-1 inhibitor comprises the heavy and light chain CDRs or variable regions (VRs) of nivolumab. In an embodiment, the PD-1 inhibitor heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:465, and the PD-1 inhibitor light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:466, and conservative amino acid substitutions thereof. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:465 and SEQ ID NO:466, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:465 and SEQ ID NO:466, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:465 and SEQ ID NO:466, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:465 and SEQ ID NO:466, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:465 and SEQ ID NO:466,

respectively.

[001204] In an embodiment, a PD-1 inhibitor comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:467, SEQ ID NO:468, and SEQ ID NO:469, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:470, SEQ ID NO:471, and SEQ ID NO:472, respectively, and conservative amino acid substitutions thereof. In an embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as any of the aforementioned antibodies.

[001205] In an embodiment, the PD-1 inhibitor is an anti-PD-1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to nivolumab. In an embodiment, the biosimilar comprises an anti-PD-1 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is nivolumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is an anti-PD-1 antibody authorized or submitted for authorization, wherein the anti-PD-1 antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is nivolumab. The anti-PD-1 antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is nivolumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is nivolumab.

TABLE 48. Amino acid sequences for PD-1 inhibitors related to nivolumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:463 nivolumab heavy chain	QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK	60 120 180 240 300 360 420 440
SEQ ID NO:464 nivolumab light chain	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:465 nivolumab variable heavy chain	QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSS	60 113
SEQ ID NO:466 nivolumab variable light chain	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIK	60 107
SEQ ID NO:467 nivolumab heavy chain CDR1	NSGMH	5
SEQ ID NO:468 nivolumab heavy chain CDR2	VIWYDGSKRY YADSVKG	17
SEQ ID NO:469 nivolumab heavy chain CDR3	NDDY	4
SEQ ID NO:470 nivolumab light chain CDR1	RASQSVSSYL A	11
SEQ ID NO:471 nivolumab light chain CDR2	DASNRAT	7
SEQ ID NO:472 nivolumab light chain CDR3	QQSSNWPRT	9

[001206] In another embodiment, the PD-1 inhibitor comprises pembrolizumab (commercially available as KEYTRUDA from Merck & Co., Inc., Kenilworth, NJ, USA), or antigen-binding fragments, conjugates, or variants thereof. Pembrolizumab is assigned CAS registry number 1374853-91-4 and is also known as lambrolizumab, MK-3475, and SCH-900475. Pembrolizumab has an immunoglobulin G4, anti-(human protein PDCD1 (programmed cell death 1)) (human-Mus musculus monoclonal heavy chain), disulfide with human-Mus musculus monoclonal light chain, dimer structure. The structure of pembrolizumab may also be described as immunoglobulin G4, anti-(human programmed cell death 1); humanized mouse monoclonal

[228-L-proline(H10-S>P)]γ4 heavy chain (134-218')-disulfide with humanized mouse monoclonal κ light chain dimer (226-226":229-229")-bisdisulfide. The properties, uses, and preparation of pembrolizumab are described in International Patent Publication No. WO 2008/156712 A1, U.S. Patent No. 8,354,509 and U.S. Patent Application Publication Nos. US 2010/0266617 A1, US 2013/0108651 A1, and US 2013/0109843 A2, the disclosures of which are incorporated herein by reference. The clinical safety and efficacy of pembrolizumab in various forms of cancer is described in Fuerst, *Oncology Times,* **2014,** *36,* 35-36; Robert, *et al.*, *Lancet,* **2014,** *384,* 1109-17; and Thomas, *et al.*, *Exp. Opin. Biol. Ther.*, **2014,** *14,* 1061-1064. The amino acid sequences of pembrolizumab are set forth in Table 49. Pembrolizumab includes the following disulfide bridges: 22-96, 22"-96", 23'-92', 23'"-92'", 134-218', 134"-218'", 138'-198', 138'"-198'", 147-203, 147"-203", 226-226", 229-229", 261-321, 261"-321", 367-425, and 367"-425", and the following glycosylation sites (N): Asn-297 and Asn-297". Pembrolizumab is an IgG4/kappa isotype with a stabilizing S228P mutation in the Fc region; insertion of this mutation in the IgG4 hinge region prevents the formation of half molecules typically observed for IgG4 antibodies. Pembrolizumab is heterogeneously glycosylated at Asn297 within the Fc domain of each heavy chain, yielding a molecular weight of approximately 149 kDa for the intact antibody. The dominant glycoform of pembrolizumab is the fucosylated agalacto diantennary glycan form (G0F).

[001207] In an embodiment, a PD-1 inhibitor comprises a heavy chain given by SEQ ID NO:473 and a light chain given by SEQ ID NO:474. In an embodiment, a PD-1 inhibitor comprises heavy and light chains having the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively. In an embodiment, a PD-1 inhibitor comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively. In an embodiment, a PD-1 inhibitor comprises

heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:473 and SEQ ID NO:474, respectively.

[001208] In an embodiment, the PD-1 inhibitor comprises the heavy and light chain CDRs or variable regions (VRs) of pembrolizumab. In an embodiment, the PD-1 inhibitor heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:475, and the PD-1 inhibitor light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:476, and conservative amino acid substitutions thereof. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:475 and SEQ ID NO:476, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:475 and SEQ ID NO:476, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:475 and SEQ ID NO:476, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:475 and SEQ ID NO:476, respectively. In an embodiment, a PD-1 inhibitor comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:475 and SEQ ID NO:476, respectively.

[001209] In an embodiment, a PD-1 inhibitor comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:477, SEQ ID NO:478, and SEQ ID NO:479, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:480, SEQ ID NO:481, and SEQ ID NO:482, respectively, and conservative amino acid substitutions thereof. In an embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as any of the aforementioned antibodies.

[001210] In an embodiment, the PD-1 inhibitor is an anti-PD-1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to pembrolizumab. In an embodiment, the biosimilar comprises an anti-PD-1 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or

reference biological product, wherein the reference medicinal product or reference biological product is pembrolizumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is an anti-PD-1 antibody authorized or submitted for authorization, wherein the anti-PD-1 antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is pembrolizumab. The anti-PD-1 antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is pembrolizumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is pembrolizumab.

TABLE 49. Amino acid sequences for PD-1 inhibitors related to pembrolizumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:473 pembrolizumab heavy chain	QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK	60 120 180 240 300 360 420 447
SEQ ID NO:474 pembrolizumab light chain	EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLPL TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC	60 120 180 218
SEQ ID NO:475 pembrolizumab variable heavy chain	QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS	60 120
SEQ ID NO:476 pembrolizumab variable light chain	EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLPL TFGGGTKVEI K	60 111
SEQ ID NO:477 pembrolizumab heavy chain CDR1	NYYMY	5

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:478 pembrolizumab heavy chain CDR2	GINPSNGGTN FNEKFK	16
SEQ ID NO:479 pembrolizumab heavy chain CDR3	RDYRFDMGFD Y	11
SEQ ID NO:480 pembrolizumab light chain CDR1	RASKGVSTSG YSYLH	15
SEQ ID NO:481 pembrolizumab light chain CDR2	LASYLES	7
SEQ ID NO:482 pembrolizumab light chain CDR3	QHSRDLPLT	9

[001211] In an embodiment, the PD-1 inhibitor is a commercially-available anti-PD-1 monoclonal antibody, such as anti-m-PD-1 clones J43 (Cat # BE0033-2) and RMP1-14 (Cat # BE0146) (Bio X Cell, Inc., West Lebanon, NH, USA). A number of commercially-available anti-PD-1 antibodies are known to one of ordinary skill in the art.

[001212] In an embodiment, the the PD-1 inhibitor is an antibody disclosed in U.S. Patent No. 8,354,509 or U.S. Patent Application Publication Nos. 2010/0266617 A1, 2013/0108651 A1, 2013/0109843 A2, the disclosures of which are incorporated by reference herein. In an embodiment, the PD-1 inhibitor is an anti-PD-1 antibody described in U.S. Patent Nos. 8,287,856, 8,580,247, and 8,168,757 and U.S. Patent Application Publication Nos. 2009/0028857 A1, 2010/0285013 A1, 2013/0022600 A1, and 2011/0008369 A1, the teachings of which are hereby incorporated by reference. In another embodiment, the the PD-1 inhibitor is an anti-PD-1 antibody disclosed in U.S. Patent No. 8,735,553 B1, the disclosure of which is incorporated herein by reference. In an embodiment, the PD-1 inhibitor is pidilizumab, also known as CT-011, which is described in U.S. Patent No. 8,686,119, the disclosure of which is incorporated by reference herein.

[001213] In an embodiment, the PD-1 inhibitor may be a small molecule or a peptide, or a peptide derivative, such as those described in U.S. Patent Nos. 8,907,053; 9,096,642; and 9,044,442 and U.S. Patent Application Publication No. US 2015/0087581; 1,2,4-oxadiazole compounds and derivatives such as those described in U.S. Patent Application Publication No.

2015/0073024; cyclic peptidomimetic compounds and derivatives such as those described in U.S. Patent Application Publication No. US 2015/0073042; cyclic compounds and derivatives such as those described in U.S. Patent Application Publication No. US 2015/0125491; 1,3,4-oxadiazole and 1,3,4-thiadiazole compounds and derivatives such as those described in International Patent Application Publication No. WO 2015/033301; peptide-based compounds and derivatives such as those described in International Patent Application Publication Nos. WO 2015/036927 and WO 2015/04490, or a macrocyclic peptide-based compounds and derivatives such as those described in U.S. Patent Application Publication No. US 2014/0294898; the disclosures of each of which are hereby incorporated by reference in their entireties.

[001214] In an embodiment, the PD-L1 or PD-L2 inhibitor may be any PD-L1 or PD-L2 inhibitor, antagonist, or blocker known in the art. In particular, it is one of the PD-L1 or PD-L2 inhibitors, antagonist, or blockers described in more detail in the following paragraphs. The terms "inhibitor," "antagonist," and "blocker" are used interchangeably herein in reference to PD-L1 and PD-L2 inhibitors. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

[001215] In some embodiments, the compositions, processes and methods described herein include a PD-L1 or PD-L2 inhibitor. In some embodiments, the PD-L1 or PD-L2 inhibitor is a small molecule. In a preferred embodiment, the PD-L1 or PD-L2 inhibitor is an antibody (*i.e.*, an anti-PD-1 antibody), a fragment thereof, including Fab fragments, or a single-chain variable fragment (scFv) thereof. In some embodiments the PD-L1 or PD-L2 inhibitor is a polyclonal antibody. In a preferred embodiment, the PD-L1 or PD-L2 inhibitor is a monoclonal antibody. In some embodiments, the PD-L1 or PD-L2 inhibitor competes for binding with PD-L1 or PD-L2, and/or binds to an epitope on PD-L1 or PD-L2. In an embodiment, the antibody competes for binding with PD-L1 or PD-L2, and/or binds to an epitope on PD-L1 or PD-L2.

[001216] In some embodiments, the PD-L1 inhibitors provided herein are selective for PD-L1, in that the compounds bind or interact with PD-L1 at substantially lower concentrations than they bind or interact with other receptors, including the PD-L2 receptor. In certain

embodiments, the compounds bind to the PD-L1 receptor at a binding constant that is at least about a 2-fold higher concentration, about a 3-fold higher concentration, about a 5-fold higher concentration, about a 10-fold higher concentration, about a 20-fold higher concentration, about a 30-fold higher concentration, about a 50-fold higher concentration, about a 100-fold higher concentration, about a 200-fold higher concentration, about a 300-fold higher concentration, or about a 500-fold higher concentration than to the PD-L2 receptor.

[001217] In some embodiments, the PD-L2 inhibitors provided herein are selective for PD-L2, in that the compounds bind or interact with PD-L2 at substantially lower concentrations than they bind or interact with other receptors, including the PD-L1 receptor. In certain embodiments, the compounds bind to the PD-L2 receptor at a binding constant that is at least about a 2-fold higher concentration, about a 3-fold higher concentration, about a 5-fold higher concentration, about a 10-fold higher concentration, about a 20-fold higher concentration, about a 30-fold higher concentration, about a 50-fold higher concentration, about a 100-fold higher concentration, about a 200-fold higher concentration, about a 300-fold higher concentration, or about a 500-fold higher concentration than to the PD-L1 receptor.

[001218] Without being bound by any theory, it is believed that tumor cells express PD-L1, and that T cells express PD-1. However, PD-L1 expression by tumor cells is not required for efficacy of PD-1 or PD-L1 inhibitors or blockers. In an embodiment, the tumor cells express PD-L1. In another embodiment, the tumor cells do not express PD-L1. In some embodiments, the methods and compositions described herein include a combination of a PD-1 and a PD-L1 antibody, such as those described herein, in combination with a TIL. The administration of a combination of a PD-1 and a PD-L1 antibody and a TIL may be simultaneous or sequential.

[001219] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds human PD-L1 and/or PD-L2 with a K_D of about 100 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 90 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 80 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 70 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 60 pM or lower, a K_D of about 50 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 40 pM or lower, or binds human PD-L1 and/or PD-L2 with a KD of about 30 pM or lower,

[001220] In some embodiments, the compositions and methods described include a PD-L1

and/or PD-L2 inhibitor that binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human PD-L1 and/ or PD-L2 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 9.5×10^5 1/M·s and/or faster, or binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001221] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower , binds to human PD-1 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower, binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, or binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[001222] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 10 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 9 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 8 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 7 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 6 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 5 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 4 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 3 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 2 nM or lower; or blocks human PD-1, or blocks binding of human PD-L1 or human PD-L2 to human PD-l with an IC_{50} of about 1 nM or lower.

[001223] In an embodiment, the PD-L1 inhibitor is durvalumab, also known as MEDI4736 (which is commercially available from Medimmune, LLC, Gaithersburg, Maryland, a subsidiary

of AstraZeneca plc.), or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an antibody disclosed in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are incorporated by reference herein. The clinical efficacy of durvalumab has been described in Page, *et al.*, *Ann. Rev. Med.*, **2014,** *65,* 185-202; Brahmer, *et al.*, *J. Clin. Oncol.* **2014,** *32,* 5s (supplement, abstract 8021); and McDermott, *et al.*, *Cancer Treatment Rev.*, **2014,** *40,* 1056-64. The preparation and properties of durvalumab are described in U.S. Patent No. 8,779,108, the disclosure of which is incorporated by reference herein. The amino acid sequences of durvalumab are set forth in Table 50. The durvalumab monoclonal antibody includes disulfide linkages at 22-96, 22"-96", 23'-89', 23'"-89'", 135'-195', 135'"-195'", 148-204, 148"-204", 215'-224, 215'"-224", 230-230", 233-233", 265-325, 265"-325", 371-429, and 371"-429'; and N-glycosylation sites at Asn-301 and Asn-301".

[001224] In an embodiment, a PD-L1 inhibitor comprises a heavy chain given by SEQ ID NO:483 and a light chain given by SEQ ID NO:484. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains having the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:483 and SEQ ID NO:484, respectively.

[001225] In an embodiment, the PD-L1 inhibitor comprises the heavy and light chain CDRs or variable regions (VRs) of durvalumab. In an embodiment, the PD-L1 inhibitor heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:485, and the PD-L1 inhibitor light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:486, and

conservative amino acid substitutions thereof. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:485 and SEQ ID NO:486, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:485 and SEQ ID NO:486, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:485 and SEQ ID NO:486, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:485 and SEQ ID NO:486, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:485 and SEQ ID NO:486, respectively.

[001226] In an embodiment, a PD-L1 inhibitor comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:487, SEQ ID NO:488, and SEQ ID NO:489, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:490, SEQ ID NO:491, and SEQ ID NO:492, respectively, and conservative amino acid substitutions thereof. In an embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-L1 as any of the aforementioned antibodies.

[001227] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to durvalumab. In an embodiment, the biosimilar comprises an anti-PD-L1 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is durvalumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is an anti-PD-L1 antibody authorized or submitted for authorization, wherein the anti-PD-L1 antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is

durvalumab. The anti-PD-L1 antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is durvalumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is durvalumab.

TABLE 50. Amino acid sequences for PD-L1 inhibitors related to durvalumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:483 durvalumab heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG GWFGELAFDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEFEG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPASIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K	60 120 180 240 300 360 420 451
SEQ ID NO:484 durvalumab light chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN EIVLTQSPGT LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY DASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSLPWTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC	60 120 180 240 265
SEQ ID NO:485 durvalumab variable heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG GWFGELAFDY WGQGTLVTVS S	60 120 121
SEQ ID NO:486 durvalumab variable light chain	EIVLTQSPGT LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY DASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSLPWTFG QGTKVEIK	60 108
SEQ ID NO:487 durvalumab heavy chain CDR1	RYWMS	5
SEQ ID NO:488 durvalumab heavy chain CDR2	NIKQDGSEKY YVDSVKG	17
SEQ ID NO:489 durvalumab heavy chain CDR3	EGGWFGELAF DY	12
SEQ ID NO:490 durvalumab light chain CDR1	RASQRVSSSY LA	12
SEQ ID NO:491 durvalumab	DASSRAT	7

Identifier	Sequence (One-Letter Amino Acid Symbols)
light chain CDR2	
SEQ ID NO:492 durvalumab light chain CDR3	QQYGSLPWT 9

[001228] In an embodiment, the PD-L1 inhibitor is avelumab, also known as MSB0010718C (commercially available from Merck KGaA/EMD Serono), or antigen-binding fragments, conjugates, or variants thereof. The preparation and properties of avelumab are described in U.S. Patent Application Publication No. US 2014/0341917 A1, the disclosure of which is specifically incorporated by reference herein. The amino acid sequences of avelumab are set forth in Table 51. Avelumab has intra-heavy chain disulfide linkages (C23-C104) at 22-96, 147-203, 264-324, 370-428, 22"-96", 147"-203", 264"-324", and 370"-428"; intra-light chain disulfide linkages (C23-C104) at 22'-90', 138'-197', 22'"-90'", and 138'"-197'"; intra-heavy-light chain disulfide linkages (h 5-CL 126) at 223-215' and 223"-215'"; intra-heavy-heavy chain disulfide linkages (h 11, h 14) at 229-229" and 232-232"; N-glycosylation sites (H CH_2 N84.4) at 300, 300"; fucosylated complex bi-antennary CHO-type glycans; and H CHS K2 C-terminal lysine clipping at 450 and 450'.

[001229] In an embodiment, a PD-L1 inhibitor comprises a heavy chain given by SEQ ID NO:493 and a light chain given by SEQ ID NO:494. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains having the sequences shown in SEQ ID NO:493 and SEQ ID NO:494, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:493 and SEQ ID NO:494, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:493 and SEQ ID NO:494, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:493 and SEQ ID NO:494, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:493 and SEQ ID NO:494, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 95% identical to the sequences shown in

SEQ ID NO:493 and SEQ ID NO:494, respectively.

[001230] In an embodiment, the PD-L1 inhibitor comprises the heavy and light chain CDRs or variable regions (VRs) of avelumab. In an embodiment, the PD-L1 inhibitor heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:495, and the PD-L1 inhibitor light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:496, and conservative amino acid substitutions thereof. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:495 and SEQ ID NO:496, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:496 and SEQ ID NO:496, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:495 and SEQ ID NO:496, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:495 and SEQ ID NO:496, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:495 and SEQ ID NO:496, respectively.

[001231] In an embodiment, a PD-L1 inhibitor comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:497, SEQ ID NO:498, and SEQ ID NO:499, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:500, SEQ ID NO:501, and SEQ ID NO:502, respectively, and conservative amino acid substitutions thereof. In an embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-L1 as any of the aforementioned antibodies.

[001232] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to avelumab. In an embodiment, the biosimilar comprises an anti-PD-L1 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal

product or reference biological product is avelumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is an anti-PD-L1 antibody authorized or submitted for authorization, wherein the anti-PD-L1 antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is avelumab. The anti-PD-L1 antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is avelumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is avelumab.

TABLE 51. Amino acid sequences for PD-L1 inhibitors related to avelumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:493 avelumab heavy chain	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS IYPSGGITFY ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK LGTVTTVDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 240 300 360 420 450
SEQ ID NO:494 avelumab light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV FGTGTKVTVL GQPKANPTVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADGSPVK AGVETTKPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	60 120 180 216
SEQ ID NO:495 avelumab variable heavy chain	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS IYPSGGITFY ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK LGTVTTVDYW GQGTLVTVSS	60 120
SEQ ID NO:496 avelumab variable light chain	QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV FGTGTKVTVL	60 110
SEQ ID NO:497 avelumab heavy chain CDR1	SYIMM	5
SEQ ID NO:498 avelumab	SIYPSGGITF YADTVKG	17

Identifier	Sequence (One-Letter Amino Acid Symbols)	
heavy chain CDR2		
SEQ ID NO:499 avelumab heavy chain CDR3	IKLGTVTTVD Y	11
SEQ ID NO:500 avelumab light chain CDR1	TGTSSDVGGY NYVS	14
SEQ ID NO:501 avelumab light chain CDR2	DVSNRPS	7
SEQ ID NO:502 avelumab light chain CDR3	SSYTSSSTRV	10

[001233] In an embodiment, the PD-L1 inhibitor is atezolizumab, also known as MPDL3280A or RG7446 (commercially available as TECENTRIQ from Genentech, Inc., a subsidiary of Roche Holding AG, Basel, Switzerland), or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an antibody disclosed in U.S. Patent No. 8,217,149, the disclosure of which is specifically incorporated by reference herein. In an embodiment, the PD-L1 inhibitor is an antibody disclosed in U.S. Patent Application Publication Nos. 2010/0203056 A1, 2013/0045200 A1, 2013/0045201 A1, 2013/0045202 A1, or 2014/0065135 A1, the disclosures of which are specifically incorporated by reference herein. The preparation and properties of atezolizumab are described in U.S. Patent No. 8,217,149, the disclosure of which is incorporated by reference herein. The amino acid sequences of atezolizumab are set forth in Table 52. Atezolizumab has intra-heavy chain disulfide linkages (C23-C104) at 22-96, 145-201, 262-322, 368-426, 22"-96", 145"-201", 262"-322", and 368"-426"; intra-light chain disulfide linkages (C23-C104) at 23'-88', 134'-194', 23'"-88'", and 134'"-194'"; intra-heavy-light chain disulfide linkages (h 5-CL 126) at 221-214' and 221"-214'"; intra-heavy-heavy chain disulfide linkages (h 11, h 14) at 227-227" and 230-230"; and N-glycosylation sites (H CH_2 N84.4>A) at 298 and 298'.

[001234] In an embodiment, a PD-L1 inhibitor comprises a heavy chain given by SEQ ID NO:503 and a light chain given by SEQ ID NO:504. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains having the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively, or antigen binding fragments, Fab fragments, single-chain variable

fragments (scFv), variants, or conjugates thereof. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively. In an embodiment, a PD-L1 inhibitor comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:503 and SEQ ID NO:504, respectively.

[001235] In an embodiment, the PD-L1 inhibitor comprises the heavy and light chain CDRs or variable regions (VRs) of atezolizumab. In an embodiment, the PD-L1 inhibitor heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:505, and the PD-L1 inhibitor light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:506, and conservative amino acid substitutions thereof. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:505 and SEQ ID NO:506, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:505 and SEQ ID NO:506, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:505 and SEQ ID NO:506, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:505 and SEQ ID NO:506, respectively. In an embodiment, a PD-L1 inhibitor comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:505 and SEQ ID NO:506, respectively.

[001236] In an embodiment, a PD-L1 inhibitor comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:507, SEQ ID NO:508, and SEQ ID NO:509, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:510, SEQ ID NO:511, and SEQ ID NO:512, respectively, and conservative amino acid substitutions thereof. In an

embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-L1 as any of the aforementioned antibodies.

[001237] In an embodiment, the anti-PD-L1 antibody is an anti-PD-L1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to atezolizumab. In an embodiment, the biosimilar comprises an anti-PD-L1 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.,* 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is atezolizumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is an anti-PD-L1 antibody authorized or submitted for authorization, wherein the anti-PD-L1 antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is atezolizumab. The anti-PD-L1 antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is atezolizumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is atezolizumab.

TABLE 52. Amino acid sequences for PD-L1 inhibitors related to atezolizumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:503 atezolizumab heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS DSWIHWVRQA PGKGLEWVAW ISPYGGSTYY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYAST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT	60 120 180 240 300 360

Identifier	Sequence (One-Letter Amino Acid Symbols)	
	KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK	420 448
SEQ ID NO:504 atezolizumab light chain	DIQMTQSPSS LSASVGDRVT ITCRASQDVS TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLYHPATFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	60 120 180 214
SEQ ID NO:505 atezolizumab variable heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGFTFS DSWIHWVRQA PGKGLEWVAW ISPYGGSTYY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSA	60 118
SEQ ID NO:506 atezolizumab variable light chain	DIQMTQSPSS LSASVGDRVT ITCRASQDVS TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLYHPATFGQ GTKVEIKR	60 108
SEQ ID NO:507 atezolizumab heavy chain CDR1	GFTFSDSWIH	10
SEQ ID NO:508 atezolizumab heavy chain CDR2	AWISPYGGST YYADSVKG	18
SEQ ID NO:509 atezolizumab heavy chain CDR3	RHWPGGFDY	9
SEQ ID NO:510 atezolizumab light chain CDR1	RASQDVSTAV A	11
SEQ ID NO:511 atezolizumab light chain CDR2	SASFLYS	7
SEQ ID NO:512 atezolizumab light chain CDR3	QQYLYHPAT	9

[001238] In an embodiment, PD-L1 inhibitors include those antibodies described in U.S. Patent Application Publication No. US 2014/0341917 A1, the disclosure of which is incorporated by reference herein. In another embodiment, antibodies that compete with any of these antibodies for binding to PD-L1 are also included. In an embodiment, the anti-PD-L1 antibody is MDX-1105, also known as BMS-935559, which is disclosed in U.S. Patent No. US 7,943,743, the disclosures of which are incorporated by reference herein. In an embodiment, the anti-PD-L1 antibody is selected from the anti-PD-L1 antibodies disclosed in U.S. Patent No. US 7,943,743, which are incorporated by reference herein.

[001239] In an embodiment, the PD-L1 inhibitor is a commercially-available monoclonal antibody, such as INVIVOMAB anti-m-PD-L1 clone 10F.9G2 (Catalog # BE0101, Bio X Cell, Inc., West Lebanon, NH, USA). In an embodiment, the anti-PD-L1 antibody is a commercially-

available monoclonal antibody, such as AFFYMETRIX EBIOSCIENCE (MIH1). A number of commercially-available anti-PD-L1 antibodies are known to one of ordinary skill in the art.

[001240] In an embodiment, the PD-L2 inhibitor is a commercially-available monoclonal antibody, such as BIOLEGEND 24F.10C12 Mouse IgG2a, κ isotype (catalog # 329602 Biolegend, Inc., San Diego, CA), SIGMA anti-PD-L2 antibody (catalog # SAB3500395, Sigma-Aldrich Co., St. Louis, MO), or other commercially-available anti-PD-L2 antibodies known to one of ordinary skill in the art.

[001241] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

EXAMPLES

[001242] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 – Methods of Expanding TILs and Treating Cancer with Expanded TILs

[001243] TILs may be expanded using methods known in the art and any method described herein. For example, methods for expanding TILs are depicted in FIG. 1. A TNFRSF agonist may be added to the method of FIG. 1 as described herein. The TNFRSF agonist may be, for example, a 4-1BB or an OX40 agonist, and may be added during the pre-REP or the REP phases, or during both phases, at concentrations sufficient to enhance TIL growth. The expansion of TILs may be further combined with any method of treating cancer in combination with a TNFRSF agonist in a patient described herein. Methods for expanding TILs and treating a cancer patient with expanded TILs are shown in FIG. 2.

Example 2 – Methods of Expanding TILs Using 4-1BB Agonists

[001244] 4-1BB-Fc hybridomas were produced and screened for their ability to activate the 4-1BB signaling pathway by cross-linking with secondary antibody. Hybridoma supernatants were

evaluated for their ability to activate 4-1BB signaling on Jurkat cells expressing NF-kB using a green fluorescent protein (GFP) reporter in a dose dependent manner. Supernatants were incubated with Jurkat cells for 20 minutes at room temperature followed by crosslinking with goat anti-mouse secondary antibody (1 mg/mL) overnight at 37 °C. Results are shown in FIG. 3 to FIG. 12 for ten clones identified that bound to 4-1BB on Jurkat cells.

[001245] Cells were analyzed on Intellicyte for NKkB Pathway activation revealed by GFP reporter expression. The results indicate that the antibodies activate the 4-1BB pathway on Jurkat cells without secondary antibody crosslinking.

Example 3 – Methods of Expanding TILs from *Ex-vivo* Cultured Solid Tumor Fragments (Multiple Histologies) Using Utomilumab or Urelumab and 11D4/18D8 and Effect of Activation with Antibodies to 4-1BB and/or OX40 on Expansion and Function of TILs

[001246] TILs are primarily antigen experienced (non-naïve) T cells found to varying degrees in all adult tumors associated with immunosuppressive microenvironments in which the local accumulation of damage associated molecular pattern molecules (DAMPs) as well as induced checkpoint receptors including CTLA-4 and PD-1 have often been engaged. Chacon, *et al.*, *Clin. Cancer Res.* **2015**, *21,* 611-21; Joseph, *et al.*, *Clin. Cancer Res.* **2011,** *17,* 4882-91. These markers, as well as TIM3, LAG3, and TIGIT, define an exhausted phenotype. As such, TIL-expressed co-stimulatory receptors modify TIL fate and expansion. Activation of 4-1BB and or OX40 on TILs enables expansion of TILs from tumor fragments beyond that achievable with IL-2 alone. Activation of other co-stimulatory receptors and/or antagonism of checkpoint receptors will further enhance TIL function (survival, circumvention of tumor immunosuppression), emigration from tumor fragments, and promote *in-vitro* expansion. Furthermore, these studies *in vitro* may predict responsiveness to *in vivo* application of these antibodies alone or in combination with adoptive transfer of TILs. Immunomodulatory mAbs specific for these two activating co-stimulator molecules (*e.g.*, OX40, 11D4 or 18D8, and 4-1BB, utomilumab or urelumab) can be tested for such capacity. It is hypothesized that activation of the costimulator receptors, 4-1BB and OX40, within tumor fragments enhances TIL emigration from fragments of tumor, proliferation, promotion of a memory phenotype and cytotoxicity of emergent T cells. The main goal of this study is to determine whether mAbs specific for (a) 4-1BB and OX40 in combination or (b) anti-4-1BB and (c) anti-OX40 alone augments the outgrowth of cytotoxic and memory phenotype of TIL from tumor fragments.

[001247] 15 mg of each purified mAb specific for (a) OX40 and (b) 4-1BB is used. Tumors of various histologies may be obtained from commercial sources. In total, 20 independent patient tumors will be obtained. Tumors will be shipped in sterile HBSS or another appropriate medium. The tumors will be handled only in a laminar flow hood to maintain sterile conditions. When possible (if tumor > 0.5 cm in diameter), a portion of the tumor will be processed for FFPE and/or cryopreserved for downstream IHC and/or DNA/RNA isolation. Biomarker analysis via IHC will include CD3, CD11c, and PD1 and PD-L1. Whenever possible, autologous blood samples (up to 20 mL) will be acquired and PBMCs will be cryopreserved. If whole exome sequencing is performed on the tumors, exome sequences from banked autologous PBMCs will be defined as normal (*i.e.*, no mutations). Alternatively, tumor single cell suspensions may be utilized. The tumors will be washed after receipt and divided into 2-3 mm fragments and placed into cell culture into 24-well plates (1 fragment per well) or 6-well plates (4 fragments per well) with culture medium supplemented with 6,000 IU/mL IL-2 (recombinant) only, OX40 agonist, anti-4-1BB agonist, and a combination of OX40 and 4-1BB agonists in triplicates. In some experiments where sufficient tumor is available, titrations of IL-2 (6,000; 600; 60; and 0 IU of IL-2) will be tested. An excipient control for the IL-2 will be used. The final concentration of each mAb will be 30 μg/mL. Following 24-48 hours of culture, 250 μL of supernatant will be collected from each condition and stored at -20 °C for subsequent analysis of cytokine and chemokine concentrations (pg/10^6 cell/24 hours). TILs will be collected from each condition on day 11, day 21 and/or day of the 'pre-REP' (at least 500,000 cells per sample). Two aliquots of TILs will be pelleted and resuspended in <10 μL of PBS and will be frozen in -80 C. If less than <10^6 cells are collected, only gene expression arrays will be performed. Cultures will be fed on day 7 by partial removal of "spent" medium and addition of an equal volume of culture medium plus 6000 IU/mL IL-2. The spent medium will be stored at -20 °C for subsequent cytokine/chemokine analysis using a multiplex assay (e.g., Luminex 100 system). Additional mAb will be added to the culture on day 7 if sufficient tumor fragments are available for initiation of more than 1 replicate of experimental conditions. TIL cultures will be maintained for an additional 14 days. On day 21, the total cell yield, viability, cell surface and intracellular immunophenotype will be determined using flow cytometry. The following markers will be included: CD45RA, CCR7, CD3, TCR-alpha/beta, CD4, CD8, CXCR3, CD56, CD27, CD28, PD-1, PD-L1, BTLA, KLRG1, CD137, CD134, CD33, CD57, CD25, CD127, TIM-3, LAG-3,

TIGIT, RAGE, and Ki67. Other biomarkers including CD107a, NKG2D, KIRS, chemokine death receptors (Fas, DR4) and anti-apoptotic/pro-autophagic proteins (BCL-2, BCL-XL, Bim, CD200, and LC3/HMGB1) will also be assessed if sufficient cells are available. Intracellular markers of cytotoxicity and regulatory T cells, Granzyme B, pSTAT3, pSTAT1, and FOXP3, respectively will be assessed. Lytic potency of TILs will be determined using a lysis assay. In cases where additional tumor material is available and (a) a tumor cell suspension generated following enzymatic digestion, (b) an autologous tumor line generated from aforementioned tumor and/or (c) homologous cell line (if available) will be co-cultured with harvested TIL and IFN-γ release measured. If excess cells are obtained, these will be cryopreserved for isolating RNA and DNA for gene expression analysis (including TCR Vβ clonotyping analysis) which can be performed at a later time using an extended budget. If efficacy (defined below) is observed with anti PDL-1 and anti-CTLA-4 or the combination thereof, the possibility of lowering the concentration of indicated mAb(s) in tumor fragment cultures or performing a more detailed dose response assessment will be explored. If tumor fragments are visible in culture on day 7, they will be harvested and if sufficient cells are available after generation of a single cell suspension, they will be subjected to genetic analysis and flow cytometric phenotypic analysis (in that priority; to be negotiated). Flow cytometric analysis will focus on the phenotype of T cells, dendritic cells, macrophages, B cells, and NK cells after staining using appropriate fluorescent mAb panels. The markers will include: CD11c, CD11b, HLA class II, CD80, CD86, CD83, CD56, CD16, CD19, and CD20.

[001248] The criteria used to assess the efficacy of the addition of 4-1BB agonist, OX40 agonist, and the combination thereof to the tumor fragment cultures are summarized as follows:

- Increased number of TIL following expansion (CD4 and/or CD8)
- Decreased number of Treg following expansion
- Changes in T-cell proliferation markers (Ki67) in effector and Tregs
- Changes in effector/memory/differentiated phenotype, CD27, CD28, CD57, CD45RA, HLA-DR, CCR7, OX40, ICOS, CD45RA; telomerase length))
- Increased NK cell ($CD3^-/CD56^+$) numbers, proliferation and activation status

- Exploratory changes in intracellular signaling protein or phosphoprotein levels (eg, AKT vs ERK) in T cells
- Increased CTL activity/lytic capacity as measured by redirected lysis
- Increased IFN-γ/HMGB1 production in TIL/tumor lysate, TIL/autologous tumor and/or TIL/homologous tumor co-cultures.

[001249] Additional experiments to be performed include (1) whole exome sequencing and RNASeq on FFPE or fresh-frozen tumor material to identify mutated genes and possible neo-epitopes, (2) cytokine and chemokine analysis of culture supernatants collected 24-48 hours following initiation of tumor fragment cultures, (3) gene expression analysis of tumor fragments removed from early culture on day 7, (4) TCR clonotype analysis of the TIL isolated using high-throughput TCR Vβ CDR3 region sequencing, (5) impact of mAbs on banked TILs for TIL effector function in the presence of IFN-γ induced upregulation of PD-L1 on autologous/homologous tumors (outlined below) and analysis of remaining fragments for residual T-cells by PCR/IHC/digest.

[001250] Differences in assay parameters will be tested for significance using paired and un-paired T-tests (Wilcoxon rank-sum and signed rank tests). Comparison of multiple parameters will use one-way and two-way ANOVA analyses. Spearman regression analysis will be used when applicable to assess correlations between continuous measurements. All data can be tabulated and analyzed.

Example 4 – Expansion of TILs Using Hexameric Ligands to 4-1BB, OX40, and Other TNFRSF Members

[001251] The effect of activation with hexameric fusion proteins of structures I-A with binding domains to 4-1BB, OX40, CD27, and other TNFRSF members, on expansion and function of tumor infiltrating lymphocytes (TIL) from *ex-vivo* cultured solid tumor fragments (multiple histologies) is studied in this example. 100 mg of each hexameric fusion protein (*e.g.*, 4-1BB, OX40, and CD27) would be used with tumors obtained from the following indications: sarcoma, colorectal cancer, acute myeloid leukemia, ovarian cancer, triple negative breast cancer, pancreatic (Ras expressing), renal cancer, and bladder cancer. Tumors of various histologies will be obtained from commercial sources. Approximately 20 independent patient tumors will be obtained (2-3 tumors per indication as listed above). Tumors will be shipped to Lion in sterile

HBSS or another appropriate medium. The tumors will be handled only in a laminar flow hood to maintain sterile conditions. Alternatively, tumor single cell suspensions may be utilized. The tumors will be washed after receipt and divided into 2-3 mm (length × width × height) fragments and placed into cell culture into 24-well plates (1 fragment per well) or 6-well plates (4 fragments per well) with culture medium supplemented with 6,000 IU/mL IL2 (recombinant) only, combination of 4-1BB HERA alone in triplicates will serve as control and three experimental conditions utilized respectively. An excipient control for the IL-2 will be used. The final concentration of HERA will be 30 μg/mL. Following 24-48 hours of culture, 250 μL of supernatant will be collected from each condition and stored at -20 °C for subsequent analysis of cytokine and chemokine concentrations (pg/10^6 cell/24 hr). TILs will be collected from each condition on day 11, day 21 and/or day of the 'pre-REP' (at least 500,000 cells per sample). Two aliquots of TILs will be pelleted and resuspended in <10 μL of PBS and will be frozen. If less than <10^6 cells are collected, only gene expression arrays will be performed. Cultures will be fed on day 7 by partial removal of "spent" medium and addition of an equal volume of culture medium plus 6000 IU/mL IL-2. The spent medium will be stored at -20^0 C for subsequent cytokine/chemokine analysis using a multiplex assay (e.g., Luminex 100 system). Additional ligand will be added to the culture on day 7 if sufficient tumor fragments are available for initiation of more than 1 replicate of experimental conditions. TIL cultures will be maintained for an additional 14 days.

[001252] On day 21, the total cell yield, viability, cell surface and intracellular immunophenotype will be determined using flow cytometry. The following markers will be included: CD45RA, CCR7, CD3, TCR-alpha/beta, CD4, CD8, CXCR3, CD56, CD27, CD28, PD-1, PD-L1, BTLA, KLRG1, CD137, CD134, CD33, CD57, CD25, CD127, TIM-3, LAG-3, TIGIT, RAGE, and Ki67. Other biomarkers including CD107a, NKG2D, KIRS, chemokine death receptors (Fas, DR4) and anti-apoptotic/pro-autophagic proteins (BCL-2, BCL-XL, Bim, CD200, and LC3/HMGB1) will also be assessed if sufficient cells are available. Intracellular markers of cytotoxicity and regulatory T cells, Granzyme B, pSTAT3, pSTAT1, and FOXP3, respectively will be assessed. Lytic potency of TILs will be determined using a lysis assay. In cases where additional tumor material is available and (a) a tumor cell suspension generated following enzymatic digestion, (b) an autologous tumor line generated from aforementioned tumor and/or (c) homologous cell line (if available) will be co-cultured with harvested TIL and

IFN-γ release measured. If excess cells are obtained, these will be cryopreserved for isolating RNA and DNA for gene expression analysis by Nanostring Human Immunology Panel (including TCR Vβ clonotyping analysis). If tumor fragments are visible in culture on day 7, they will be harvested and if sufficient cells are available after generation of a single cell suspension, they will be subjected to genetic analysis and flow cytometric phenotypic analysis. Flow cytometric analysis will focus on the phenotype of T cells, dendritic cells, macrophages, B cells, and NK cells after staining using appropriate fluorescent mAb panels. The markers will include: CD11c, CD11b, HLA class II, CD80, CD86, CD83, CD56, CD16, CD19, and CD20.

[001253] The criteria used to assess the efficacy of the addition of hexameric fusion proteins to the tumor fragment cultures are summarized above in Example 3, and further optional criteria are described in Table 53.

TABLE 53. Additional criteria for experimental performance for TNFRSF agonist fusion proteins in TIL expansion processes.

Threshold of success	**Cell Count**	**Viability**	**Potency by IFNγ**	**Phenotyping**	**↓Tregs following expansion**	**Increases in T-cell Central Memory (CCR7+, CD45RA-)**
Good	>1e6	>75%	>500pg/10^6 cells/24 hr	>40% CD8s	<10%	>1%
Very Good	>3e6	>80%	>1000/10^6 cells/24 hr	>50% CD8s	<3%	>3%
Excellent	>10e6	>85%	>2000/10^6 cells/24 hr	>75% CD8s	<1%	>10%
Outstanding	>30e6	>90%	>4000/10^6 cells/24 hr	>90% CD8s	Not detected	>30%

[001254] Additional experiments include: (1) whole exome sequencing and RNASeq on FFPE or fresh-frozen tumor material to identify mutated genes and possible neo-epitopes, (2) cytokine and chemokine analysis of culture supernatants collected 24-48 hours following initiation of tumor fragment cultures, (3) gene expression analysis of tumor fragments removed from early culture on day 7, (4) TCR clonotype analysis of the TIL isolated using high-throughput TCR Vβ CDR3 region sequencing, (5) impact of hexameric fusion proteins on Lion banked TILs for TIL effector function in the presence of IFN-γ induced upregulation of PD-L1 on autologous/homologous tumors and analysis of remaining fragments for residual T-cells by PCR/IHC/digest.

[001255] Differences in assay parameters will be tested for significance using paired and un-paired T-tests (Wilcoxon rank-sum and signed rank tests). Comparison of multiple parameters will use one-way and two-way ANOVA analyses. Spearman regression analysis will be used when applicable to assess correlations between continuous measurements.

Example 5 – Evaluation of the Impact of 4-1BB and anti-OX40 Agonistic Antibodies on TIL Expansion and Effector function

[001256] The objective of this work is to evaluate the impact of 4-1BB (urelumab) and anti-OX40 agonistic antibodies on TIL expansion and effector function and to obtain information on ICOS and GITR expression during expansion.

[001257] *In vitro* assessment of anti-4-1BB and anti-OX40 agonistic antibodies on TIL expansion and phenotype is performed as follows. Antibody titration is conducted with tumor fragments and aspirates to determine suitable concentration for use with TIL expansion. The impact of anti-4-1BB and anti-OX40 agonists on TIL expansion in both pre-REP and REP (in these specific conditions) is evaluated for (1) IL-2 + anti-4-1BB alone, (2) IL-2 anti-OX40 alone, (3) IL-2+ anti-41BB + anti-OX40, and (4) IL-2 alone (control). TIL expansion and phenotype will be assessed by (1) expansion of $CD3^+$ subset, $CD3^+CD8^+$ subset, and $CD3^+CD4^+$ in both percentage and absolute cell counts and viability, and (2) assessment of differentiation and activation status by flow cytometry using 18 color flow; including staining for ICOS and GITR, Ki67, and apoptosis markers.

[001258] *In vitro* assessment of TCR repertoire and expression profiling of TIL expanded with anti-4-1BB and anti-OX40 agonistic antibodies is performed as follows. TCR repertoire in TILs expanded with IL-2 alone in comparison with treatment conditions is shown by staining with specific anti-TRBV antibodies and using commercially-available TCR repertoire assays from iRepertoire, Inc. Expression profiling on individual TILs is performed using nCounter Vantage™ RNA Adaptive Immunity Panel with Nanostring analysis

[001259] *In vitro* assessment of tumor reactivity and effector function is performed as follows. An autologous tumor cell suspension or tumor cell line is generated (as possible). Tumor reactivity in tumor lysis assay is assessed by co-culturing autologous tumor cells/sorted autologous tumor cell suspension with autologous TIL expanded with IL-2 alone in comparison with treatment conditions described above. In case autologous tumor cell suspensions/tumor cell

lines are not available, T cell activation assay by anti-CD3/CD28/CD137 will be conducted to assess effector functions by measuring IFN-gamma production/CD107a expression instead.

Example 6 – Further Evaluation of 4-1BB and OX40 Antibodies on the *Ex Vivo* Expansion of TIL and their Effector Function Activity

[001260] OX40 and 4-1BB have been found to be expressed by antigen specific $CD4^+$ and $CD8^+$ subset, respectively. Activation of co-stimulatory molecules (4-1BB and OX40) on T-cells enhance effector function, cell survival, and cell expansion. Activation of OX40 and 4-1BB receptors was shown to improve TIL expansion and anti-tumor function in murine models. Anti-4-1BB agonistic antibody was shown to increase the yield of melanoma TIL obtained from *in vitro* expansion. According to the following protocol, the effect of agonistic antibodies against 4-1BB and OX40, alone and in combination, on the *ex vivo* expansion of TIL and their effector function activity may be studied.

[001261] FIG. 13 describes the TIL expansion protocol used in this study. As illustrated in FIG. 15, tumor tissue was retrieved from the patient, fragmented and subjected to a pre-REP process in the presence of IL-2, as described herein. The tissues were then subjected to a REP process in the presence of IL-2 and anti-CD3 anti-bodies with irradiated PBMCs (FIG. 13).

[001262] The following experimental conditions were implemented in this study:

	No treatment	**Anti-4-1BB**	**Anti-OX40**	**Combination**	**Isotype**
pre-REP		10 μg/ml	0.5 -10 μg/ml	0.5 -10 μg/ml	10 μg/ml
REP		10 μg/ml	0.5 -10 μg/ml	0.5 -10 μg/ml	10 μg/ml

Phase	**Agent**	**Pre-REP**	**REP**
I	**anti-4-1BB**	3 tumors	N/A
	anti-OX40	3-5 tumors	

II	**combo**	3-5 tumors

[001263] T-Cell activation, proliferation, and exhaustion may be monitored by flow-cytommetry according to the following list, where Panel 1 illustrates immune cell lineage, T-cell subsets, and T-cell differentiation, and Panel 2 illustrates T-cell activation and exhaustion:

Panel 1	**Panel 2**
CD3	CD3
L/D Blue	L/D Blue
CD19	CD25
CD56	CD95
CD62L	PD-1
CD57	2B4/CD244
CD11b	CD4
CD123	TIM-3
CD14	CD183
CD8	CD103
CD28	CD8
CD45	TIGIT
CD4	CD127
CCR7	CD272
CD27	KLRG1
TCRg/d	CD194
CD45RA	CD69
CD16	LAG-3

[001264] Without being limited to any one theory of the invention, it is expected that the combination of anti-4-1BB and anti-OX40 agonists, alone or in combination with process 2A, may improve the expansion of pre-REP TILs, particulary in the $CD3^{+}CD8^{+}$ TIL subset; improve the success rate of certain tumors; shorten duration pre-REP TIL expansion; and/or enhance multi-functionalities of TIL including effector function and cell survival following antigen re-stimulation.

Example 7 – Clinical Study to Assess Efficacy and Safety of Autologous TIL

[001265] This Example describes a Phase 1/2 clinical study for evaluating the efficacy of autologous TIL across multiple tumor types. The objectives of this investigation are to evaluate efficacy using objective response rate (ORR) according to RECIST v1.1 in subjects with ovarian cancer and osteosarcoma. The primary objective for a pancreatic ductal adenocarcinoma (PDAC) cohort is to evaluate efficacy as measured by the 6-month survival rate.

[001266] Secondary objectives may include: (1) evaluating ORR using RECIST v.1.1 in PDAC; (2) determining the disease control rate (DCR) within and across cohorts; (3) determining the duration of response (DOR); (4) determining progression-free survival (PFS) and overall survival (OS); and (5) further characterizing the safety profile of adoptive cell therapy with TIL across multiple tumor types.

Definitions/Abbreviations

ACT	Adoptive Cell Therapy
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ASMR	Age-standardized Mortality Rate
aPTT	Activated Partial Thromboplastin Time
BID	Twice Per Day
BSA	Body Surface Area
CBC	Complete Blood Count
CD4+T	CD4+ T Cells
CD8+T	CD8+ T Cells
CFR	Code of Federal Regulations
CI	Confidence Interval
CLS	Capillary Leak Syndrome
CMO	Contract Manufacturing Organization
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
D5W	Dextrose 5% by weight
DCR	Disease control rate
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECHO	Echocardiogram
EKG	Electrocardiogram
EOC	Epithelial Ovarian Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 instrument
EWV	Early Withdrawal Visit
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume

FVC	Forced Vital Capacity
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality-of-life
ICH	International Conference on Harmonization
IL	Interleukin
IND	Investigational New Drug (Application)
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous
IVPB	Intravenous Piggyback
LVEF	Left Ventricular Ejection Fraction
M1	HLA-DR+CD68+ M1 Macrophages
M2	CD163+ or CD204+ M2 Macrophages
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
Neu	CD66b+ Neutrophils
NMA	Nonmyeloablative
NS	Normal Saline
OC	Ovarian Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PDAC	Pancreatic Ductal Adenocarcinoma
PE	Physical Exam
PET	Positron Emission Tomography
PFS	Progression-free survival
PHI	Personal Health Information
PI	Principal Investigator
PJP	Pneumonitis Jiroveci Pneumonia
PO	Per Os (by mouth)
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QTc	Corrected QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Rapid Expansion Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SMX	Sulfamethoxazole
STS	Soft Tissue Sarcoma
TCR	T-cell Receptor
TIL	Tumor-infiltrating lymphocyte
TMA	Tissue Microarray
TMP	Trimethoprim
Treg	FOXP3+ Regulatory T Cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

[001267] Study Design and Endpoints: This study is aimed at evaluating the efficacy of TIL in subjects with: a) osteosarcomas relapsed or refractory to conventional therapy, b) platinum-resistant ovarian cancer, and c) PDAC who have progressed on, or received maximal benefit from, front-line therapy. Each cohort begins with ten subjects in the first stage, and expansion to the second stage is guided by a modified Simon's two stage design.

[001268] The primary endpoint is ORR by RECIST v1.1 for ovarian cancer and osteosarcoma, and the 6-month survival rate in PDAC. The primary endpoint for the PDAC cohort is the 6-month survival rate.

[001269] The secondary efficacy endpoints include ORR (for PDAC) CRR, DCR, DOR, PFS using RECIST v1.1, and OS. DCR includes complete response (CR), partial response (PR), and stable disease (SD). Safety endpoints may include overall assessment of AEs including grade 3 or greater non-hematological toxicities, SAEs and treatment-emergent AEs by grade and relationship to the study treatment. The secondary endpoint for the PDAC cohort is ORR using RECIST v1.1.

[001270] Exploratory endpoints may include: (1) duration of TIL persistence as determined by T cell receptor (TCR) sequencing of infused T cells serially isolated following TIL infusion, or alternatively iRepertoire assessment of mRNA for the TCRs; (2) response as determined by the immune-related response criteria; (3) immunological Phenotype of TIL at the time of infusion by multichannel flow cytometry; (4) baseline and post-treatment tumor assessment via IHC, TCR sequencing, and transcriptional analysis; and (5) HRQOL as assessed per EORTC QLQ-C30 questionnaire.

[001271] Participant Inclusion Criteria. Subjects may be between 18 and 70 (subjects aged 16 - 70 may be enrolled into the osteosarcoma cohort). Subjects should be willing and able to provide informed consent. For patients < 18 years of age, their parents or legal guardians should sign a written informed consent. Assent, when appropriate, may be obtained according to institutional guidelines. Clinical performance status of ECOG 0 or 1 at enrollment and within 7 days of initiating lymphodepleting chemotherapy. Subjects should have an area of tumor amenable to excisional biopsy for the generation of TIL separate from, and in addition to, a target lesion to be used for response assessment. Any prior therapy directed at the malignant

tumor, including radiation therapy, chemotherapy, and biologic/targeted agents should be discontinued at least 28 days prior to tumor resection for preparing TIL therapy.

[001272] Within 7-14 (e.g., 7 days) days of enrollment and within 12 h to 48 h (e.g., 24 h) of starting lymphodepleting chemotherapy subjects may meet one or more of the following laboratory criteria: (1) absolute neutrophil count (ANC) > 1000/mm^3; (2) hemoglobin > 8.0 g/dL (transfusion allowed); (3) platelet count > 100,000/mm^3; (4) ALT/SGPT and AST/SGOT < 2.5 x the upper limit of normal (ULN) (Patients with liver metastases may have LFT ≤ 5.0 x ULN); (5) calculated creatinine clearance (Cockcroft-Gault) ≥ 40.0 mL/min; (6) total bilirubin ≤ 1.5 X ULN; (7) prothrombin Time (PT) & Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN (correction with vitamin K allowed) unless subject is receiving anticoagulant therapy (which should be managed according to institutional norms prior to and after excisional biopsy); and (8) negative serum pregnancy test (female subjects of childbearing potential).

[001273] Furthermore, subjects should not have a confirmed human immunodeficiency virus (HIV) infection. Subjects should have a 12-lead electrocardiogram (EKG) showing no active ischemia and corrected QT interval (QTc) less than 480 ms. Subjects 40 years of age and older should also have a negative stress cardiac test (i.e. EKG stress test, stress thallium, dobutamine echocardiogram or other stress test that may rule out cardiac ischemia). Stress test may be required of subjects less than 40 years of age if warranted by family history or risk factors by the treating investigator. Subjects of childbearing potential should be willing to practice an approved highly effective method of birth control starting at the time of informed consent and for 1 year after the completion of the lymphodepletion regimen. Subjects should be able to adhere to the study visit schedule and other protocol requirements. Finally, pulmonary function tests (spirometry) demonstrating forced expiratory value (FEV) 1 greater than 65% predicted or forced vital capacity (FVC) greater than 65% of predicted.

[001274] In addition to meeting the above general inclusion criteria, subjects should also meet cohort specific criteria.

[001275] For ovarian cancer, subjects may have high grade non-mucinous histology (carcinosarcomas are allowed). Moreover, subjects may have failed at least two prior lines of chemotherapy (i.e. frontline adjuvant chemotherapy plus one additional line for recurrent/progressive disease).

[001276] For osteosarcoma, subjects may have relapsed or become refractory to conventional therapy and have received a regimen including some combination of high-dose methotrexate, doxorubicin, cisplatin, and/or ifosfamide.

[001277] For pancreatic adenocarcincoma, subjects may have histologically or cytologically documented diagnosis of PDAC with oligo-metastatic disease. Subjects may have progressed on, or received maximal benefit from, front-line therapy. Patients may have received unlimited lines of prior standard of care therapy. Patients with ascites or carcinomatosis are not eligible for the study. Patients may need an albumin of $\geq$ 3.0 mg/dL within 7 days of enrollment.

[001278] **Participant Exclusion Criteria.** A number of criteria may result in exclusion of a participant from the study:

a. Active systemic infections requiring intravenous antibiotics, coagulation disorders or other major medical illnesses of the cardiovascular, respiratory or immune system. PI or his/her designee shall make the final determination regarding appropriateness of enrollment.
b. Patients with active viral hepatitis.
c. Patients who have a left ventricular ejection fraction (LVEF) < 45% at Screening.
d. Patients with a history of prior adoptive cell therapies.
e. Persistent prior therapy-related toxicities greater than Grade 2 according to Common Toxicity Criteria for Adverse Events (CTCAE) v4.03, except for peripheral neuropathy, alopecia, or vitiligo prior to enrollment.
f. Primary immunodeficiency.
g. History of organ or hematopoietic stem cell transplant.
h. Chronic steroid therapy, however prednisone or its equivalent is allowed at < 10 mg/day.
i. Patients who are pregnant or nursing.
j. Presence of a significant psychiatric disease, which in the opinion of the principal investigator or his/her designee, would prevent adequate informed consent.
k. History of clinically significant autoimmune disease including active, known, or suspected autoimmune disease. Subjects with resolved side effects from prior checkpoint inhibitor therapy, vitiligo, psoriasis, type 1 diabetes or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome may not be excluded.

l. History of clinically significant chronic obstructive pulmonary disease (COPD), asthma, or other chronic lung disease.

m. History of a second malignancy (diagnosed in the last 5 years). Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

n. History of known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to initiation of lymphodepletion.

o. Has received a live vaccine within 30 days prior to the initiation of lymphodepletion.

p. Any other condition that in the investigator's judgement would significantly increase the risks of participation.

[001279] Completion or Discontinuation of Treatment. Completion of treatment may be defined as having received any volume of TIL infusion followed by at least 1 dose of adjuvant IL-2.

[001280] This study includes a one-time treatment regimen consisting of lymphodepleting chemotherapy, TIL infusion, and adjuvant IL-2 (up to 6 doses). Discontinuation from study treatment should be considered if any of the following criteria are met. However, unless the patient also meets criteria for discontinuation from study participation, every effort may be made to continue follow-up and assessment of all patients, including those that do not complete the full course of therapy, as specified in the Schedule of Events.

[001281] Criteria for early discontinuation from treatment are:

a. Grade 3 or greater autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following TIL infusion;

b. Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator;

c. Grade 3 or greater toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management;

d. Determination by the Investigator that continued treatment is not in the best interest of the patient;

e. Withdrawal by patient. The patient (or parents/legal guardian for patients < 18 years of age) may withdraw consent to treatment but continue consent for follow-up evaluations and/or survival status;

f. Pregnancy;

g. Patient meets criteria for early discontinuation from study; and

h. Patient has become ineligible for study after tumor harvest and prior to TIL or IL-2 administration.

[001282] Criteria for early discontinuation from study are:

a. Withdrawal by patient. The patient (or parents/legal guardian for patients < 18 years of age) may withdraw consent. All efforts should be made to continue consent for survival status follow-up;

b. Patient has become ineligible for study after tumor harvest or did not receive any study treatment;

c. Have any complication or delayed healing from excisional procedure that in the investigator's opinion would increase the risks of lymphodepletion, adoptive TIL therapy and adjuvant IL-2;

d. Have a decline in performance status to ECOG > 1 (within seven days prior to starting lymphodepletion);

e. Death; and

f. Lost to follow-up after 3 documented attempts to contact the patient.

[001283] Some subjects may undergo tumor harvest and TIL manufacture but may not receive the infusion of investigational product. If TIL is not administered to the patient for whatever reason, even if after lymphodepleting chemotherapy, then the patient should remain on study, but data collection may be reduced to survival status and start of any new anticancer therapy for 3 years. Such subjects may be considered unevaluable for statistical analysis of efficacy and may be replaced.

[001284] If a patient initiates anti-cancer therapy or exhibits disease progression after TIL infusion they may remain in the study, but the data collection may be reduced to response status, survival status and other anti-cancer therapy for 3 years.

[001285] **Study Agents.** The lymphodepletion regimen is scheduled to start on Day -7, after notification that TIL production is expected to be successful for the patient. Patients may receive lymphodepleting chemotherapy as inpatient or outpatient at the discretion of the investigator. Modification of the lymphodepletion regimen is allowed as clinically indicated and should be guided by daily hematological parameters as described below for fludarabine in heavily pre-

treated patients or subjects with a history of prolonged myeloid recovery. The regimen comprises 2 daily doses of cyclophosphamide (with mesna) followed by 5 daily doses of fludarabine and should be administered as per institutional protocol/standards for nonmyeloablative chemotherapy. Guidelines for preparation and administration are described below. Subjects should be dosed using actual body weight but not to exceed 140% of Ideal Body Weight as defined below:

a. **Ideal Body Weight for Males** = 50 kg + 2.3 x (number of inches over 60 inches in height).
Example: ideal body weight of a 5'10'' male subject
50 + 2.3 x 10 = 73 kg

b. **Ideal Body Weight for Females** = 45.5 kg + 2.3 (number of inches over 60 inches in height).
Example: ideal body weight of a 5'3'' female subject
45.5 + 2.3 x 3 = 52.4 kg

[001286] Drugs required for lymphodepletion include cyclophosphamide, fludarabine, and/or mesna.

[001287] Variations from the lymphodepletion (e.g. infusion times; schedule of treatments, etc.) prior to day 0 may be documented in the medical record but may not be considered protocol violations/deviations.

[001288] Cyclophosphamide may be administered at 20 to 80 mg/kg/day (e.g., 60 mg/kg/day) IV in 250 mL normal saline (NS) over approximately 2 hours on Days -7 and -6. Mesna 60 mg/kg with dextrose 5% by weight (D5W) or NS infused intravenously over 24 h on Days -7 and -6. As noted above the dose may be based on the patient's actual body weight, but to prevent undue toxicity, it may not exceed the dose based on 140% of the maximum ideal body weight (defined above). There may be dose adjustments for cyclophosphamide.

[001289] Fludarabine will then be infused at 15 to 50 mg/m^2 (e.g., 25 mg/m^2) IV piggyback (PB) daily over approximately 15-30 minutes on Days -5 to -1. To prevent undue toxicity with fludarabine, the dose may be based on body surface area (BSA), but may not exceed a dose calculated on surface areas based on body weights greater than 140% of the maximum ideal body weight. Hematological parameters (complete blood count [CBC] and differential) are to be reviewed daily during lymphodepletion. If after 3 or 4 doses of fludarabine, the absolute lymphocyte count falls below 100 cells/mm^3 the remaining dose(s) of fludarabine may be

omitted following discussion with the PI. Fludarabine dose may be adjusted according to estimated creatinine clearance (CrCl) as follows: (1) CrCl 50-79 mL/min: Reduce dose to 20 mg/m^2; and/or (2) CrCl 40-49 mL/min: Reduce dose to 15 mg/m^2.

[001290] The TIL product that may be used in this protocol is a cellular investigational product comprising a live cell suspension of autologous TIL derived from the patient's own tumor. Each dose may contain up to 150 x 10^9 total viable lymphocytes. The total volume to be infused may be up to 600 mL dependent on total cell dose.

[001291] If not already hospitalized for the lymphodepleting chemotherapy, the patient may be admitted 1-2 days prior to planned TIL administration and prepared with overnight intravenous hydration prior to the TIL administration. Patients may remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

[001292] The IL-2 infusion may begin 3-24 h after completion of the TIL infusion. IL-2 may be administered at a dose of 200,000 to 1,000,000 IU/kg (e.g., 600,000 IU/kg) (based on total body weight) and may be administered by IV infusion at a frequency of every 8-12 hours as per institutional standard of care and continued for up to a maximum of six doses or as tolerated. IL-2 doses may be skipped if patient experiences a Grade 3 or 4 toxicity due to IL-2 except for reversible Grade 3 toxicities common to IL-2 such as diarrhea, nausea, vomiting, hypotension, skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes. Management of IL-2 is detailed in Table 54. If these toxicities can be easily reversed within 24 hours by supportive measures, then additional doses may be given. If greater than 2 doses of IL-2 are skipped, IL-2 administration may be stopped. In addition, discretion may be used to hold or stop the dosing.

TABLE 54. Management of Potential Aldesleukin Toxicities.

Expected toxicity	Expected grade	Supportive Measures	Stop Treatment*
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethicin 50-75 mg, po, q8h	No
Pruritis	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL25-50 mg, po, q4h, prn	No

Nausea/ Vomiting/ Anorexia	3	Ondansetron 10 mg, IV, q8h, prn; Granisetron 0.01 mg/kg IV daily prn; Droperidol 1 mg, IV q4-6h, prn; Prochlorperazine 25 mg q4h p.r., prn or 10 mg IV q6h prn	No
Diarrhea	3	Loperamide 2 mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 mcg, po, q3h, prn; codeine sulfate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures
Neutropenia	4	Observation	No
Edema/Weight gain	3	Diuretics prn	No
Hypotension	3	Fluid resuscitation; Vasopressor support	If uncontrolled despite all supportive measures
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures
Increased creatinine	3 or 4	Observation	Yes (grade 4)
Renal failure	3 or 4	Dialysis	Yes
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures
Bowel perforation	3	Surgical intervention	Yes
Confusion	3	Observation	Yes
Somnolence	3 or 4	Intubation for airway protection	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures
Elevated Troponin levels	3 or 4	Observation	Yes
Myocardial Infarction	4	Supportive care	Yes
Elevated transaminases	3 or 4	Observation	For grade 4 without liver metastases
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures

*Unless the toxicity is not reversed within 12 hours.

[001293] Study Procedures and Schedule. The following procedures may be used in this study.

[001294] Potential subjects may be informed about the study by the investigator. The risks, benefits, and alternatives may be discussed and the Informed Consent Document may be signed before any study related assessments are performed.

[001295] Subjects should meet most, or preferably all, inclusion criteria and preferably do not have any of the conditions specified in the exclusion criteria. Confirmation of general, cohort, specific, and treatment inclusion/exclusion criteria should be documented within seven days of starting lymphodepletion chemotherapy.

[001296] The demographic data may include date of birth (as allowed per local regulations), age, gender, and race/ethnic origin.

[001297] Relevant and significant medical/surgical history and concurrent illnesses may be collected for all patients at Screening (Visit 1) and updated as applicable. Any worsening from pre-existing conditions should be reported as AEs. Patient's prior anti-cancer treatment may also be collected.

[001298] Documentation of cohort-specific diagnosis of cancer may be made and confirmed histologically.

[001299] All medications and therapies (prescription, and non-prescription, including herbal supplements) taken by the patient up to 28 days prior to Screening (Visit 1) may be collected in the database, including the stop dates for medications prohibited in the study, at the time of consent. All medications and therapies being taken by the patients, or changes thereof, at any time during the study, may be recorded in the medical record.

[001300] All baseline grade 2 and higher toxicities may be assessed as per CTCAE v4.03. Any events occurred after screening, but prior to enrollment/tumor resection, may be recorded as Medical History in the database, unless the events are related to protocol mandated procedures. Any events occurring after enrollment/tumor resection may be captured as AEs in the database until the 6 Month visit, subject is taken off the study, or starts other cancer therapy.

[001301] Vital signs shall include height, weight, pulse, respirations, blood pressure and temperature. Height may be measured at Screening (Visit 1) only. All other vital signs may be measured at applicable time points. On Day 0 (Visit 11/ TIL infusion), vital signs may be monitored for up to approximately 24 hours post TIL infusion.

[001302] An ECOG performance status may be assessed at Screening (Visit 1) and other time points indicated on the schedule of events.

[001303] Physical examination may be conducted for all visits except for Tumor Resection and shall include vital signs and weight, head and neck, cardiovascular, pulmonary, extremities, and other relevant evaluation. Exams during conducted during follow-up may be symptom directed. Clinically significant changes in the exam findings may be recorded as adverse events as indicated.

[001304] Safety blood and urine tests may be collected and analyzed locally at every visit as indicated in the Schedule of Events.

[001305] Sample collection for high resolution HLA Class I typing may be conducted at Screening (Visit 1).

[001306] Serology for the following diseases may be completed at Screening (Visit 1) to be analyzed locally per institutional standard: HIV, Hepatitis B Virus, Hepatitis C Virus, Cytomegalovirus (CMV), Herpes Simplex Virus; Epstein-Barr virus (EBV) (may be within previous 3 months to Tumor Resection/Visit 2), Chagas Disease, Human T cell Lymphotropic Virus, and West Nile Virus. Sickle Cell Disease may also be screened. Additional testing is to be done as clinically indicated.

[001307] The creatinine clearance may be calculated by site using the Cockcroft-Gault formula at Screening only.

[001308] All subjects can have a baseline 12-lead ECG and assessment of ventricular function by echocardiogram or MUGA. In addition, subjects age 40 or older and those younger than 40 with a history of cardiovascular disease or chest pain may have a stress test documenting absence of ischemia. Patients with an abnormal MUGA or echocardiogram may meet ejection fraction requirements and obtain cardiology clearance prior to enrollment.

[001309] Pulmonary evaluation may be completed within 28 days from Screening (Visit 1). Prior evaluations completed within 6 months prior to Screening (Visit 1) may be accepted. An FEV1 greater than 65% of predicted or FVC greater than 65% of predicted is required. Patients who are unable to conduct reliable PFT spirometry measurements due to abnormal upper airway anatomy (e.g. tracheostomy) may undergo a 6-minute walk test to be evaluate pulmonary

function. These patients should, and preferably can, walk a distance of at least 80% predicted for age and sex as well as maintain oxygen saturation greater than 90% throughout.

[001310] Colonoscopy is only required for patients who have had a documented Grade 2 or greater diarrhea or colitis due to previous immunotherapy within six months of Screening. Patients that have been asymptomatic for at least 6 months from Screening or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment, with uninflamed mucosa by visual assessment may not need to repeat the colonoscopy.

[001311] A health related quality of life (HRQOL) questionnaire may be conducted in person at baseline Day -21 (Visit 3) and be performed as the first procedure on the subsequent visits. See the Schedules of Events for specific timepoints. Failure to complete any questionnaires may not be considered a deviation requiring reporting.

[001312] Radiographic assessments by computed tomography (CT) scans with contrast of the chest, abdomen and pelvis are required for all patients for tumor assessments. CT scans are performed as indicated in the Schedule of Events until progressive disease by modified RECIST v1.1 is noted (or if the patient withdraws full consent). Response assessments should be evaluated and documented by a qualified radiologist participating in the trial. Magnetic Resonance Imaging (MRI) or positron emission tomography (PET) scans of the chest, abdomen and pelvis in lieu of CT scans may be allowed for patients who have an intolerability to contrast media. The same method of assessment (CT or MRI) and the same technique for acquisition of data should be used consistently throughout the study to characterize each identified and reported lesion. Initial radiographic assessments may be made at 6, 12, 18 and 24 weeks post TIL infusion. Thereafter, Patients may be evaluated for response approximately every 12 weeks. Additional radiological assessments may be performed as clinically indicated.

[001313] Prior to surgical biopsy, subject eligibility may be confirmed, and the PI or designee may provide approval for patient enrollment into the clinical trial and subsequent tumor resection. Subjects may undergo a pre-procedural consultation and a separate informed consent by the team performing the surgical biopsy per institutional standards. Ideally, the targeted tumor should have not been previously irradiated. If the tumor has been previously irradiated a minimum period of 1 to 6 months (e.g., 3 months) may have elapsed between irradiation and resection, during which time additional target-tumor growth may have been demonstrated. If

enrolled, tumor resection is expected to occur approximately 1 to 12 weeks (e.g., 6 weeks) prior to the anticipated TIL infusion (Day 0). TIL is an autologous investigational product which is procured and delivered by means that have more in common with autologous blood product delivery than those of traditional drug production. It is imperative that only the patient's own (autologous) study treatment (TIL) be administered to the same individual patient. For these reasons, the patient specimen can be procured and handled per a strict protocol to ensure optimal quality of the specimen and minimum transport time to and from the processing lab facility, as well as to ensure the appropriate identification of the study product at all times including infusion back into the patient.

[001314] In cases where additional or excess tumor tissue can be safely procured at the time of the initial excisional biopsy for TIL harvest, excess tumor tissue for research may be procured. Provision of adequate amount of tumor tissue for TIL manufacturing is priority over the collection of additional tumor tissue that is sent for research. Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis. In addition, a mandatory on-study biopsy may be used to ascertain molecular and immunological changes following treatment and as well as to document presence of infused T cells in the tumor. The tumor tissue analysis may include: 1) immunohistochemistry to identify individual immune cell populations; and/or 2) DNA and RNA analysis, including possible exploratory genomic and transcriptomic evaluation and TCR sequencing to evaluate infused TIL homing to tumor (in the post-treatment biopsy). Provision of adequate amount of tumor tissue for TIL manufacturing is priority over the collection of additional tumor tissue for research. Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis.

[001315] Up to 500 x 10^6 TIL from the infusion product (and genetic material extracted from these samples) may be stored for research. Flow cytometry analysis of the infused TIL may be performed, and DNA from the infusion product may be sent for TCR sequencing. The samples in these research studies may be used to gain further information about the disease and the characteristics of the TIL before and after infusion. Peripheral blood may be collected from the patients for immune monitoring and T cell tracking using TCR sequencing. Blood for Immune Monitoring may be drawn at Tumor Resection (Visit 2) and subsequent collections may be drawn at applicable time points (See Tables 55 and 56).

TABLE 55. Exemplary Schedule of Events – Pre-Treatment Treatment Phases.

	Pre-treatment Phase			**Treatment Phase**								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6, 7, 8, 9, 10**	**11**	**12, 13, 14, 15**	**16**	**17**	**18**	**19**
Visit Name	**Screening**	**Biopsy**	**Baseline (Day -14 to -21)**	**Day -7**	**Day -6**	**Days -5, -4, -3, -2, -1**	**Day 0 (TIL Infus.)**	**Days 1, 2, 3, 4**	**Day 14**	**Day 28**	**Day 42 (Wk 6)**	**Day 84 (Wk 12)**
Visit Window	≤28 days	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(± 7 days)	(± 7 days)	(± 7 days)	(± 7 days)
Written Informed Consent	X											
Medical History	X											
Documentation of diagnosis	X											
Physical Exam	X		X	X	X	X	X	X	X	X	X	X
Vital Signs[a]	X	X	X	X	X	X[b]	X	X	X	X	X	X
ECOG performance status	X	X	X	X			X			X	X	X
CBC, Chem Panel, and urine tests[c]	X	X	X	X	X	X	X	X	X	X	X	X
ß-HCG Serum Pregnancy Test	X		X	X								
Infection testing	X											
HLA typing	X											
Cardiac Evaluations	X											
Pulmonary function tests	X											
Colonoscopy	X											
Tumor Assessments (CT/MRI)	X		X								X	X
Response Assessments										X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X

Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsy		X									X	
NMA lymphodepletion[d]				X	X	X						
TIL Infusion[e]							X					
IL-2[f]								X				
Immune Monitoring		X		X					X	X	X	X
HRQOL Questionnaire			X									X
Prophylactic Medications												
PJP				X	X	X	X	X	X	X	X	X
Filgrastim								X				
Fungal Prophylaxis							X	X	X	X	X	X
Herpes Virus Prophylaxis							X	X	X	X	X	X

[a]Vital signs may include height, weight, heart rate, respiratory rate, blood pressure, and temperature. Height may be measured at Screening only. BSA and BMI may be Calculated at Day -7 (Visit 4) only.

[b]On Day 0 (TIL infusion), vital signs may be monitored every 30 minutes during infusion then hourly (+/-15 minutes) for four hours and then routinely (every four to six hours), unless otherwise clinically indicated, for up to approximately 24 hours post TIL infusion.

[c]Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid, and serum creatinine. Thyroid panel (to include TSH and Free T4) is to be done at Visits 1 and 19 and as clinically indicated. Coagulations: PT, PTT, and INR. Hematology: CBC with differential; Urinalysis: Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific gravity, Color and Appearance.

[d]Cyclophosphamide with mesna for 2 days at Day -7 and Day -6 (Visits 4 thru 5) followed by 5 days of fludarabine at Day -5 thru Day -1 (Visits 6 thru 10).

[e]TIL infusion is to be done 1 to 2 days after the last dose of agent in the NMA lymphodepletion regimen.

[f]Initiate IL-2 at 600,000 IU/kg within approximately 3 to 24 hours after TIL infusion and continue every 8-12 hours for up to six doses.

TABLE 56. Exemplary Schedule of Events: Post-Treatment and Long-Term Follow-Up.

	Post-treatment Follow-up							**Long-term Follow-up**
Visit Number	**20**	**21**	**22**	**23**	**24**	**25**	**EWV**	
Visit Name	**Day 126 (Month 4.5/ Week 18)**	**Day 168 (Month 6)**	**Day 252 (Month 9)**	**Day 336 (Month 12)**	**Day 504 (Month 18)**	**Day 672 (Month 24)**	**Early Withdrawal Visit**	**Quarterly Contact**
Visit Window	(± 14 days)	(± 14 days)	(± 14 days)	(± 14 days)	(± 21 days)	(± 21 days)		(± 21 days)
Physical Exam[a]	X	X	X	X	X	X	X	
Vital Signs[b]	X	X	X	X			X	
ECOG performance status	X	X	X	X	X	X	X	
CBC, Chem Panel, and urine tests[c]	X	X					X	
Tumor Assessments (CT/MRI)[d]	X	X	X	X	X	X	X	
Response Assessments	X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X			X	
Adverse events[e]	X	X					X	
Immune Monitoring[f]		X	X	X			X	
HRQOL Questionnaire		X		X		X		
Survival Follow-up								X
Prophylactic Medications								
PJP	X	X						
Herpes Virus Prophylaxis	X	X						

[a]PE may include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition. PE conducted during follow-up may be symptom directed.

[b]Vital signs may include weight, heart rate, respiratory rate, blood pressure, and temperature.

[c]Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid, and serum creatinine. Thyroid panel (to include TSH and Free T4) is to be done as clinically indicated. Coagulations: PT/PTT/INR. Hematology: CBC with differential; Urinalysis: Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific gravity, Color and Appearance.

[d]CT Scans of the chest, abdomen and pelvis, are required at the indicated time points. Additional radiological assessments may be performed per Investigator's discretion. MRI may be used if patients are intolerable to contrast media.

[e]Any AEs occurred after Screening, but prior to enrollment/tumor resection, may be recorded as Medical History in the database. Any AEs occurred after enrollment/tumor resection may be captured as AEs through Day 168 (Visit 21/Month 6) and as clinically indicated, or until the first dose of the subsequent

anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment may be collected through Day 672 (Visit 25/Month 24).

[f]Blood draw for Immune Monitoring is to be collected at visits between Day 168 (Visit 21/Month 6) through Day 336 (Visit 23/Month 12) and ETV.

[001316] Concomitant Medications, Treatments, and Procedures. Medications for medical problems other than antineoplastic agents are permitted. Those with conditions requiring anti-inflammatory drugs for chronic conditions potentially affecting TIL administration may be considered only with approval of the PI. Palliative radiation therapy is permitted between tumor resection and lymphodepletion as long as it does not affect target and non-target lesions. Use of systemic steroid therapy $\leq$ 10 mg/day of prednisone or equivalent is permitted. Use of > 10 mg/day of prednisone or equivalent is permitted in cases of exacerbation of known disease or for treatment of new symptoms on study per Investigator's discretion. Any changes in concomitant medications may be recorded only in the patient's medical record throughout the trial. For subject who have CT IV contrast allergy, radiologic evaluation using MRI or PET-CT (without intravenous contrast is the preferred management. Every attempt should be made to maintain consistency in imaging modality for each patient.

[001317] All other anti-neoplastic drugs and radiation are prohibited. Subjects are also discouraged from using over-the-counter supplements and homeopathic products, especially those with purported anti-inflammatory properties, such as boswelia.

[001318] Patients treated with lymphodepletion are subject to opportunistic infections and appropriate infectious agent prophylaxis is required. The prophylaxis regimens and duration listed below may be modified as clinically indicated in consultation with an Infectious Diseases specialist.

[001319] Patients may receive levofloxacin at 100 to 1000 mg (e.g., 500 mg) daily (or an equivalent antibiotic) until ANC recovers to greater than 500/mm^3.

[001320] Patients may receive the fixed combination of trimethoprim (TMP) and sulfamethoxazole (SMX) as double strength (DS) tablet [DS tabs = TMP 160 mg/tab and SMX 800 mg/tab] PO BID twice a week. TMP/SMX-DS may be taken by patients beginning on Day -7 and continuing for a minimum of 6 months after lymphodepletion. For patients with sulfa allergies, Pentamidine may be given (once discharged from the hospital) 300 mg IV every 21 days for 6 months after lymphodepletion. If IV Pentamidine is not feasible after discharge, PCP

prophylaxis can be substituted with oral antimicrobials such as Atovaquone as per standard of care for 6 months after lymphodepletion. Patients may be given prophylactic antibiotics intravenously during high dose IL-2 therapy.

[001321] Starting on the day of TIL infusion subjects may be administered valacylcovir 100 to 1000 mg (e.g., 500 mg) PO daily if patient is able to take oral medications or acyclovir 5 mg/kg IVPB every 8 hours if patient needs intravenous medications, which is continued for 6 months (or at the discretion of the treating physician). Reversible renal insufficiency has been reported with IV administered acyclovir but not with oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal electroencephalograms has been reported with higher doses of acyclovir. If symptoms occur, a dosage adjustment may be made or the drug be discontinued. Acyclovir may not be used concomitantly with other nucleoside analogs (e.g. ganciclovir), which interfere with DNA synthesis. In patients with renal disease, the dose is adjusted as per product labeling.

[001322] Patients may begin Fluconazole 50 to 500 mg (e.g., 200 mg) PO daily with the T cell infusion (Day 0) and continue for 6 months (or at the discretion of the treating physician).

[001323] To reduce the duration of neutropenia following NMA lymphodepletion chemotherapy, filgrastim (G-CSF) may be given at 1 to 10 μg/kg/day (e.g., 5 μg/kg/day) daily subcutaneously until ANC > 500/mm^3 for at least 2 consecutive days. Approximate dosing to correspond to the 300 mcg or 480 mcg dosage forms is allowed.

[001324] Ondansetron may be used to control nausea and vomiting during the chemotherapy preparative regimen. It can cause headache, dizziness, myalgias, drowsiness, malaise, and weakness. Less common side effects include chest pain, hypotension, pruritus, constipation and urinary retention. Consult the package insert for a complete list of side effects and specific dose instructions.

[001325] Furosemide may be used to enhance urine output during the chemotherapy preparative regimen with cyclophosphamide. Adverse effects include dizziness, vertigo, paresthesias, weakness, orthostatic hypotension, photosensitivity, rash and pruritus. Consult the package insert for a complete list of side effects and specific dose instructions.

[001326] Patients may start on broad-spectrum antibiotics, either a 3rd or 4th generation cephalosporin with adequate pseudomonas coverage as per local antibiogram or a quinolone for temperature $\geq$ 38.5°C with an ANC less than 500/mm^3. Aminoglycosides should be avoided if possible. Infectious disease consultation may be obtained from all patients with unexplained fever or any infectious complications.

[001327] Using daily CBC values as a guide, the patient may also receive platelets and packed red blood cells as needed. Attempts may be made to keep Hgb > 8.0 g/dL, and platelets > 20,000/mL guided by the clinical scenario. Leukocyte filters may be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBC's and decrease the risk of CMV infection. Irradiated blood and blood products should be used.

[001328] **Description of Statistical Methods.** The primary endpoint for ovarian cancer and osteosarcoma cohorts is the ORR as assessed by investigators using RECIST 1.1 criteria. The ORR is derived as the sum of the number of patients with a confirmed CR or partial response (PR) divided by the number of patients in the All-Treated analysis set x 100%. The primary endpoint for the cohort of PDAC is the percentage of patients who survive for 183 days. The 6-month landmark survival rate may be calculated based on the Kaplan Meier method.

[001329] PFS is defined as the time (in months) from the start date of lymphodepletion to PD or death due to any cause, whichever event is earlier. Patients not experiencing PD or death at the time of data cut or end of study (i.e., database lock) may have their event times censored on the last adequate tumor assessment. DOR is measured from the first time measurement criteria are met for a CR or PR, whichever response is observed first, until the first date that progressive disease (PD) or death occurs. Patients not experiencing PD or death prior to the time of data cut or end of study may have their event times censored on the last adequate tumor assessment. The analysis of DOR is based on responders only as assessed by investigators per RECIST v1.1. DCR is derived as the sum of the number of patients who achieved PR/CR or SD per the RECIST v1.1 divided by the number of patients in the All-Treated analysis set x 100%. OS is defined as the time (in months) from the start date of the lymphodepletion to death due to any cause. Patients not having expired at the time of data cut or end of study may have their event times censored on the last date of their known survival status.

[001330] All exploratory analyses may be descriptive and performed by cohort. Some analysis results may be reported separated from the final clinical study report. T-cell repertoire analysis may be used to determine TIL persistence. Molecular and immunological features of tumors before and after TIL therapy may be determined using exome sequencing and immunohistochemistry/immunofluorescence analyses. Sensitivity analyses on ORR, DCR, DOR, and PFS as measured by investigators using the irRECIST criteria may be performed. Pearson correlation coefficient and linear regression, when appropriate, may be used to quantify the relationship between phenotypic attributes (CD8 %, CD27 and CD28 expression, etc.) and tumor response to therapy. Baseline CA19-9 of patients with PDAC and baseline CA-125 of patients with ovarian cancer may be assessed for potential correlations with the efficacy outcome.

[001331] Grade 3 or higher treatment-emergent AEs and their incidence rates may be compared descriptively to historical data of TIL in other cancer disease types. AE incidence rates may be estimated with 95% CIs per cohort and all cohorts combined. The treatment-emergent AEs start from the first dose of cyclophosphamide and up to 6 months from the last dose of IL-2.

[001332] A study disposition summary may display number and percentages of patients who exit the study early by the primary reason in 2 parts: (1) After the tumor harvest prior to lymphodepletion; and (2) On or after the first dose of cyclophosphamide. Patients who are treated and being followed for the survival status at the time of study termination (i.e., completers) are not a part of this summary. Patients who did not receive planned full study treatment doses may also be summarized by its primary reason.

[001333] Summary of tumor response data per cohort may be based on the best overall response as assessed by investigators per RECIST 1.1. The summary may display percentages with 80% confidence intervals (CIs) for ORR and 95% CIs for DCR by the Wilcoxon score method among patients in the All-Treated analysis set. The median time-to-event and the landmark rate may also be measured with 80% CIs for the 6-month survival rate and 95% CIs for DOR, PFS, OS, and other landmark rates by the KM method.

[001334] All exploratory analyses may be descriptive and performed by cohort. The analysis may be defined separately from the statistical analysis plan for this study and reported independently outside the clinical study report (CSR). HRQOL may be assessed using the EORTC QLQ-C30 instrument and analyzed per thepublished evaluation manual.

[001335] **Sample Size.** For ovarian cancer and osteosarcoma, the Simon's two stage minimax design may be used to monitor the efficacy of each cohort independently. The null hypothesis that the historical response rate of 5% to be tested against the estimated experimental cohort response rate of 20%. In the first stage, 10 patients may be treated per cohort. If there is no confirmed response in these 10 patients, so long as the patient are evaluable, the cohort may be terminated. Other efficacy estimates including maximum % reductions in target lesion sum of diameters and/or time to PD/death may be considered for termination. A confirmed response shall be determined by RECIST 1,1 criteria with first assessment at 6 weeks and second confirmatory scan at 12 weeks. If the study moves forward to Stage II, an additional 8 patients may be treated leading to a total of 18 patients for that cohort. Three or more responders out of 18 treated patients for the cohort may be considered clinically relevant to justify further investigation. The power of this design is >=70% under the 1-sided type I error rate of 10%.

[001336] For PDAC, the Simon's minimax two-stage design may also be used to monitor the 6-month survival rate. The null hypothesis that the historical 6-month survival rate of 35% to be tested against the estimated experimental cohort survival rate of 50% (ASCO Jan 2016). In the first stage, 11 patients may be treated and followed for ≥6 months without holding further enrollment. If there are 8 or more deaths among first 11 patients within 183 days counting from the first study drug administration, this cohort may be considered termination.

[001337] Otherwise, an additional 11 patients may be treated for a total of 22. The final result for the cohort may be clinically meaningful if ≥10 patients survive at least for 183 days. The power of this design is approximately 70% under the 1-sided type I error rate of 10%.

Example 8 – Methods of Expanding TILs Using TNFRSF Agonists During Pre-REP and REP Steps

[001338] The antibodies used in this Example are described elsewhere herein and are further described in Table 57.

TABLE 57. 4-1BB and OX40 Agonistic Monoclonal Antibodies.

	4-1BB		**OX40**
Short name	CB 4-1BB	BPS 4-1BB	CB OX40
Source	Creative Biolabs (Shirley, NY, USA)	BPS Biosciences (San Diego, CA, USA)	Creative Biolabs (Shirley, NY, USA)
Clone and Product Information	Urelumab; Catalog no. TAB-179	Unknown; Catalog no. 79097-2, Lot no. 170718	Unknown; Catalog no. MOM-18455
Isotype	IgG4	IgG1	IgG
Formulation	PBS	PBS and 20% glycerol	PBS
Purity	>95%	Unknown	>98%
Sequence and epitope	Available	Unknown	Unknown
Publication	N/A	Wilcox, R.A., et al., J. Clin. Invest. 2002; Foell, J. et. al., J. Clin. Invest. 2003.	N/A

[001339] In addition to the monoclonal antibodies described above, the OX40 agonistic antibody clone Ber-ACT35 (BioLegend, San Diego, CA, USA) was also used in selected experiments described herein.

[001340] The overall experimental strategy included the following steps: reagent procurement and validation; ex vivo expansion experimental design; adding anti-4-1BB or anti-OX40 at day 0 of pre-REP experiments, using fresh melanoma, lung, cervical tumor samples; assessing the anti-OX40 in 21 mini-REP carried out on thawed head & neck, lung, melanoma, triple-negative breast cancer, and breast cancer pre-REP TIL samples; and assessment of TIL yield and cell lineage phenotype (CD4:CD8), T-cell subsets/extended phenotype, and functional assays.

[001341] The comparability of anti-4-1BB binding affinity for two 4-1BB agonists was assessed. 4-1BB reporter cells were stained with anti-4-1BB antibody (Creative Biolabs) or anti-4-1BB (BPS Biosciences) at concentrations of 0.01, 0.03, 0.1, 0.3, 1, and 3 μg/ml together with FITC-conjugated mouse anti-human IgG and analyzed by flow cytometry. The results are shown

in FIG. 16 and FIG. 17 (for % of 4-1BB$^+$ cells and mean fluorescence intensity (MFI) of 4-1BB$^+$ cells, respectively) and indicate that the Creative Biolabs (CB) 4-1BB urelumab antibody has the highest binding affinity.

[001342] An assessment of NF-κB pathway activation of 4-1BB agonistic antibodies was also performed. 4-1BB reporter cells were treated with either anti-4-1BB (CB or BPS antibodies) at a concentration of 1, 2, 4, and 8 μg/mL for 24 hours. The cells were lysed using One-Step Luciferase reagent, and luciferase activity was measured by a luminometer. The results are shown in FIG. 18. Log EC50 for the CB antibody was determined to be 3.9 μg/mL and for the BPS antibody was determined to be 2.13 μg/mL. Both CB and BPS anti-4-1BB agonists had similar Log EC50 values even though the BPS antibody exhibited greater NF-kB signaling activation.

[001343] The binding affinity of the CB OX40 agonist was also assessed. OX40 reporter cells were stained with anti-OX40 Creative Biolabs (CB) agonist at the concentrations of 0.01, 0.03, 0.1, 0.3, 1, and 3 μg/ml together with FITC-conjugated mouse anti-human IgG and analyzed by flow cytometry. Results are shown in FIG. 19 and FIG. 20 for % of OX40$^+$ cells and MFI of OX40$^+$ cells, respectively, and indicate that the CB OX40 has a high binding affinity.

[001344] The comparability of OX40 binding affinity for two OX40 agonists, the CB OX40 agonist and the OX40 agonistic antibody clone Ber-ACT35 (BioLegend, San Diego, CA, USA), was assessed. Five different histologic TIL lines (including cervical, head and neck, lung, and melanoma) were stained with either anti-OX40 agonistic antibody at concentration of 0.1, 0.3, 1, 3, 10 (μg/mL) together with anti-human IgG secondary antibody or anti-OX40 (clone Ber-ACT35) alone. The results are shown in FIG. 21, and indicate comparable binding affinity for the two agonists.

[001345] An assessment of NF-kB pathway activation of the CB OX40 agonist antibody was also performed, with results shown in FIG. 22. OX40 reporter cells were treated with either anti-OX40 alone or isotype control at concentrations of 1, 2, 4, 8, and 16 μg/mL with or without feeder cells for 24 hours. The cells were lysed using One-Step Luciferase reagent, and luciferase activity was measured by luminometer. The use of PBMC feeders initiated NF-κB activation using the OX40 reporter cell line, suggesting that clustering is involved in activation.

[001346] The experimental design for use of 4-1BB and OX40 agonists during the pre-REP step is shown in FIG. 23. The tumor histologies explored are shown in FIG. 24. The data analysis strategy is shown in FIG. 25. No treatment (IL-2 alone), anti-4-1BB, and anti-OX40 were analyzed in matched-pair manner. Using this approach, the samples were assigned into three different groups including: Group 1, No treatment and anti-4-1BB (n=3); Group 2, No treatment and anti-OX40 (n=5); and Group 3, No treatment and anti-4-1BB and anti-OX40 (n=2). Total cell count results from expansions are shown in FIG. 26 (CB 4-1BB agonist versus not tested, N = 3); FIG. 27 (CB OX40 agonist versus not tested, N = 5); and FIG. 28 (CB 4-1BB agonist and OX-40 agonist, N = 2). $CD8^+$ cell count results for cell expansion are shown in FIG. 29 (CB 4-1BB agonist versus not tested, N = 3); FIG. 30 (CB OX40 agonist versus not tested, N = 5); and FIG. 31 (CB 4-1BB agonist and OX-40 agonist, N = 2). Total $CD8^+/CD4^+$ cell count ratio results for cell expansions are shown in FIG. 32 (CB 4-1BB agonist versus not tested, N = 3); FIG. 33 (CB OX40 agonist versus not tested, N = 5); and FIG. 34 (CB 4-1BB agonist and OX-40 agonist, N = 2).

[001347] REP propagation of pre-REP TILs expanded in the presence of 4-1BB or OX40 agonists was also explored using the scheme shown in FIG. 35. Pre-REP TILs were expanded with either CB 4-1BB agonist or CB OX40 agonist were further propagated in a REP protocol in the presence of irradiated PBMCs, anti-CD3 antibody (30 ng/mL), and IL-2 (3000 IU/mL) for 11 days. TILs were harvested and counted, and fold expansion determined. Results are shown in FIG. 36, FIG. 37, and FIG. 38.

[001348] Assessment of OX40 during the REP phase was also tested. Twenty-one TIL lines from different histologies (FIG. 39) were propagated with REP with addition of CB OX40 agonist or isotype control antibody at concentration of 5 μg/mL. The experimental scheme is shown in FIG. 40. Results are shown in FIG. 41, FIG. 42, and FIG. 43. Surprisingly, the OX40 agonist preferentially expands $CD8^+$ TILs during REP. TILs treated with OX40 agonist were classified as responders or non-responders.

[001349] Anti-OX40 dose titration in non-responder and responder TIL lines was performed to further study this effect and to define the optimal concentration of OX40 agonist in responders and non-responders. TIL lines were categorized into two groups (responder and non-responder) based on enhanced $CD8^+$ skewness following anti-OX40 treatment. Three non-responders

(L4005, H3005, and M1022) and responders (T6001, T6003, and L4002) were propagated with REP in the presence of OX40 agonist or isotype control antibody following the conditions shown in FIG. 44. FIG. 45 and FIG. 46 illustrates that a dose-dependent manner of $CD8^+$ skewness following anti-OX40 treatment was observed in responders, with concentrations in the 1 to 10 μg/mL range promoting skewness. Non-responders did not exhibit $CD8^+$ skewness following anti-OX40 treatment even at high concentration (30 μg/mL).

[001350] The impact of OX40 agonist on TCRvb repertoire in responders was also investigated. To determine whether anti-OX40, previously shown to skew CD8+ population, preferentially expand certain TCR vb repertoire. Responder TIL lines were propagated with REP in 24-well plates with either IL-2 alone or IL-2 with CD OX40 agonist monoclonal antibody (5 μg/mL). On day 11, TIL were harvested and stained with anti-CD3, anti-CD8, anti-CD4, and TCRvb repertoire antibodies, and analyzed by flow cytometry. Results are shown for three responders with three histologies in FIG. 47, FIG. 48, and FIG. 49. Minimal changes in TCRvb repertoire was observed, indicating that the high degree of polyclonality exhibited by the shortened 22-day process in an embodiment of FIG. 1 or FIG. 2 is surprisingly preserved in conjunction with the use of OX40 agonists during REP.

[001351] In conclusion, use of CB anti-OX40 antibody significantly enhanced pre-REP $CD8^+$ TIL expansion, while use of CB anti-4-1BB antibody also demonstrated a promising trend. REP-fold expansion was comparable regardless of pre-treatment condition. Surprisingly, OX40 agonistic antibody increased $CD8^+/CD4^+$ ratio in REP TIL previously grown with IL-2 alone. In non-responder TILs, down-regulation of OX-40 was not observed in the $CD4^+$ subset following anti-OX40 treatment. The dose-dependent manner of $CD8^+$ skewness following anti-OX40 treatment was observed in responders. The change in TCRvb repertoire was very subtle even though significant $CD8^+$ skewness was observed.

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CLAIMS

We claim:

1. A population of tumor infiltrating lymphocytes (TILs) when used in treating cancer, wherein the population of TILs is obtained from a method comprising the steps of:

(a) obtaining a first population of TILs from a tumor resected from a patient;

(b) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs,

wherein the first cell culture medium comprises IL-2 and a first tumor necrosis factor receptor superfamily (TNFRSF) agonist selected from the group consisting of an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof, and

wherein the initial expansion is performed over a period of 21 days or less;

(c) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3) antibody, peripheral blood mononuclear cells (PBMCs), a second TNFRSF agonist selected from the group consisting of an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof, and wherein the rapid expansion is performed over a period of 14 days or less; and

(d) harvesting the third population of TILs, wherein the third population of TILs exhibits an increased ratio of CD8+ TILs to CD4+ TILs in comparison to the reference ratio of CD8+ TILs to CD4+ TILs in the second population of TILs.

2. The population of TILs when used in treating cancer according to Claim 1, wherein the first TNFRSF agonist or the second TNFRSF agonist is selected from the group consisting of an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof,

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wherein the first TNFRSF agonist or the second TNFRSF agonist is an OX40 agonist, and the OX40 agonist is selected from the group consisting of tavolixizumab, an OX40 agonist fusion protein, and combinations thereof; and/or

wherein the first TNFRSF agonist or the second TNFRSF agonist is a CD27 agonist, and the CD27 agonist is selected from the group consisting of varlilumab, a CD27 agonist fusion protein; and/or

wherein the first TNFRSF agonist or the second TNFRSF agonist is a GITR agonist; and/or

wherein the first TNFRSF agonist or the second TNFRSF agonist is selected from the group consisting of urelumab, utomilumab, tavolixizumab, and combinations thereof.

3. The population of TILs when used in treating cancer according to any one of Claims 1 to 2, which is for use in combination with the first TNFRSF agonist, wherein the first TNFRSF is for administration starting on the day after administration of the third population of TILs to the patient, wherein the first TNFRSF agonist is for administration intravenously at a dose of between 0.1 mg/kg and 50 mg/kg every four weeks for up to eight cycles.

4. The population of TILs when used in treating cancer according to any one of Claims 1 to 3, wherein the first cell culture medium comprises the second TNFRSF agonist.

5. The population of TILs when used in treating a cancer according to any one of Claims 1 to 4, wherein the first TNFRSF agonist is added to the first cell culture medium during the initial expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks;

and optionally wherein the second TNFRSF agonist is added to the second cell culture medium during the rapid expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks, and further optionally wherein the first TNFRSF agonist and/or the second TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 μg/mL and 100 μg/mL.

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6. The population of TILs when used in treating cancer according to any one of Claims 1 to 5, wherein IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the first cell culture medium and optionally wherein IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the second cell culture medium, and further optionally wherein OKT-3 antibody is present at an initial concentration of about 10 ng/mL to about 60 ng/mL in the second cell culture medium.

7. The population of TILs when used in treating cancer according to any one of Claims 1 to 6, wherein the initial expansion and the rapid expansion each is performed using a gas permeable container.

8. The population of TILs when used in treating cancer according to any one of Claims 1 to 7, which is for use in treating the patient, wherein the patient is treated with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

9. The population of TILs when used in treating cancer according to any one of Claims 1 to 8, wherein the patient is treated with a PD-1 inhibitor or PD-L1 inhibitor after administering the third population of TILs to the patient, wherein optionally the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and combinations thereof.

10. The population of TILs when used in treating cancer according to any one of Claims 1 to 9, wherein the initial expansion is performed over a period of 11 days or less, and optionally wherein the rapid expansion is performed over a period of 11 days or less.

11. A process for the preparation of a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

(a) obtaining a first population of TILs;

(b) performing an initial expansion of the first population of TILs in a first cell culture medium to obtain a second population of TILs, wherein the first cell culture medium comprises IL-2 and a first tumor necrosis factor receptor superfamily (TNFRSF) agonist selected from the group consisting of an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95

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agonist, and combinations thereof, and wherein the initial expansion is performed over a period of 21 days or less;

(c) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), peripheral blood mononuclear cells (PBMCs), a second TNFRSF agonist selected from the group consisting of an OX40 agonist, a CD27 agonist, a GITR agonist, a HVEM agonist, a CD95 agonist, and combinations thereof, and wherein the rapid expansion is performed over a period of 14 days or less; and

(d) harvesting the third population of TILs.

12. The process according to claim 11, wherein the first population of TILs is obtained from a tumor which tumor has been resected from a patient,

wherein optionally the first TNFRSF agonist is added to the first cell culture medium during the initial expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks,

and further optionally wherein the second TNFRSF agonist is added to the second cell culture medium during the rapid expansion at an interval selected from the group consisting of every day, every two days, every three days, every four days, every five days, every six days, every seven days, and every two weeks.

13. The process according to any one of claims 11 to 12, wherein the first TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the first cell culture medium of between 0.1 μg/mL and 100 μg/mL, wherein optionally IL-2 is present at an initial concentration of about 10 to about 6000 IU/mL in the first cell culture medium and further optionally wherein OKT-3 antibody is present at an initial concentration of about 10 ng/mL to about 60 ng/mL in the second cell culture medium, and further optionally wherein the initial expansion and the rapid expansion each is performed using a gas permeable container.

14. A population of tumor infiltrating lymphocytes (TILs) obtained from a process according to any one of claims 11 to 13.

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15. A pharmaceutical composition comprising a population of tumor infiltrating lymphocytes (TILs) when used in treating cancer wherein the population of tumor infiltrating lymphocytes (TILs) is obtained by a process according to any one of claims 11 to 13, wherein optionally the pharmaceutical composition comprises the third population of TILs.

16. The pharmaceutical composition when used in treating cancer according to claim 15, when used in combination with a non-myeloablative lymphodepletion regimen, and/ or

when used in combination with a myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient, and/or

when used in combination with a PD-1 inhibitor or PD-L1 inhibitor, wherein optionally the PD-1 inhibitor or PD-L1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, biosimilars, and combinations thereof, and

further wherein optionally the PD-1 inhibitor or PD-L1 inhibitor is administered prior to or after resection of the tumor from the patient, and/or wherein said PD-1 inhibitor or PD-L1 inhibitor is administered after administering the third population of TILs to the patient.

17. The population of TILs when used in treating cancer according to any one of claims 1 to 10 or the pharmaceutical composition when used in treating cancer according to claim 15 or 16, wherein the cancer is selected from the group consisting of melanoma, cutaneous melanoma, double-refractory melanoma, uveal (ocular melanoma), ovarian cancer, platinum-resistant ovarian cancer, cervical cancer, lung cancer, non-small cell lung cancer (NSCLC), bladder cancer, breast cancer, triple-negative breast cancer, head and neck cancer, head and neck squamous cell cancer, renal cell carcinoma, acute myeloid leukemia, colorectal cancer, pancreatic ductal adenocarcinoma, glioblastoma, cholangiocarcinoma, osteosarcoma, and sarcoma.

18. Use of the population of TILs of any one of claims 1-10 or the pharmaceutical composition of any one of claims 15-16 for the manufacture of a medicament for treating cancer.

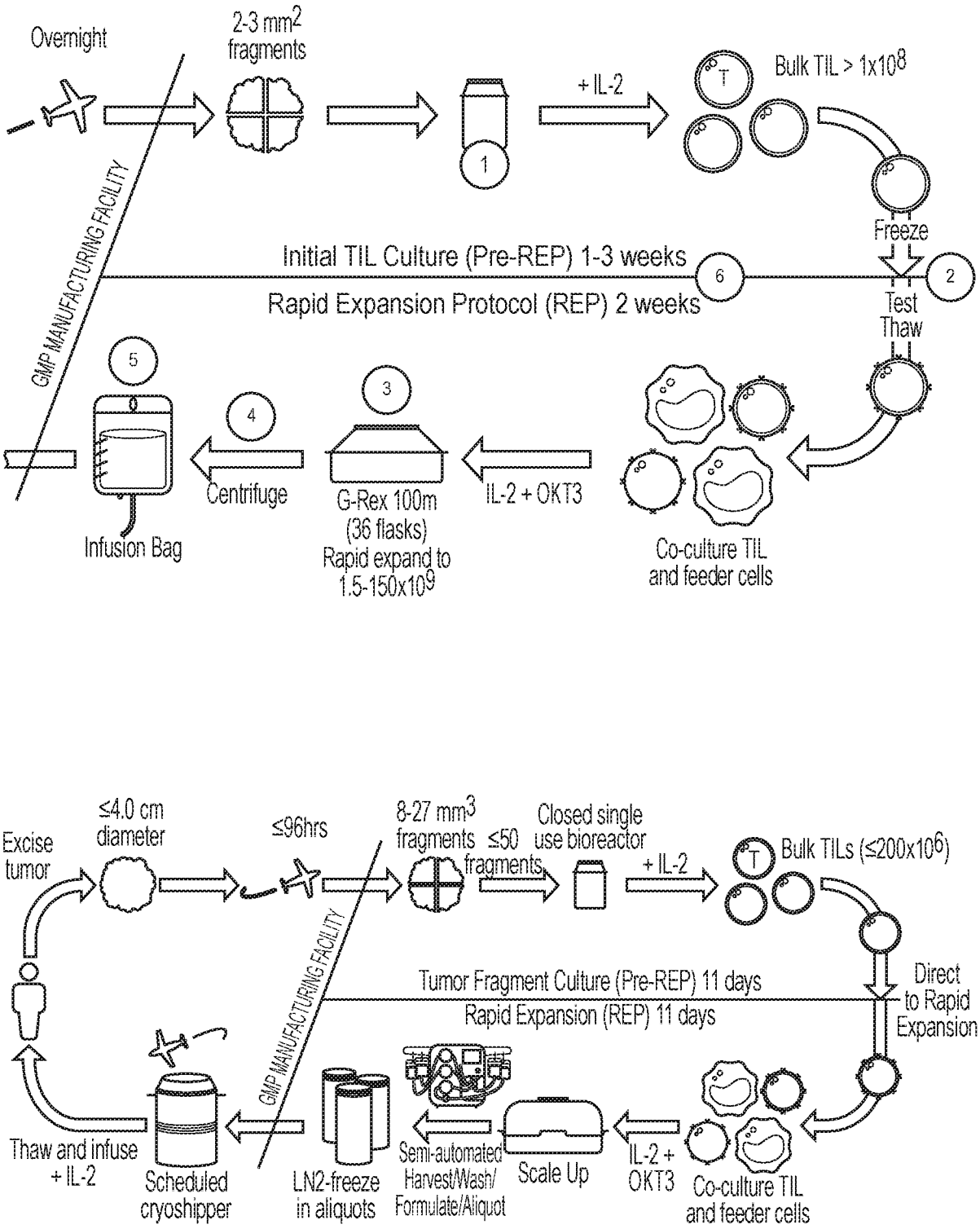
Overnight
2-3 mm2 fragments
+ IL-2
Bulk TIL > 1x10^8
Freeze
Initial TIL Culture (Pre-REP) 1-3 weeks
Rapid Expansion Protocol (REP) 2 weeks
Test Thaw
GMP MANUFACTURING FACILITY
Infusion Bag
Centrifuge
G-Rex 100m (36 flasks) Rapid expand to 1.5-150x10^9
IL-2 + OKT3
Co-culture TIL and feeder cells
Excise tumor
≤4.0 cm diameter
≤96hrs
8-27 mm3 fragments
≤50 fragments
Closed single use bioreactor
+ IL-2
Bulk TILs (≤200x10^6)
Direct to Rapid Expansion
Tumor Fragment Culture (Pre-REP) 11 days
Rapid Expansion (REP) 11 days
Thaw and infuse + IL-2
Scheduled cryoshipper
LN2-freeze in aliquots
Semi-automated Harvest/Wash/ Formulate/Aliquot
Scale Up
IL-2 + OKT3
Co-culture TIL and feeder cells

FIG. 1

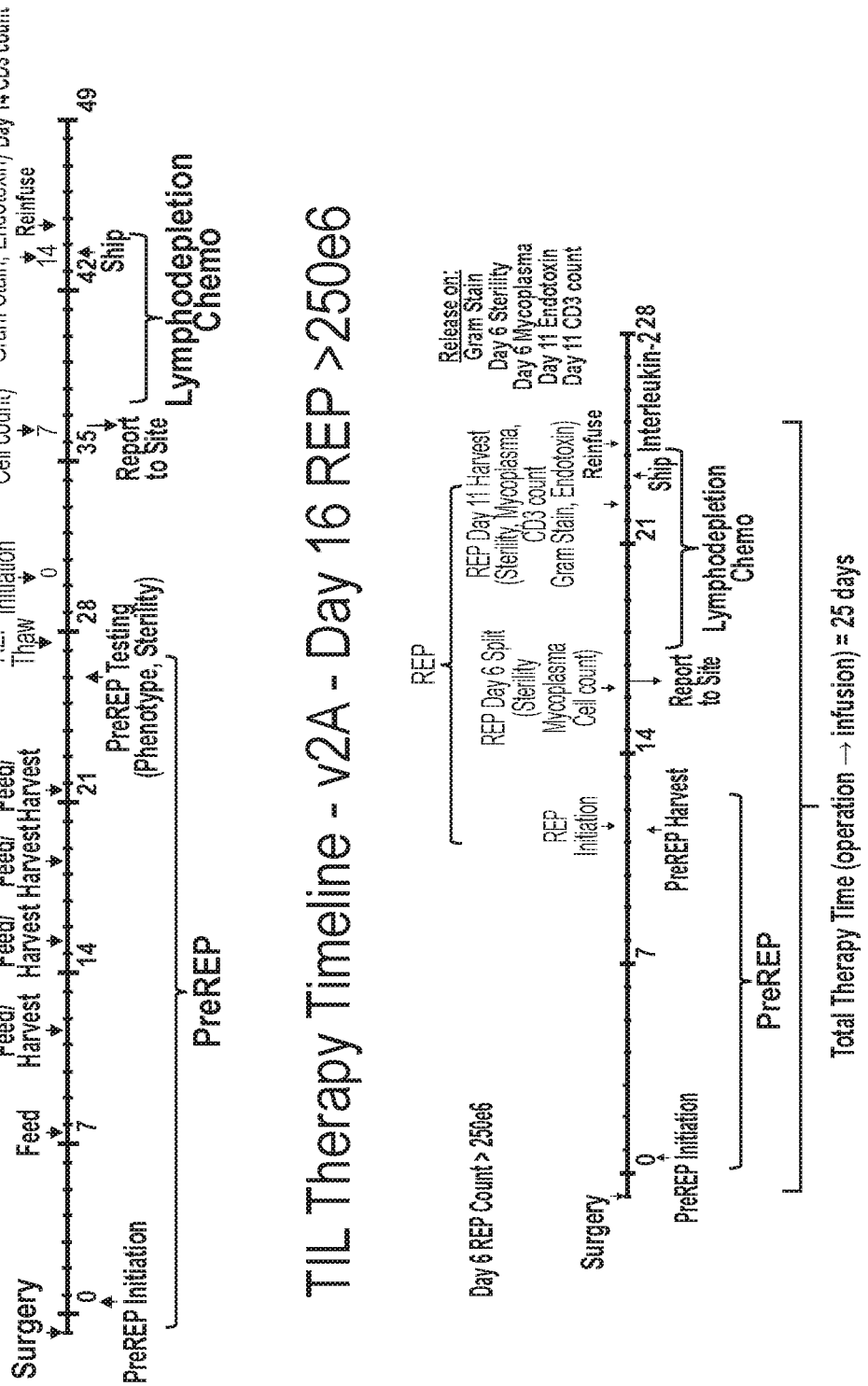
TIL Therapy Timeline - v2A - Day 16 REP >250e6
REP
REP Day 7 Split (Sterility, Mycoplasma Cell count)
REP Day 14 Harvest (Sterility, Mycoplasma, CD3 count Gram Stain, Endotoxin)
Release on: Gram Stain Day 7 Sterility Day 7 Mycoplasma Day 14 Endotoxin Day 14 CD3 count
Reinfuse
Ship
Report to Site
Lymphodepletion Chemo
Surgery
Feed
Feed/ Harvest
Feed/ Harvest
Feed/ Harvest
Feed/ Harvest
PreREP Testing (Phenotype, Sterility)
REP Initiation
Thaw
PreREP Initiation
PreREP
0
7
14
21
28
35
42
49
Day 6 REP Count > 250e6
REP Day 6 Split (Sterility Mycoplasma Cell count)
REP Day 11 Harvest (Sterility, Mycoplasma, CD3 count Gram Stain, Endotoxin)
Release on: Gram Stain Day 6 Sterility Day 6 Mycoplasma Day 11 Endotoxin Day 11 CD3 count
Reinfuse
Ship
Interleukin-2
Report to Site
Lymphodepletion Chemo
PreREP Harvest
REP Initiation
Surgery
PreREP Initiation
PreREP
0
7
14
21
28
Total Therapy Time (operation → infusion) = 25 days

FIG. 2

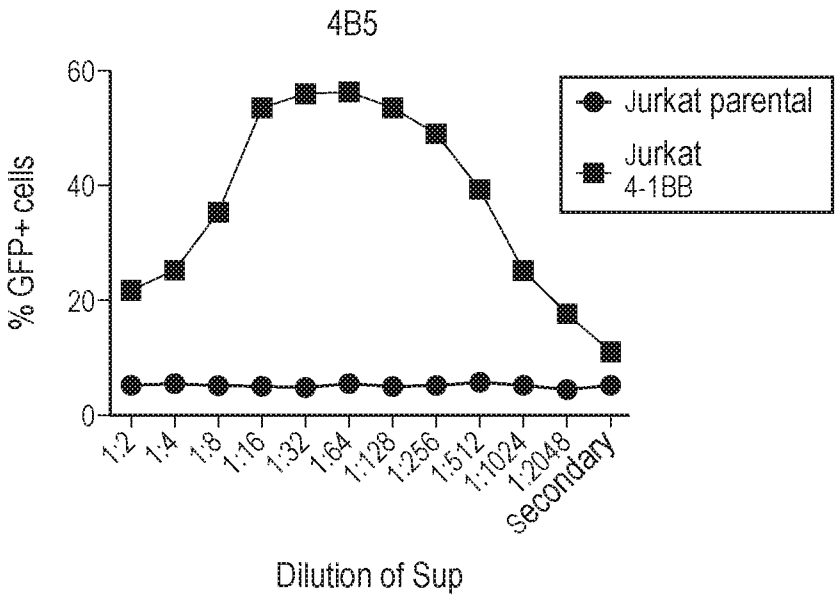
4B5
60
40
20
0
% GFP+ cells
Jurkat parental
Jurkat
4-1BB
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 3

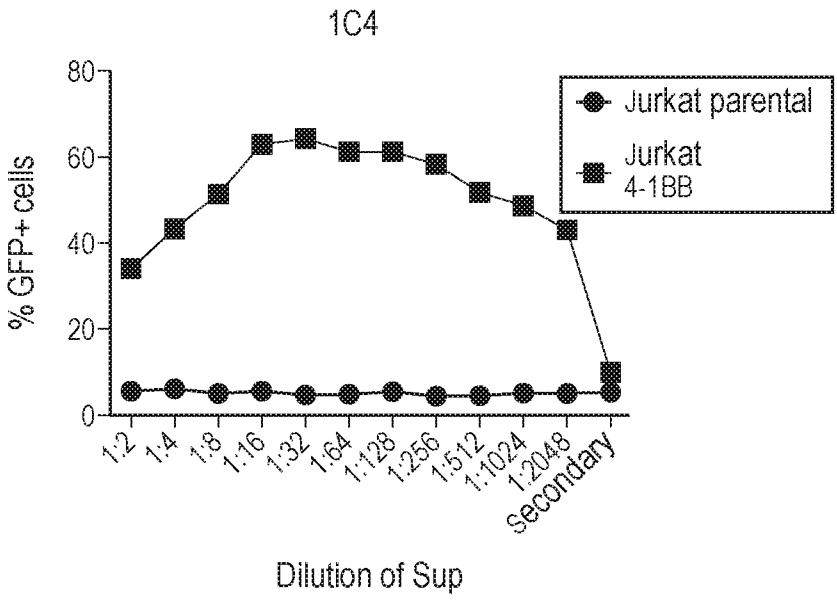
1C4
80
60
40
20
0
% GFP+ cells
Jurkat parental
Jurkat
4-1BB
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 4

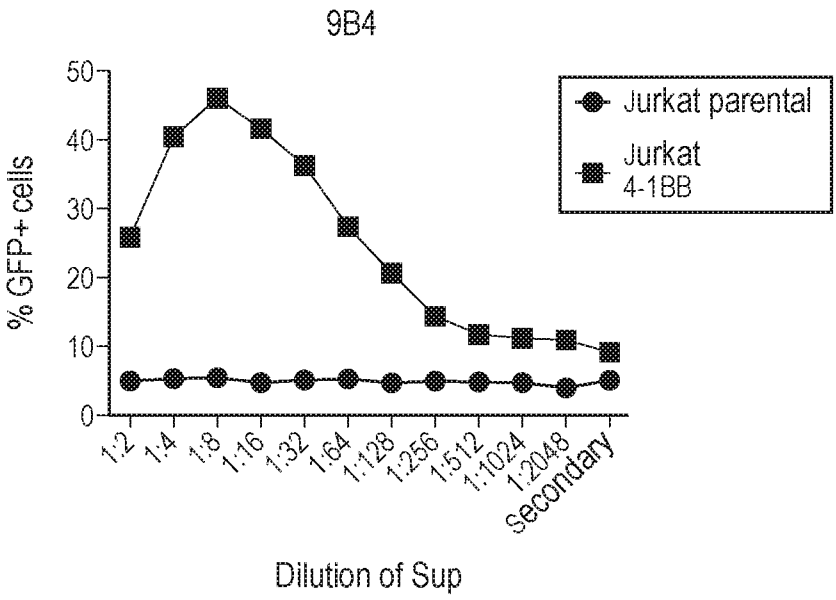
9B4
% GFP+ cells
50
40
30
20
10
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup
Jurkat parental
Jurkat
4-1BB

FIG. 5

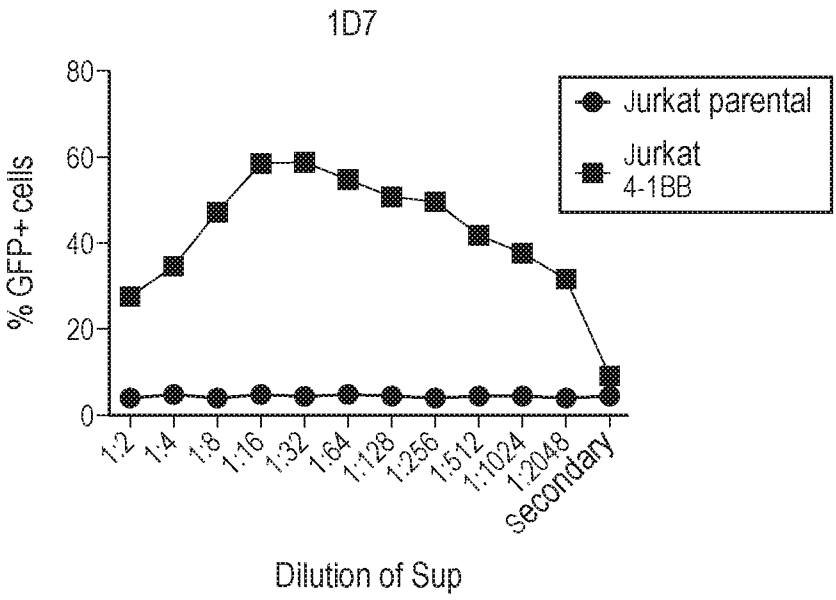
1D7
% GFP+ cells
80
60
40
20
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup
Jurkat parental
Jurkat
4-1BB

FIG. 6

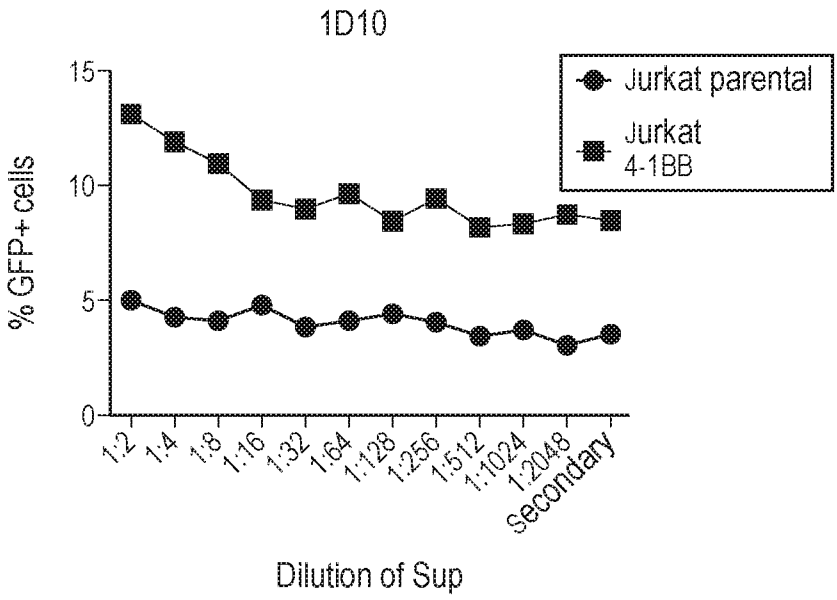
1D10
Jurkat parental
Jurkat
4-1BB
% GFP+ cells
15
10
5
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 7

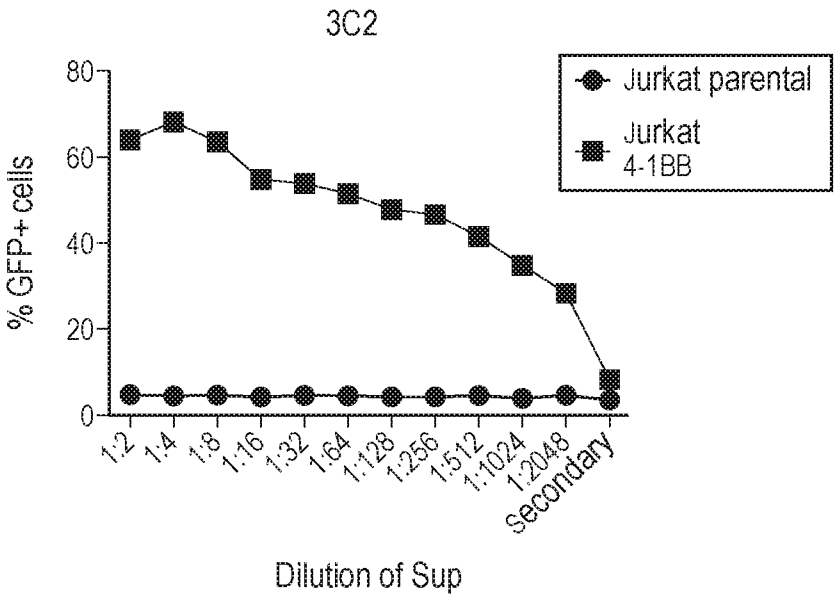
3C2
Jurkat parental
Jurkat
4-1BB
% GFP+ cells
80
60
40
20
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 8

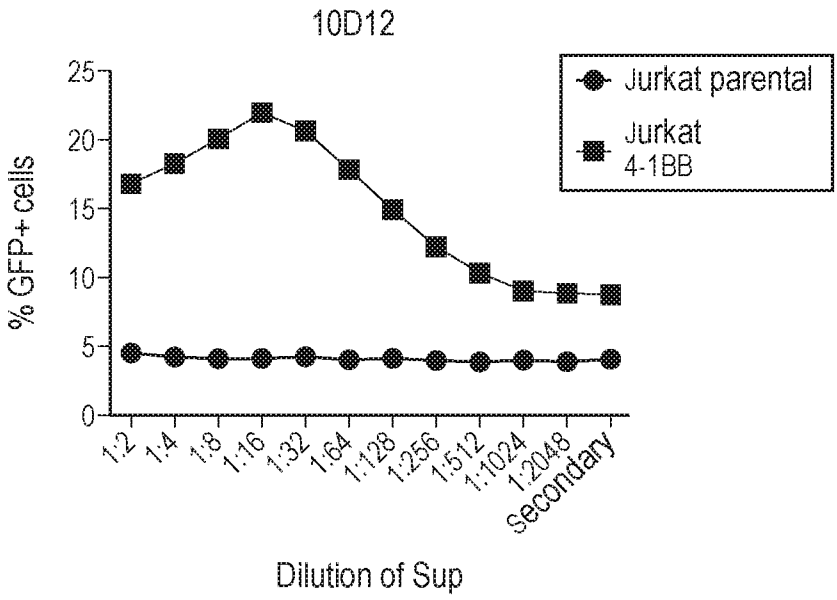
10D12
Jurkat parental
Jurkat
4-1BB
% GFP+ cells
25
20
15
10
5
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 9

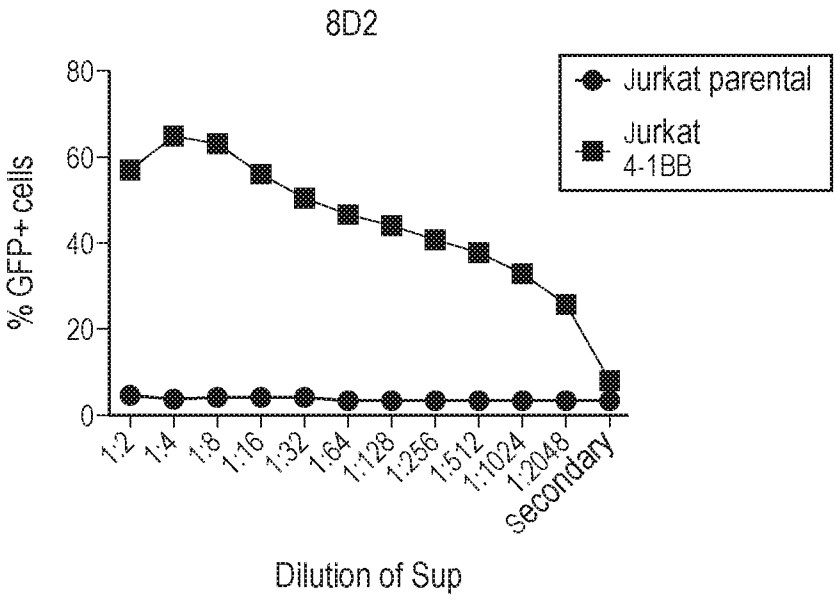
8D2
Jurkat parental
Jurkat 4-1BB
% GFP+ cells
80
60
40
20
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 10

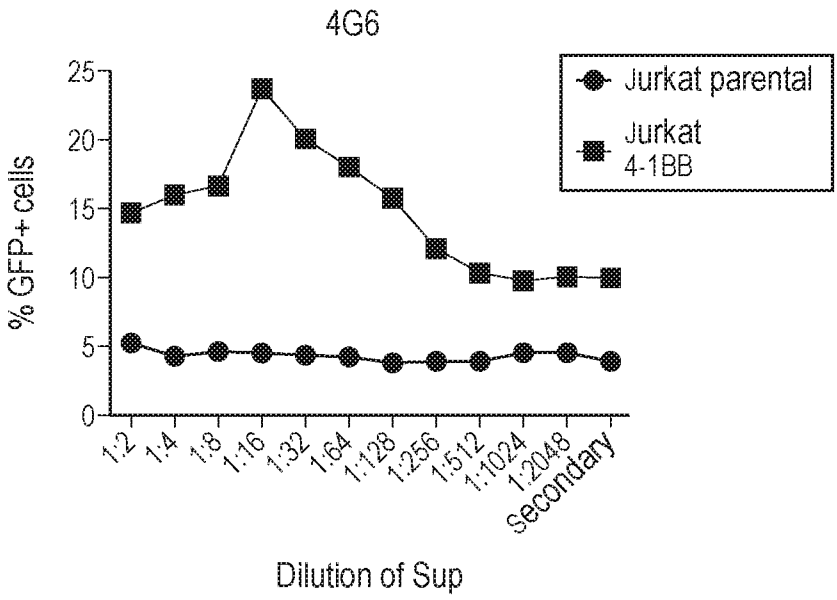
4G6
Jurkat parental
Jurkat
4-1BB
% GFP+ cells
25
20
15
10
5
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 11

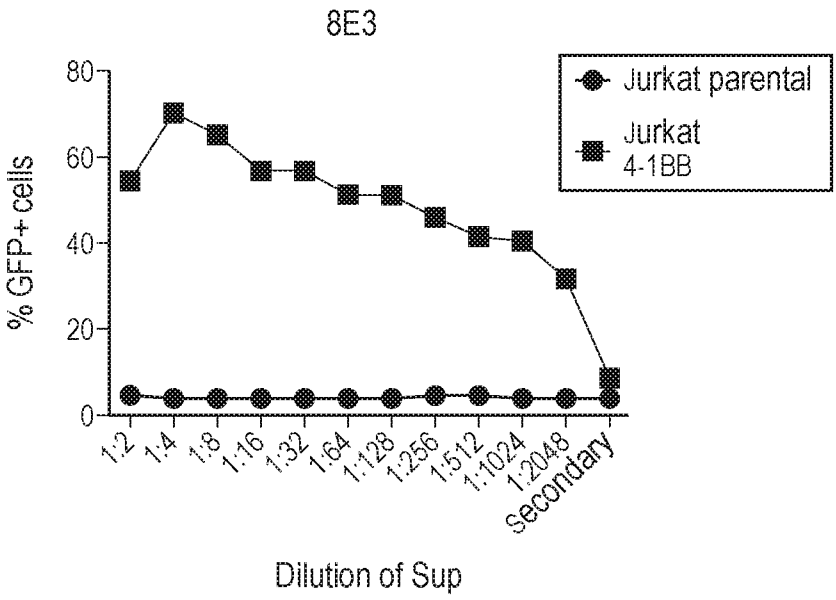
8E3
Jurkat parental
Jurkat
4-1BB
% GFP+ cells
80
60
40
20
0
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1024
1:2048
secondary
Dilution of Sup

FIG. 12

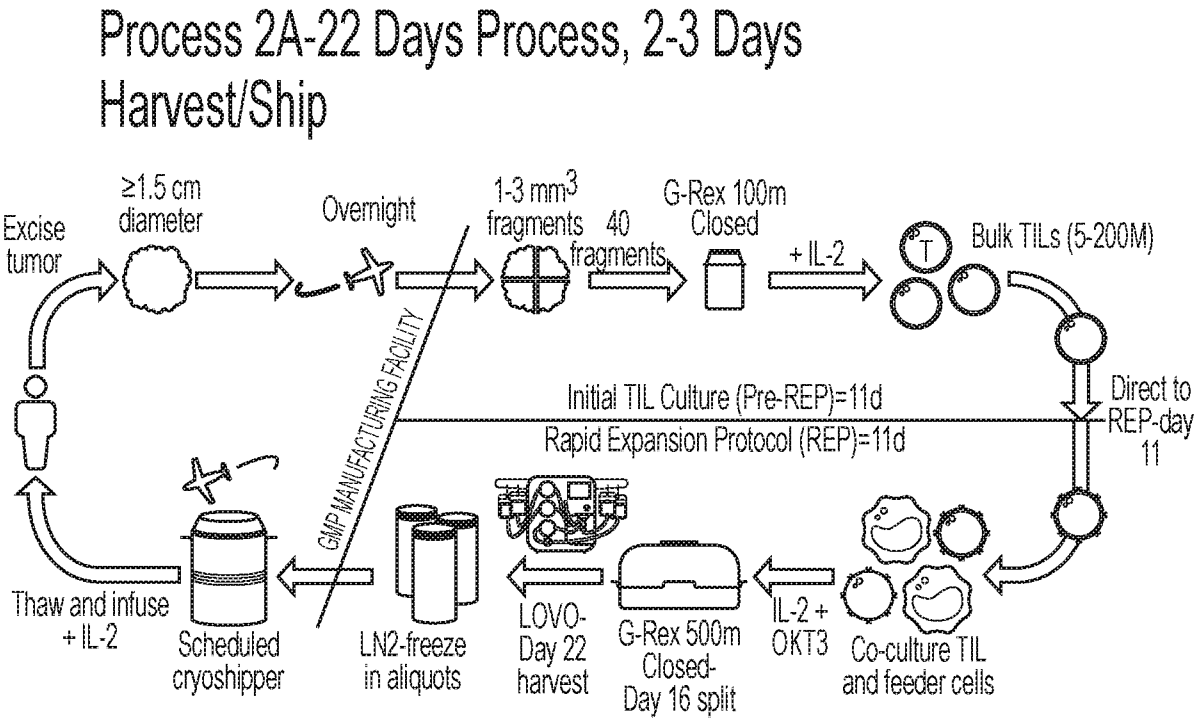
Process 2A-22 Days Process, 2-3 Days Harvest/Ship
Excise tumor
≥1.5 cm diameter
Overnight
1-3 mm3 fragments
40 fragments
G-Rex 100m Closed
+ IL-2
Bulk TILs (5-200M)
Direct to REP-day 11
Initial TIL Culture (Pre-REP)=11d
Rapid Expansion Protocol (REP)=11d
GMP MANUFACTURING FACILITY
Co-culture TIL and feeder cells
IL-2 + OKT3
G-Rex 500m Closed-Day 16 split
LOVO-Day 22 harvest
LN2-freeze in aliquots
Scheduled cryoshipper
Thaw and infuse + IL-2

FIG. 13

Process 2A: about 22 days from Steps A - E

1. **STEP A**

Obtain Patient Tumor Sample

2. **STEP B**

Fragmentation and First Expansion
3 days to 14 days

3. **STEP C**

First expansion to Second Expansion Transition
No Storage and Closed System

4. **STEP D**

Second Expansion
IL-2, OKT-3, and antigen-presenting feeder cells
Closed System

5. **STEP E**

Harvest TILS from Step D
Closed System

6. **STEP F**

Final Formulation and/or Transfer to Infusion Bag
(optionally cryopreserve)

FIG. 14

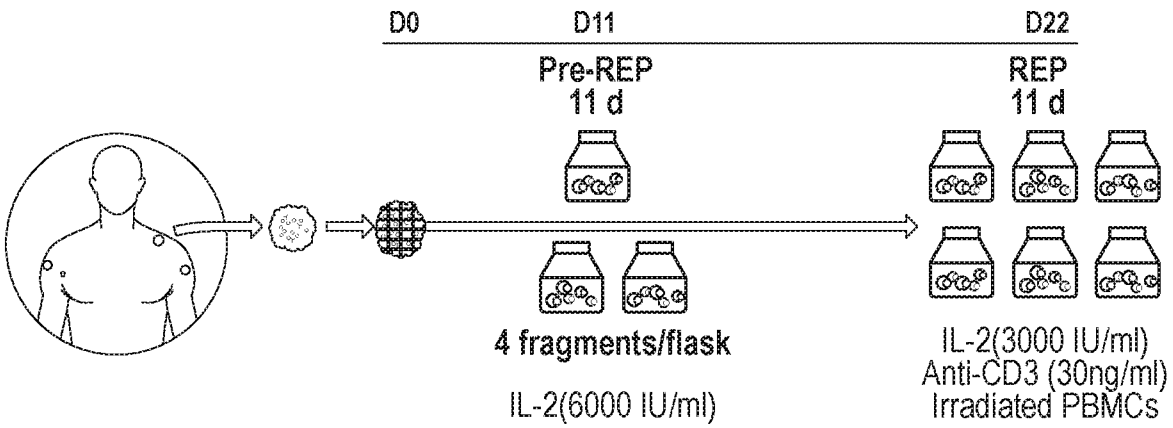
D0
D11
D22
Pre-REP
11 d
REP
11 d
4 fragments/flask
IL-2(6000 IU/ml)
IL-2(3000 IU/ml)
Anti-CD3 (30ng/ml)
Irradiated PBMCs

FIG. 15

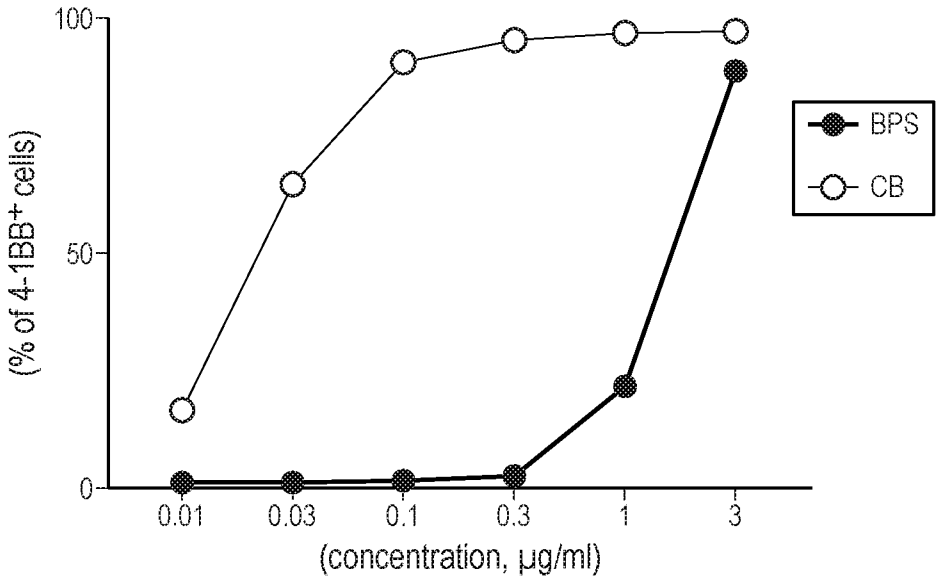
100
50
0
(% of 4-1BB+ cells)
0.01
0.03
0.1
0.3
1
3
(concentration, µg/ml)
BPS
CB

FIG. 16

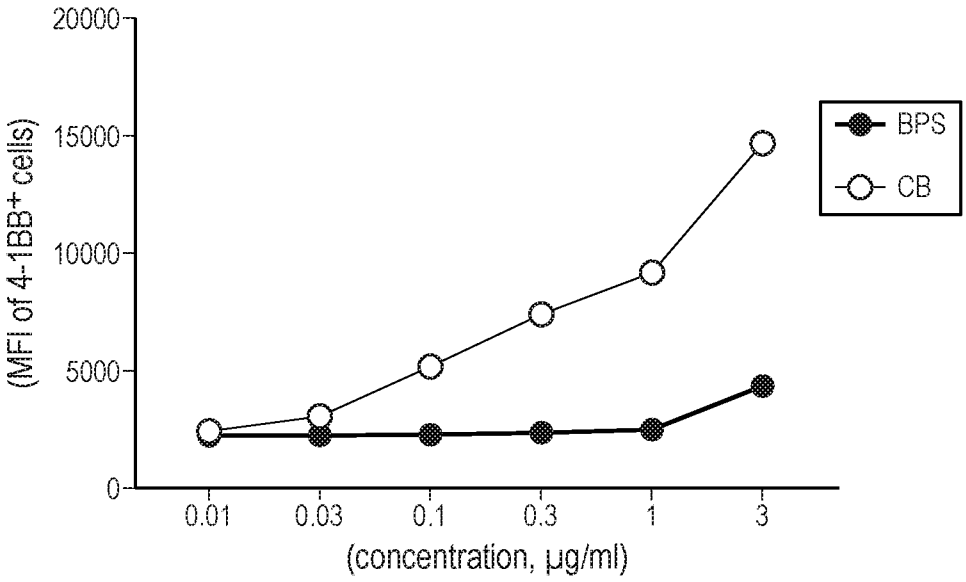
20000
15000
10000
5000
0
(MFI of 4-1BB+ cells)
0.01
0.03
0.1
0.3
1
3
(concentration, µg/ml)
BPS
CB

FIG. 17

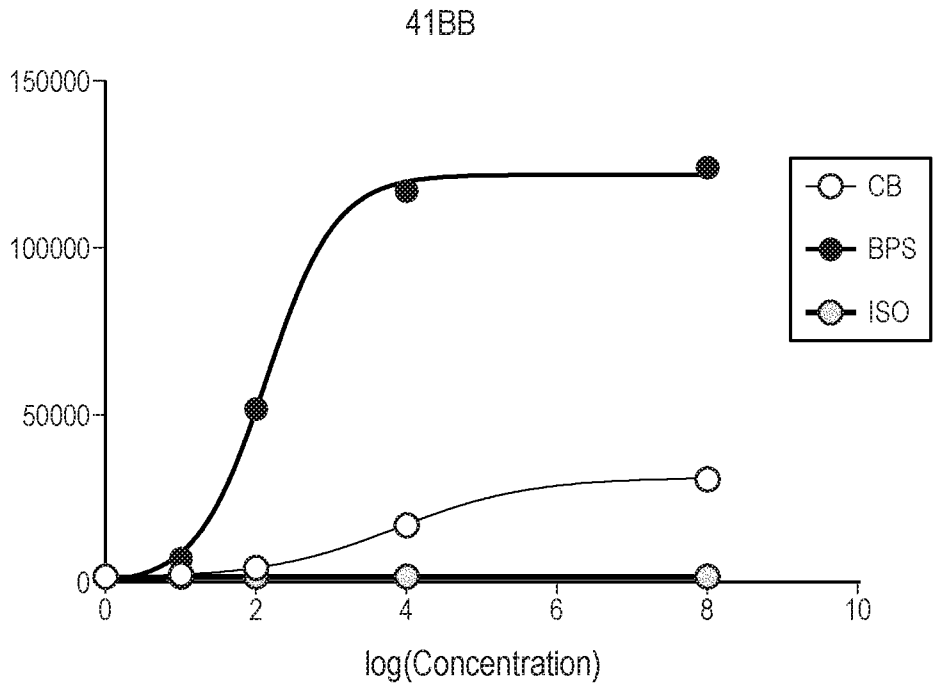
41BB
150000
100000
50000
0
0
2
4
6
8
10
log(Concentration)
CB
BPS
ISO

FIG. 18

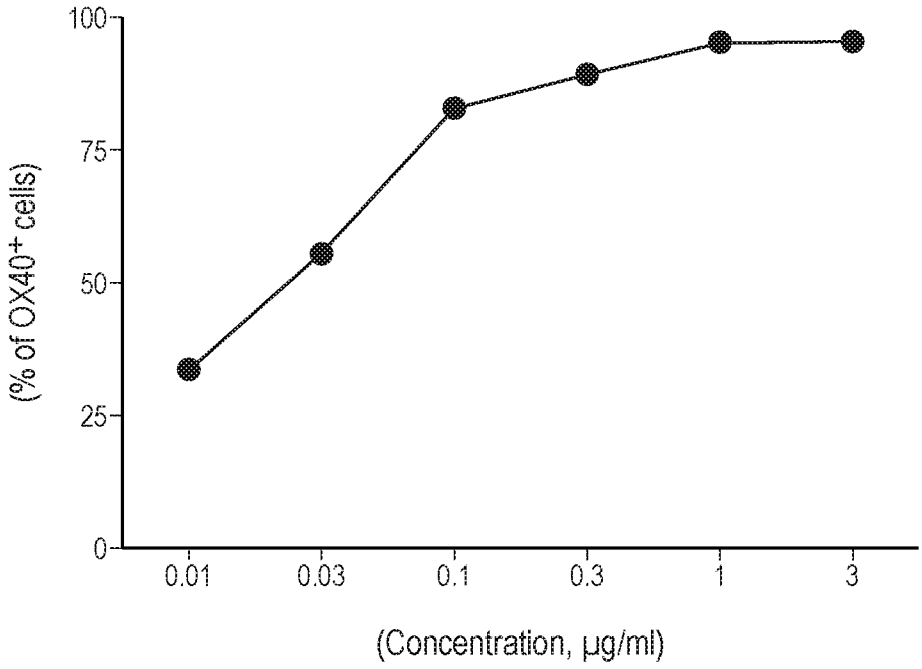
100
75
50
25
0
(% of OX40+ cells)
0.01
0.03
0.1
0.3
1
3
(Concentration, µg/ml)

FIG. 19

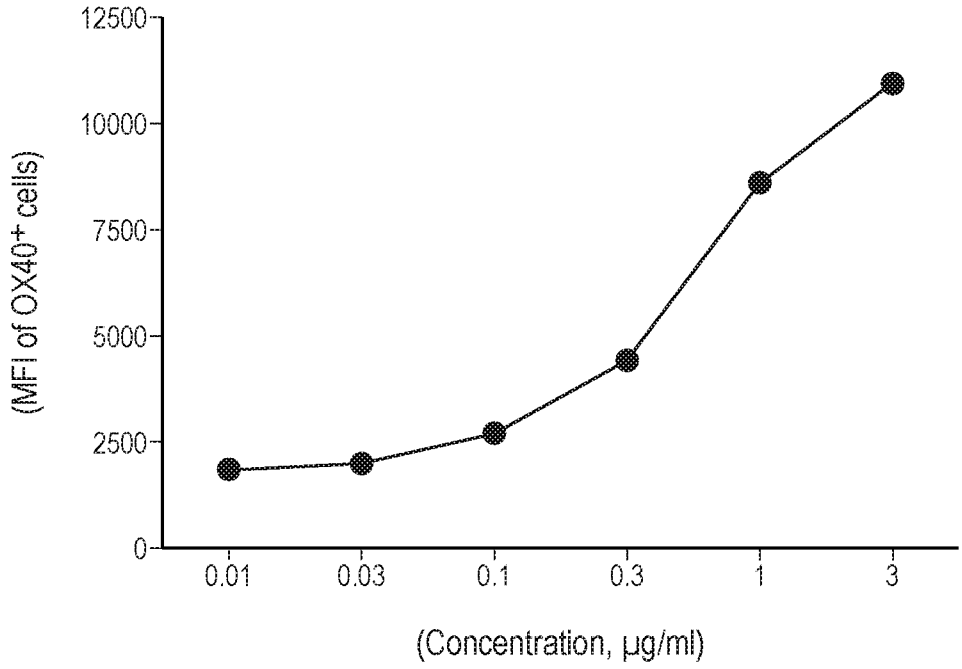
12500
10000
7500
5000
2500
0
(MFI of OX40+ cells)
0.01
0.03
0.1
0.3
1
3
(Concentration, µg/ml)

FIG. 20

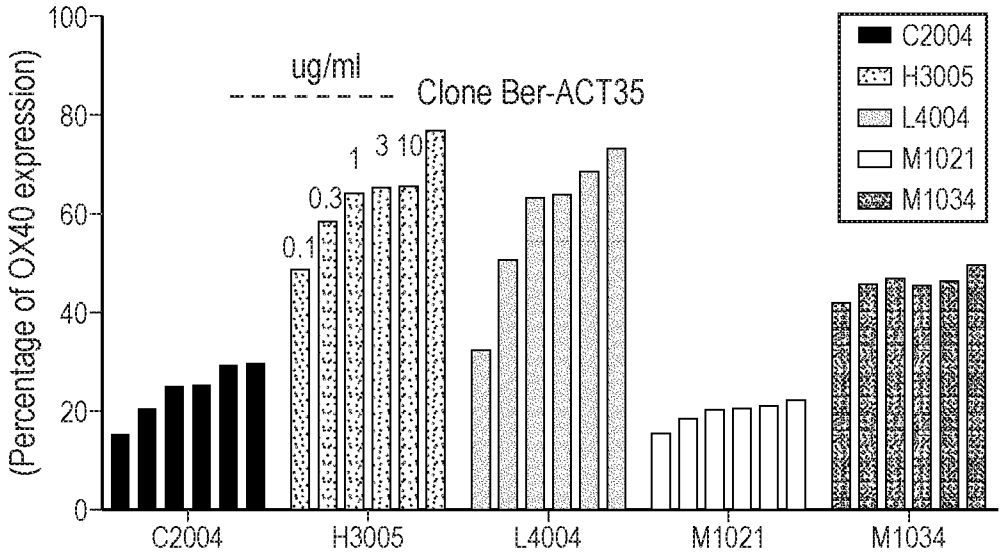
(Percentage of OX40 expression)
100
80
60
40
20
0
ug/ml
Clone Ber-ACT35
0.1
0.3
1
3
10
C2004
H3005
L4004
M1021
M1034
C2004
H3005
L4004
M1021
M1034

FIG. 21

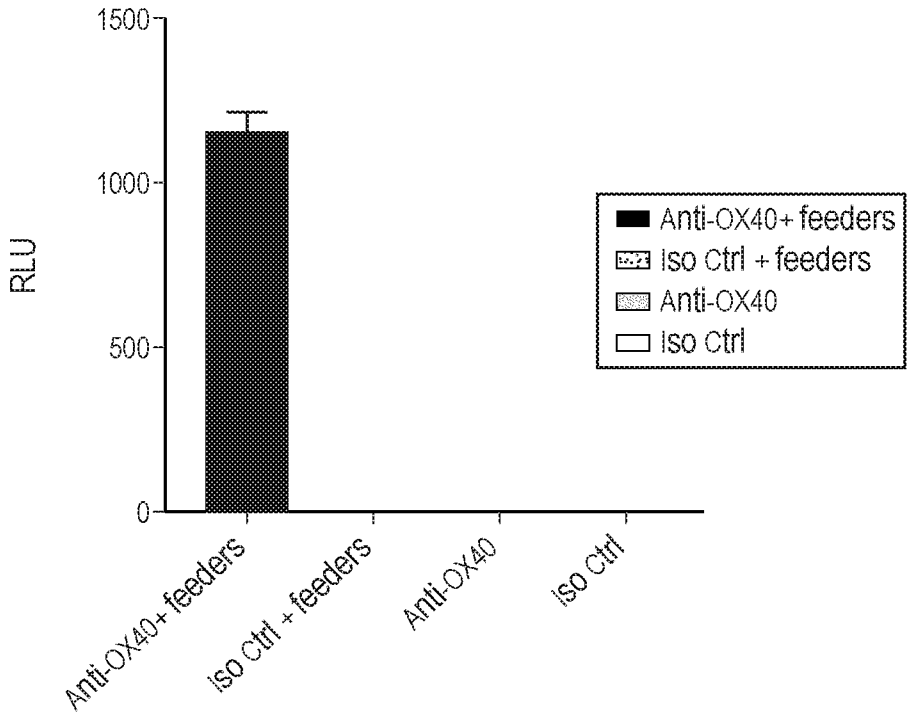
1500
1000
500
0
RLU
Anti-OX40+ feeders
Iso Ctrl + feeders
Anti-OX40
Iso Ctrl
Anti-OX40+ feeders
Iso Ctrl + feeders
Anti-OX40
Iso Ctrl

FIG. 22

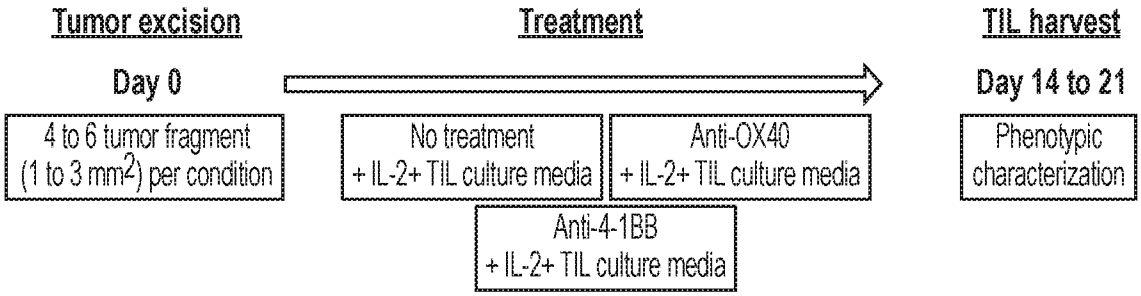
Tumor excision
Day 0
4 to 6 tumor fragment (1 to 3 mm2) per condition
Treatment
No treatment + IL-2+ TIL culture media
Anti-OX40 + IL-2+ TIL culture media
Anti-4-1BB + IL-2+ TIL culture media
TIL harvest
Day 14 to 21
Phenotypic characterization

FIG. 23

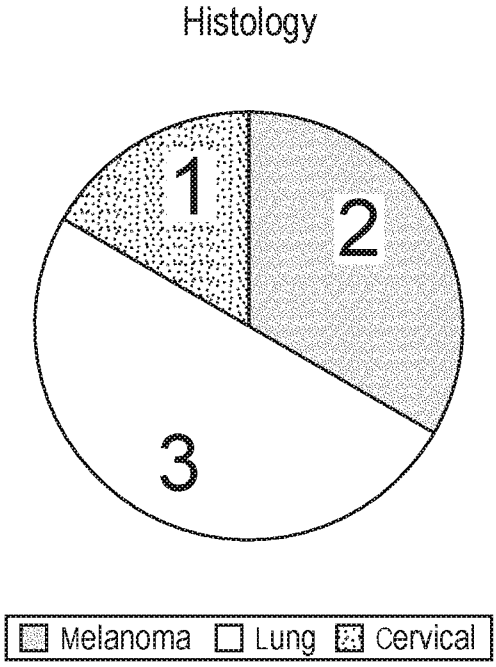

FIG. 24

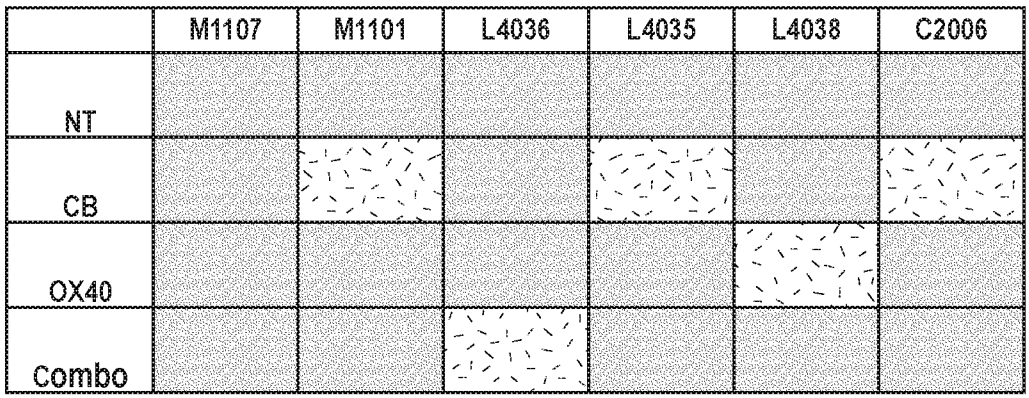

FIG. 25

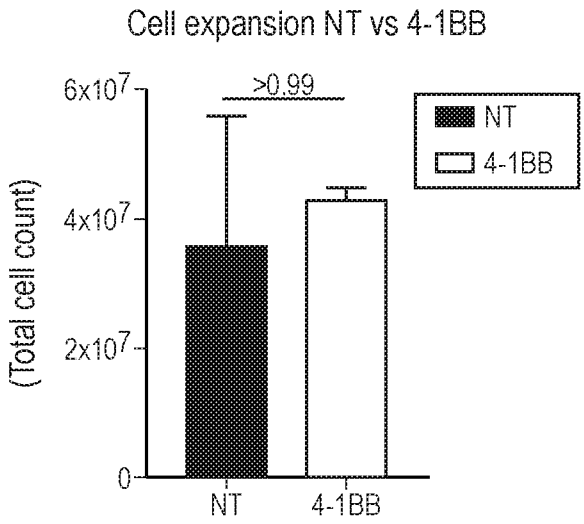
Cell expansion NT vs 4-1BB
(Total cell count)
6x10^7
4x10^7
2x10^7
0
>0.99
NT
4-1BB
NT
4-1BB

FIG. 26

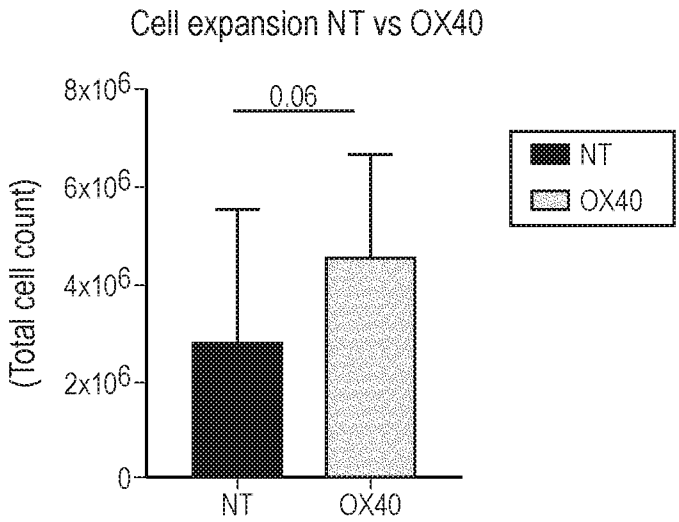
Cell expansion NT vs OX40
8x10^6
6x10^6
4x10^6
2x10^6
0
(Total cell count)
0.06
NT
OX40
NT
OX40

FIG. 27

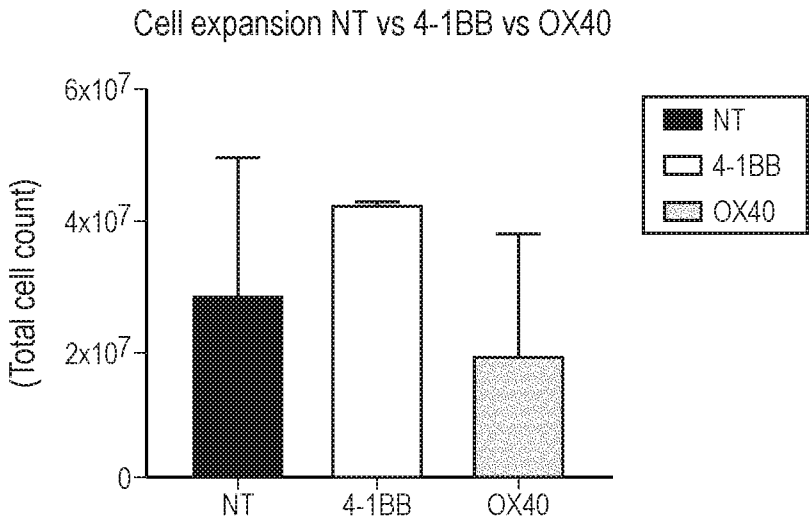
Cell expansion NT vs 4-1BB vs OX40
6x10^7
4x10^7
2x10^7
0
(Total cell count)
NT
4-1BB
OX40
NT
4-1BB
OX40

FIG. 28

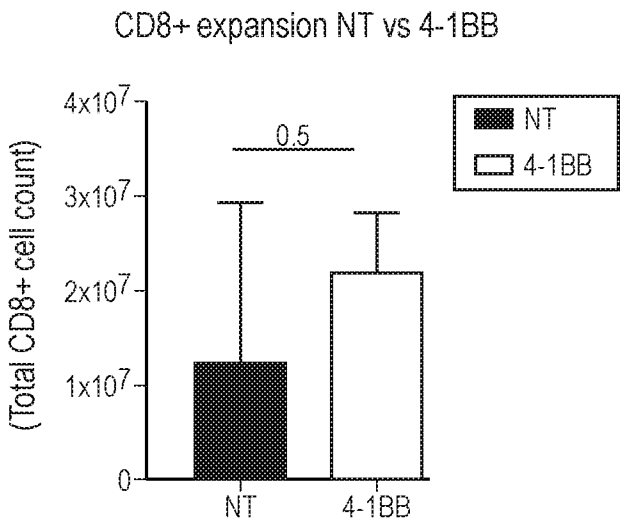
CD8+ expansion NT vs 4-1BB
(Total CD8+ cell count)
4x10^7
3x10^7
2x10^7
1x10^7
0
0.5
NT
4-1BB
NT
4-1BB

FIG. 29

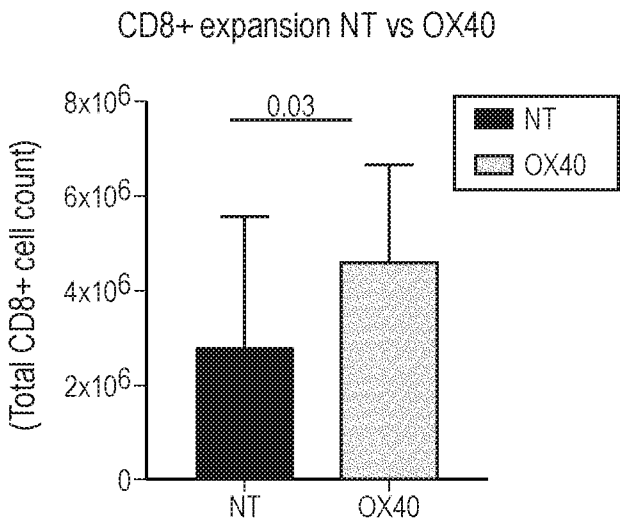
CD8+ expansion NT vs OX40
(Total CD8+ cell count)
8x10^6
6x10^6
4x10^6
2x10^6
0
0.03
NT
OX40
NT
OX40

FIG. 30

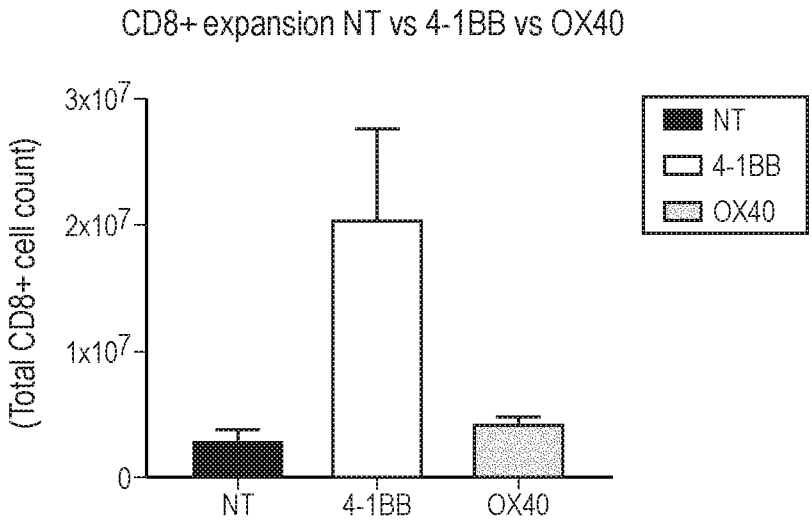
CD8+ expansion NT vs 4-1BB vs OX40
(Total CD8+ cell count)
3x10^7
2x10^7
1x10^7
0
NT
4-1BB
OX40
NT
4-1BB
OX40

FIG. 31

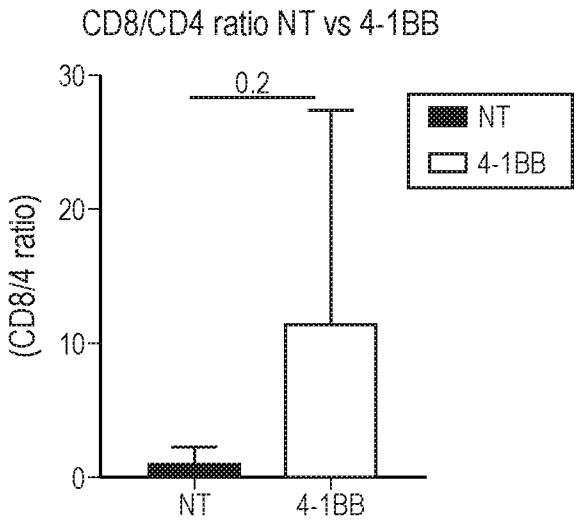

FIG. 32

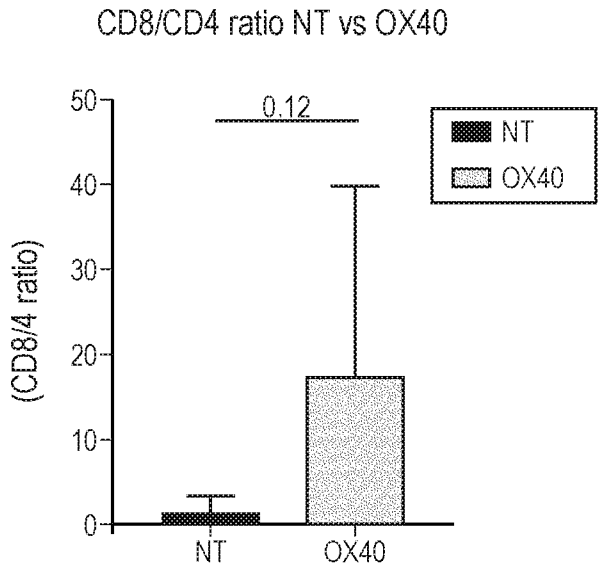
CD8/CD4 ratio NT vs OX40
0.12
NT
OX40
(CD8/4 ratio)
50
40
30
20
10
0
NT
OX40

FIG. 33

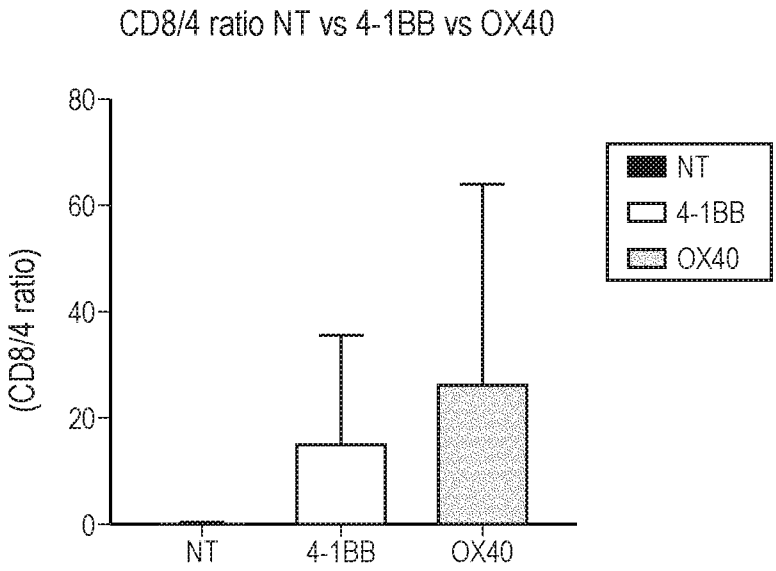
CD8/4 ratio NT vs 4-1BB vs OX40
(CD8/4 ratio)
80
60
40
20
0
NT
4-1BB
OX40
NT
4-1BB
OX40

FIG. 34

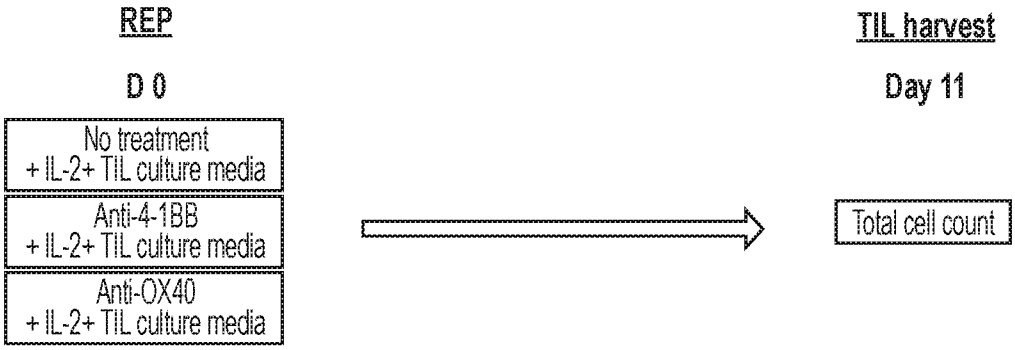
REP
D 0
No treatment
+ IL-2+ TIL culture media
Anti-4-1BB
+ IL-2+ TIL culture media
Anti-OX40
+ IL-2+ TIL culture media
TIL harvest
Day 11
Total cell count

FIG. 35

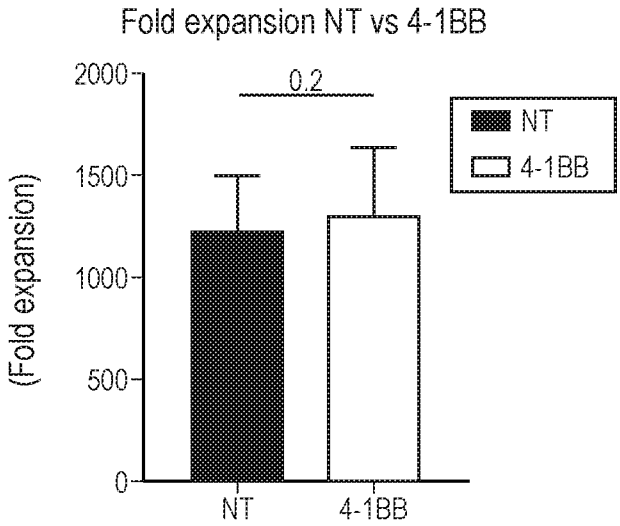
Fold expansion NT vs 4-1BB
0.2
NT
4-1BB
(Fold expansion)
2000
1500
1000
500
0
NT
4-1BB

FIG. 36

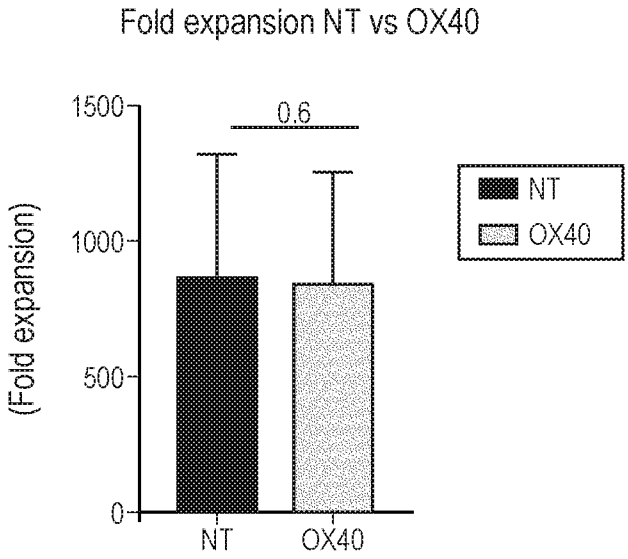
Fold expansion NT vs OX40
1500
1000
500
0
(Fold expansion)
0.6
NT
OX40
NT
OX40

FIG. 37

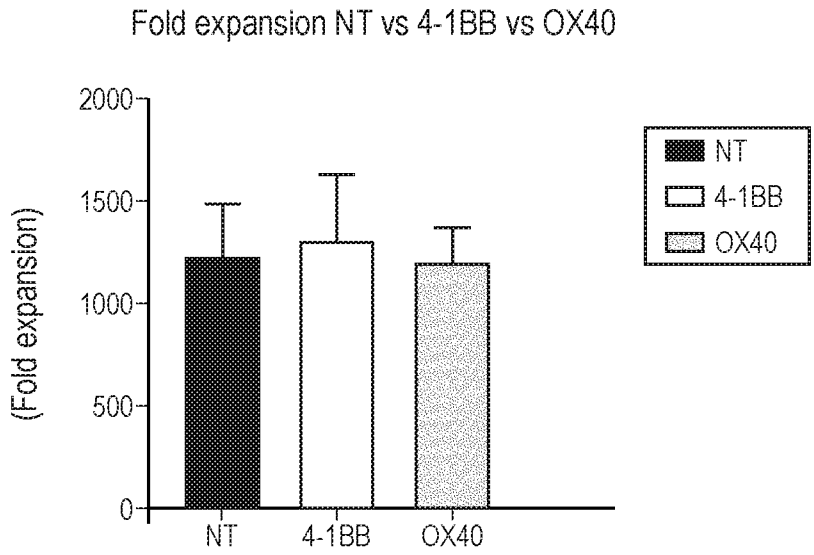
Fold expansion NT vs 4-1BB vs OX40
(Fold expansion)
2000
1500
1000
500
0
NT
4-1BB
OX40
NT
4-1BB
OX40

FIG. 38

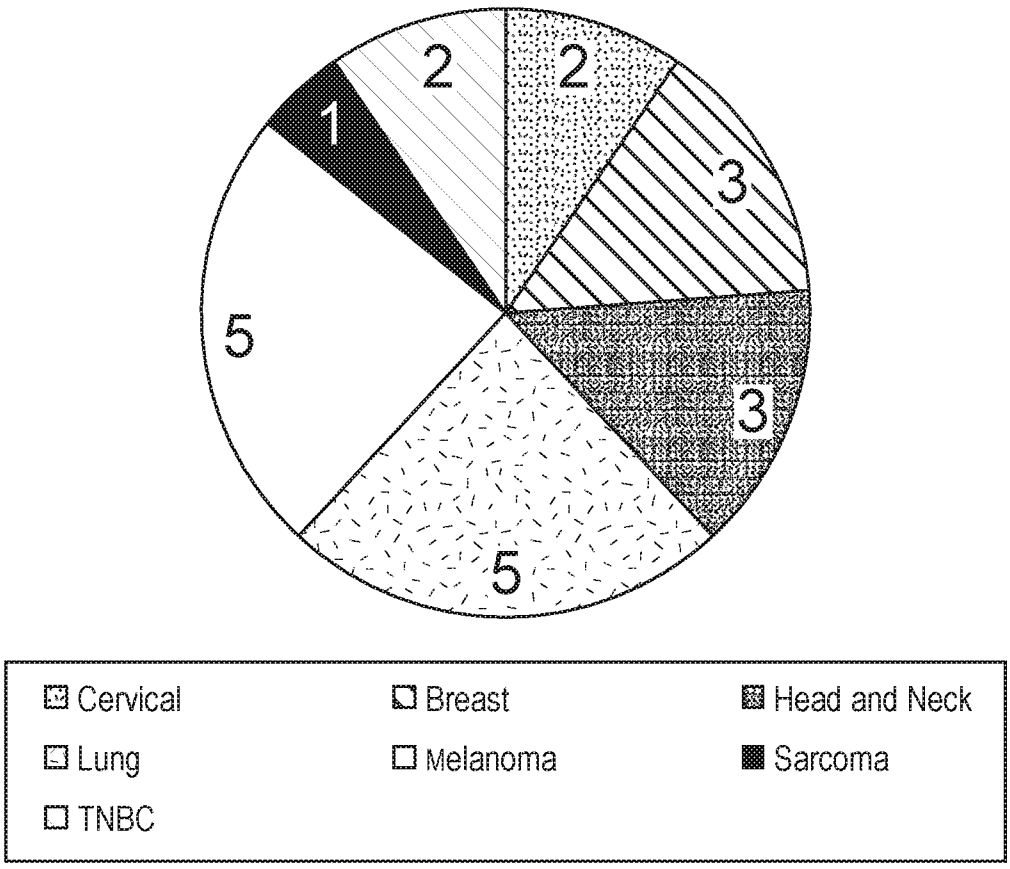
2
2
3
3
5
5
1
Cervical
Breast
Head and Neck
Lung
Melanoma
Sarcoma
TNBC

FIG. 39

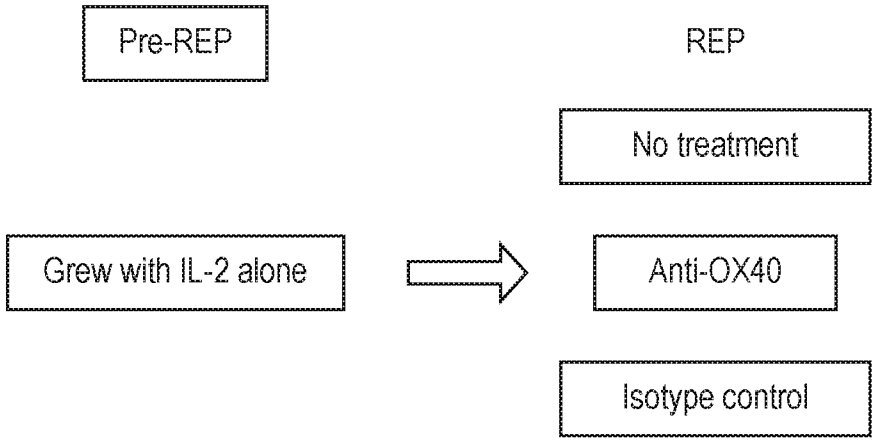
Pre-REP
REP
No treatment
Grew with IL-2 alone
Anti-OX40
Isotype control

FIG. 40

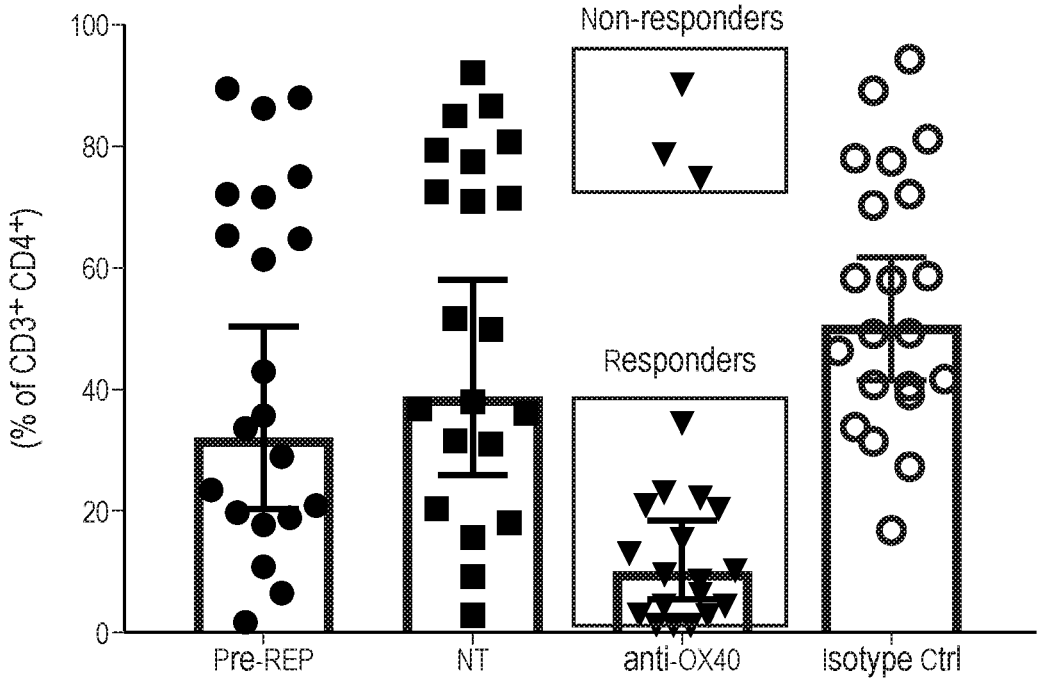
Non-responders
Responders
100
80
60
40
20
0
(% of CD3+ CD4+)
Pre-REP
NT
anti-OX40
Isotype Ctrl

FIG. 41

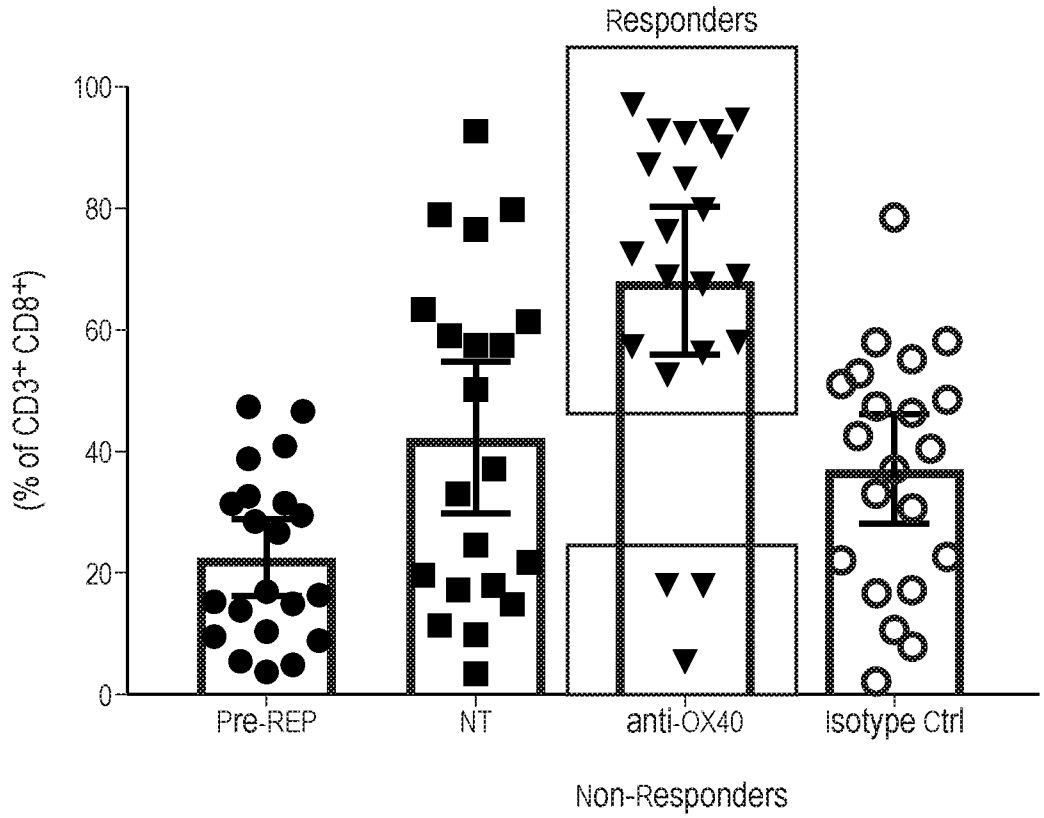
Responders
100
80
60
40
20
0
(% of CD3+ CD8+)
Pre-REP
NT
anti-OX40
Isotype Ctrl
Non-Responders

FIG. 42

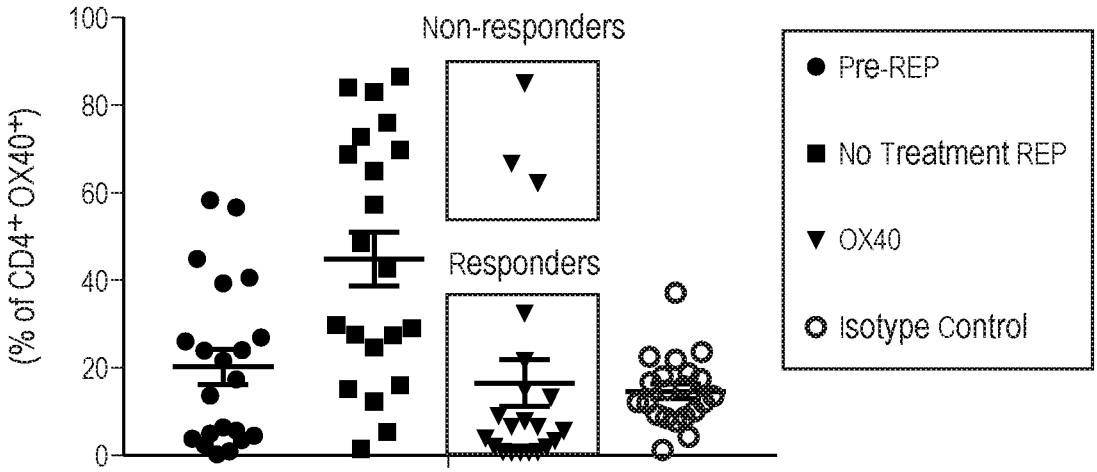
100
80
60
40
20
0
(% of CD4+ OX40+)
Non-responders
Responders
Pre-REP
No Treatment REP
OX40
Isotype Control

FIG. 43

	Anti-OX40 (ug/ml)						Isotype (ug/ml)
Responders	0.1	0.3	1	3	5	10	10
Non-responders	5	10	30				30

FIG. 44

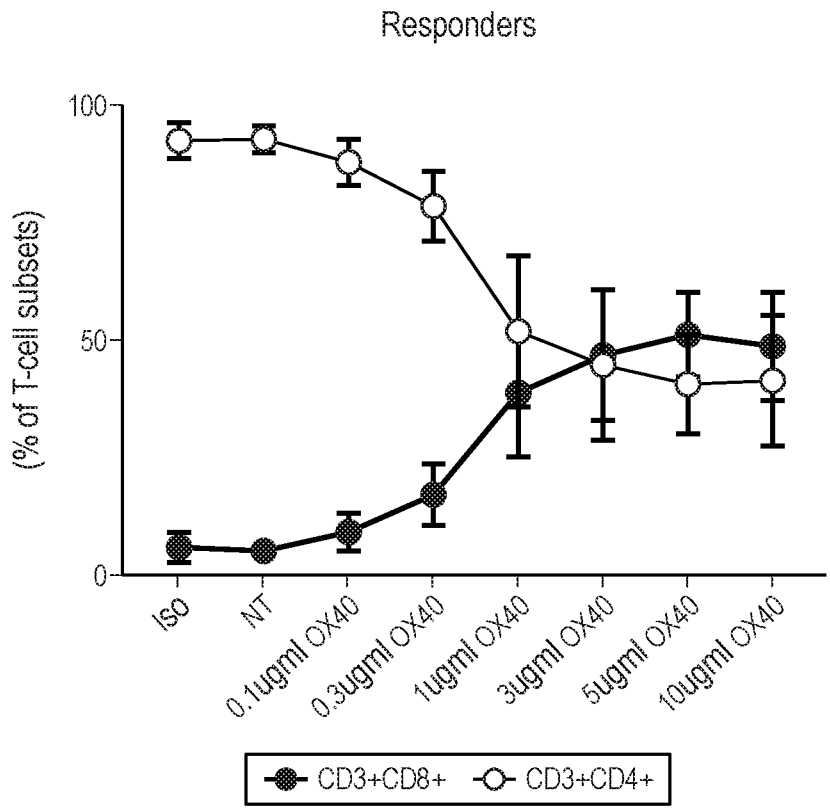
Responders
100
50
0
(% of T-cell subsets)
Iso
NT
0.1ugml OX40
0.3ugml OX40
1ugml OX40
3ugml OX40
5ugml OX40
10ugml OX40
CD3+CD8+
CD3+CD4+

FIG. 45

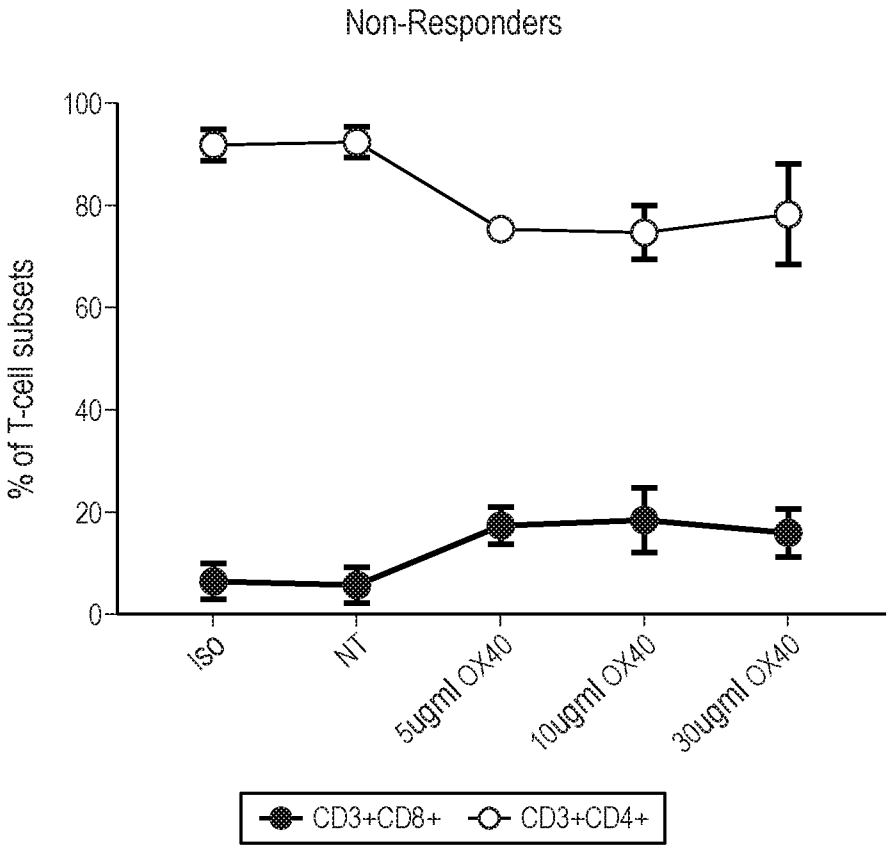
Non-Responders
% of T-cell subsets
100
80
60
40
20
0
ISO
NT
5ugml OX40
10ugml OX40
30ugml OX40
CD3+CD8+
CD3+CD4+

FIG. 46

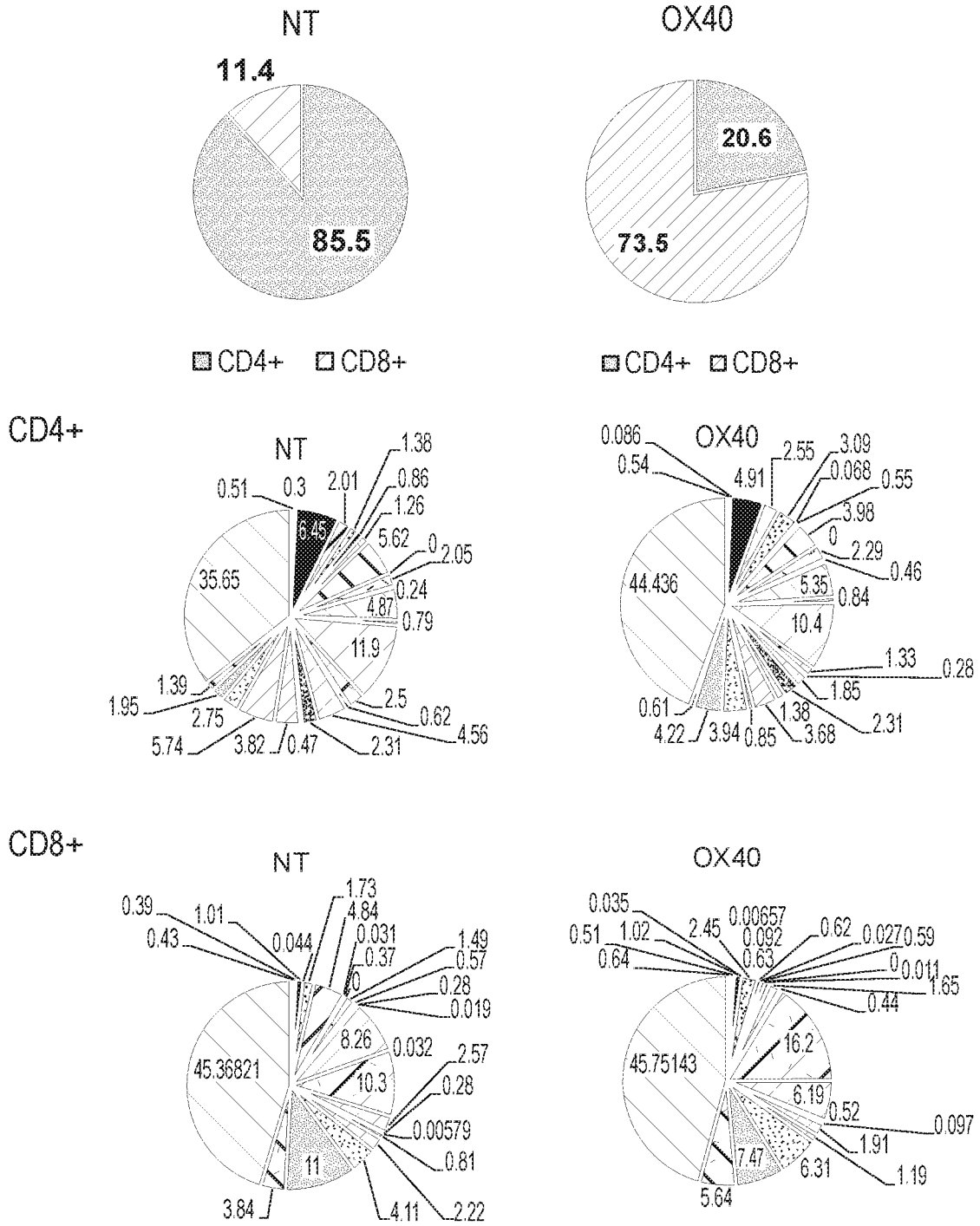
NT
11.4
85.5
CD4+ CD8+
OX40
20.6
73.5
CD4+ CD8+
CD4+
NT
1.38
0.86
1.26
5.62
0
2.05
0.24
0.79
11.9
2.5
0.62
4.56
2.31
0.47
3.82
5.74
1.95
1.39
2.75
35.65
4.87
6.45
0.51
0.3
2.01
OX40
0.086
0.54
4.91
2.55
3.09
0.068
0.55
3.98
0
2.29
0.46
0.84
10.4
1.33
0.28
1.85
2.31
1.38
3.68
0.85
3.94
4.22
0.61
44.436
5.35
CD8+
NT
1.73
4.84
0.031
0.37
0
1.49
0.57
0.28
0.019
0.032
2.57
0.28
0.00579
0.81
2.22
4.11
11
10.3
8.26
3.84
45.36821
0.39
1.01
0.43
0.044
OX40
0.035
0.51
1.02
2.45
0.00657
0.092
0.63
0.62
0.027
0.59
0.64
0
0.011
1.65
0.44
16.2
6.19
0.52
0.097
1.91
1.19
6.31
7.47
5.64
45.75143

FIG. 47

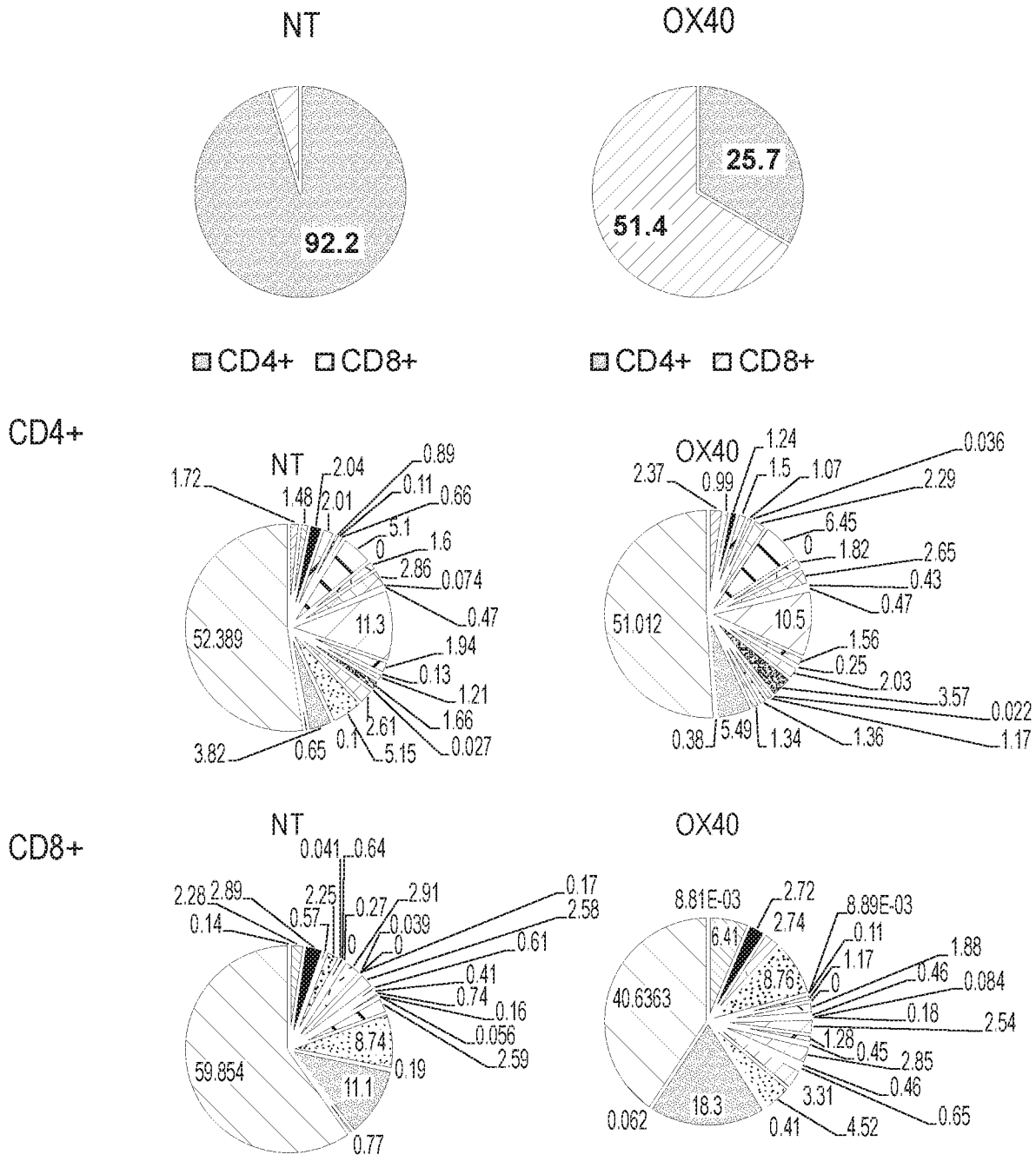
NT
OX40
92.2
25.7
51.4
CD4+ CD8+
CD4+ CD8+
CD4+
NT
1.72
1.48
2.04
2.01
0.89
0.11
0.66
5.1
0
1.6
2.86
0.074
0.47
11.3
52.389
1.94
0.13
1.21
1.66
0.027
2.61
0.1
5.15
0.65
3.82
OX40
2.37
0.99
1.24
1.5
1.07
0.036
2.29
6.45
0
1.82
2.65
0.43
0.47
10.5
51.012
1.56
0.25
2.03
3.57
0.022
1.17
0.38
5.49
1.34
1.36
CD8+
NT
0.041
0.64
2.28
2.89
0.14
2.25
0.57
0.27
2.91
0.039
0
0
0.17
2.58
0.61
0.41
0.74
0.16
0.056
2.59
8.74
0.19
59.854
11.1
0.77
OX40
8.81E-03
2.72
2.74
8.89E-03
0.11
1.17
0
6.41
8.76
40.6363
1.88
0.46
0.084
0.18
2.54
1.28
0.45
2.85
0.46
3.31
0.65
18.3
0.062
0.41
4.52

FIG. 48

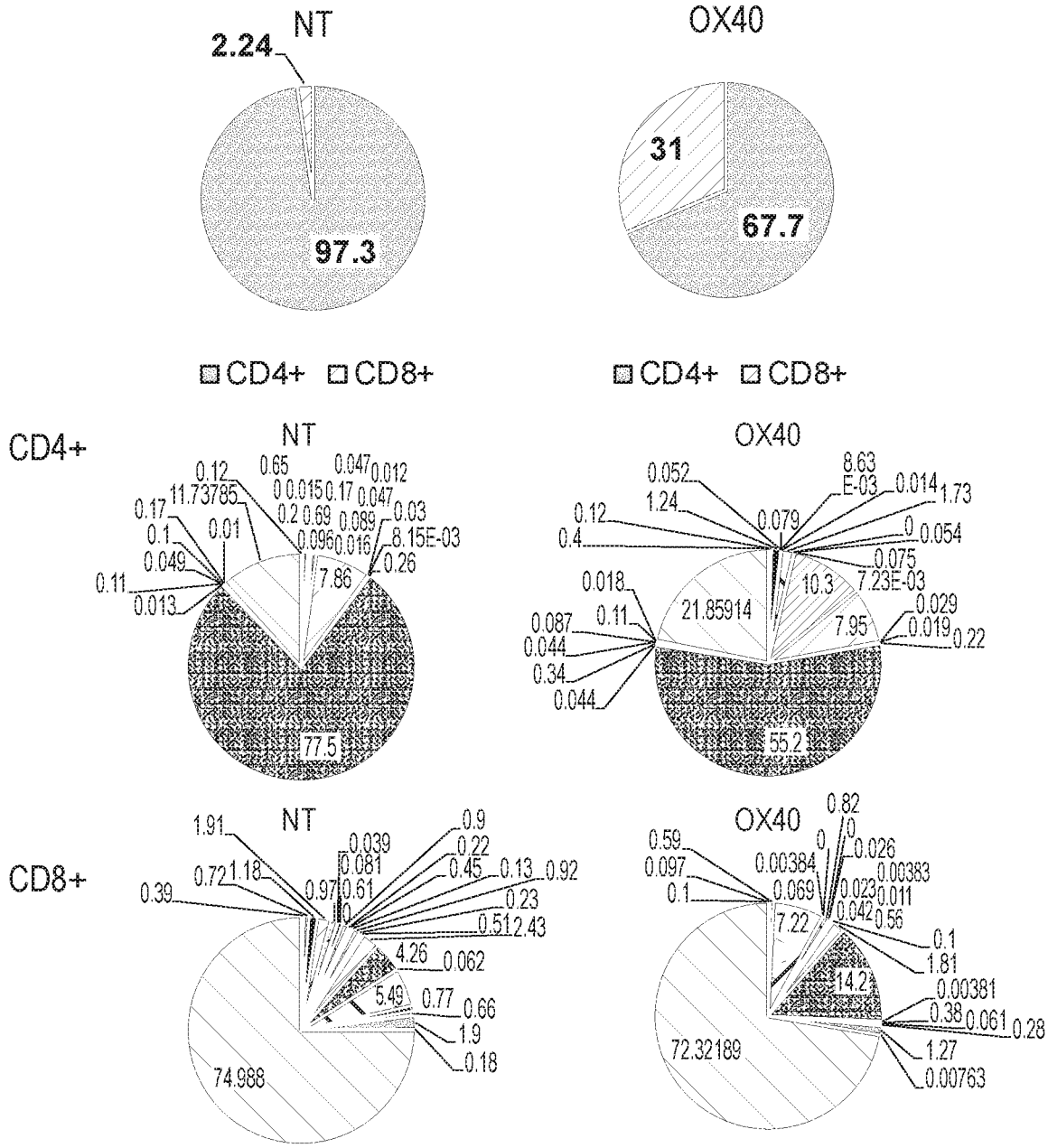
NT
2.24
97.3
OX40
31
67.7
CD4+ CD8+
CD4+ CD8+
CD4+
NT
0.12
0.65
0.047
0.012
11.73785
0.015
0.17
0.047
0.17
0.2
0.69
0.089
0.03
0.1
0.01
0.096
0.016
8.15E-03
0.049
0.26
0.11
7.86
0.013
77.5
OX40
0.052
8.63
E-03
0.014
1.73
1.24
0.12
0.079
0.4
0
0.054
0.075
0.018
10.3
7.23E-03
21.85914
0.029
0.087
0.11
7.95
0.019
0.044
0.22
0.34
0.044
55.2
CD8+
NT
1.91
0.9
0.039
0.22
0.081
0.72
1.18
0.45
0.13
0.92
0.39
0.97
0.61
0
0.23
0.51
2.43
4.26
0.062
5.49
0.77
0.66
1.9
0.18
74.988
OX40
0.82
0.59
0
0.026
0.097
0.00384
0.00383
0.1
0.069
0.023
0.011
0.042
0.56
7.22
0.1
1.81
14.2
0.00381
0.38
0.061
0.28
72.32189
1.27
0.00763

FIG. 49

SEQUENCE LISTING

<110> Iovance Biotherapeutics, Inc.

<120> Expansion of Tumor Infiltrating Lymphocytes (TILS) With Tumor Necrosis Factor Receptor Superfamily (TNFRSF) Agonists and Therapeutic Combinations of TILS and TNFRSF Agonists

<130> 116983-5008-WO

<160> 512

<170> PatentIn version 3.5

<210> 1
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Muromonab heavy chain

<400> 1

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30


Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Gly Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285
```

```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> 2
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Muromonab light chain

<400> 2

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                  10                  15


Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35                  40                  45


Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
65                  70                  75                  80


Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85                  90                  95


Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg Ala Asp Thr Ala Pro
            100                 105                 110


Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115                 120                 125


Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130                 135                 140


Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145                 150                 155                 160


Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175
```

```
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190


Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205


Asn Arg Asn Glu Cys
    210


<210>  3
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  recombinant human IL-2 (rhIL-2)

<400>  3

Met Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu
1               5                   10                  15


His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr
            20                  25                  30


Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro
        35                  40                  45


Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu
    50                  55                  60


Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His
65                  70                  75                  80


Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu
                85                  90                  95
```

Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr
100 105 110

Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser
115 120 125

Ile Ile Ser Thr Leu Thr
130

<210> 4
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> Aldesleukin

<400> 4

Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu
1 5 10 15

Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn
20 25 30

Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys
35 40 45

Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro
50 55 60

Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg
65 70 75 80

Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys
85 90 95

Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr
100 105 110

Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ser Gln Ser Ile Ile
        115   120   125

Ser Thr Leu Thr
    130

<210> 5
<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> recombinant human IL-4

(rhIL-4)

<400> 5

Met His Lys Cys Asp Ile Thr Leu Gln Glu Ile Ile Lys Thr Leu Asn
1   5   10   15

Ser Leu Thr Glu Gln Lys Thr Leu Cys Thr Glu Leu Thr Val Thr Asp
            20   25   30

Ile Phe Ala Ala Ser Lys Asn Thr Thr Glu Lys Glu Thr Phe Cys Arg
        35   40   45

Ala Ala Thr Val Leu Arg Gln Phe Tyr Ser His His Glu Lys Asp Thr
    50   55   60

Arg Cys Leu Gly Ala Thr Ala Gln Gln Phe His Arg His Lys Gln Leu
65   70   75   80

Ile Arg Phe Leu Lys Arg Leu Asp Arg Asn Leu Trp Gly Leu Ala Gly
                85   90   95

Leu Asn Ser Cys Pro Val Lys Glu Ala Asn Gln Ser Thr Leu Glu Asn
            100   105   110

Phe Leu Glu Arg Leu Lys Thr Ile Met Arg Glu Lys Tyr Ser Lys Cys
115 120 125

Ser Ser
130

<210> 6
<211> 153
<212> PRT
<213> Artificial Sequence

<220>
<223> recombinant human IL-7

(rhIL-7)

<400> 6

Met Asp Cys Asp Ile Glu Gly Lys Asp Gly Lys Gln Tyr Glu Ser Val
1 5 10 15

Leu Met Val Ser Ile Asp Gln Leu Leu Asp Ser Met Lys Glu Ile Gly
20 25 30

Ser Asn Cys Leu Asn Asn Glu Phe Asn Phe Phe Lys Arg His Ile Cys
35 40 45

Asp Ala Asn Lys Glu Gly Met Phe Leu Phe Arg Ala Ala Arg Lys Leu
50 55 60

Arg Gln Phe Leu Lys Met Asn Ser Thr Gly Asp Phe Asp Leu His Leu
65 70 75 80

Leu Lys Val Ser Glu Gly Thr Thr Ile Leu Leu Asn Cys Thr Gly Gln
85 90 95

Val Lys Gly Arg Lys Pro Ala Ala Leu Gly Glu Ala Gln Pro Thr Lys
100 105 110

Ser Leu Glu Glu Asn Lys Ser Leu Lys Glu Gln Lys Lys Leu Asn Asp
        115   120   125

Leu Cys Phe Leu Lys Arg Leu Leu Gln Glu Ile Lys Thr Cys Trp Asn
    130   135   140

Lys Ile Leu Met Gly Thr Lys Glu His
145   150

<210> 7
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> recombinant human IL-15

(rhIL-15)

<400> 7

Met Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
1   5   10   15

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
            20   25   30

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
        35   40   45

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
    50   55   60

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
65   70   75   80

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
                85   90   95

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
100 105 110

Asn Thr Ser
115

<210> 8
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> recombinant human IL-21

(rhIL-21)

<400> 8

Met Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val
1 5 10 15

Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro
20 25 30

Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys
35 40 45

Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg
50 55 60

Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser Thr
65 70 75 80

Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp
85 90 95

Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser
100 105 110

```
Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly
        115                 120                 125


Ser Glu Asp Ser
    130


<210>  9
<211>  255
<212>  PRT
<213>  Homo Sapiens

<400>  9

Met Gly Asn Ser Cys Tyr Asn Ile Val Ala Thr Leu Leu Leu Val Leu
1               5                   10                  15


Asn Phe Glu Arg Thr Arg Ser Leu Gln Asp Pro Cys Ser Asn Cys Pro
            20                  25                  30


Ala Gly Thr Phe Cys Asp Asn Asn Arg Asn Gln Ile Cys Ser Pro Cys
        35                  40                  45


Pro Pro Asn Ser Phe Ser Ser Ala Gly Gly Gln Arg Thr Cys Asp Ile
    50                  55                  60


Cys Arg Gln Cys Lys Gly Val Phe Arg Thr Arg Lys Glu Cys Ser Ser
65                  70                  75                  80


Thr Ser Asn Ala Glu Cys Asp Cys Thr Pro Gly Phe His Cys Leu Gly
                85                  90                  95


Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu
            100                 105                 110


Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln
        115                 120                 125
```

```
Lys Arg Gly Ile Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Lys
    130                 135                 140


Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro
145                 150                 155                 160


Ser Pro Ala Asp Leu Ser Pro Gly Ala Ser Ser Val Thr Pro Pro Ala
                165                 170                 175


Pro Ala Arg Glu Pro Gly His Ser Pro Gln Ile Ile Ser Phe Phe Leu
            180                 185                 190


Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu
        195                 200                 205


Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
    210                 215                 220


Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
225                 230                 235                 240


Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
                245                 250                 255


<210>  10
<211>  256
<212>  PRT
<213>  Mus Musculus

<400>  10

Met Gly Asn Asn Cys Tyr Asn Val Val Val Ile Val Leu Leu Leu Val
1               5                   10                  15


Gly Cys Glu Lys Val Gly Ala Val Gln Asn Ser Cys Asp Asn Cys Gln
            20                  25                  30
```

```
Pro Gly Thr Phe Cys Arg Lys Tyr Asn Pro Val Cys Lys Ser Cys Pro
        35                  40                  45

Pro Ser Thr Phe Ser Ser Ile Gly Gly Gln Pro Asn Cys Asn Ile Cys
    50                  55                  60

Arg Val Cys Ala Gly Tyr Phe Arg Phe Lys Lys Phe Cys Ser Ser Thr
65                  70                  75                  80

His Asn Ala Glu Cys Glu Cys Ile Glu Gly Phe His Cys Leu Gly Pro
                85                  90                  95

Gln Cys Thr Arg Cys Glu Lys Asp Cys Arg Pro Gly Gln Glu Leu Thr
            100                 105                 110

Lys Gln Gly Cys Lys Thr Cys Ser Leu Gly Thr Phe Asn Asp Gln Asn
        115                 120                 125

Gly Thr Gly Val Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Arg
    130                 135                 140

Ser Val Leu Lys Thr Gly Thr Thr Glu Lys Asp Val Val Cys Gly Pro
145                 150                 155                 160

Pro Val Val Ser Phe Ser Pro Ser Thr Thr Ile Ser Val Thr Pro Glu
                165                 170                 175

Gly Gly Pro Gly Gly His Ser Leu Gln Val Leu Thr Leu Phe Leu Ala
            180                 185                 190

Leu Thr Ser Ala Leu Leu Leu Ala Leu Ile Phe Ile Thr Leu Leu Phe
        195                 200                 205

Ser Val Leu Lys Trp Ile Arg Lys Lys Phe Pro His Ile Phe Lys Gln
    210                 215                 220
```

Pro Phe Lys Lys Thr Thr Gly Ala Ala Gln Glu Glu Asp Ala Cys Ser
225 230 235 240

Cys Arg Cys Pro Gln Glu Glu Glu Gly Gly Gly Gly Gly Tyr Glu Leu
245 250 255

<210> 11
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain for utomilumab

<400> 11

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

```
Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
            180                 185                 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
    210                 215                 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320
```

```
Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
            340                 345                 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 12
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain for utomilumab

<400> 12

```
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1               5                   10                  15
```

```
Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45

Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu
                85                  90                  95

Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
```

Ala Pro Thr Glu Cys Ser
    210

<210> 13
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region for utomilumab

<400> 13

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr
            20   25   30

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45

Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser
        115

<210> 14
<211> 108

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region for utomilumab

<400> 14

```
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1               5                   10                  15


Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala
            20                  25                  30


His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45


Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu
                85                  90                  95


Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 15
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for utomilumab

<400> 15

```
Ser Thr Tyr Trp Ile Ser
1               5
```

<210> 16
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for utomilumab

<400> 16

Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 17
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for utomilumab

<400> 17

Arg Gly Tyr Gly Ile Phe Asp Tyr
1 5

<210> 18
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for utomilumab

<400> 18

Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala His
1 5 10

<210> 19
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for utomilumab

<400> 19

Gln Asp Lys Asn Arg Pro Ser
1 5

<210> 20
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for utomilumab

<400> 20

Ala Thr Tyr Thr Gly Phe Gly Ser Leu Ala Val
1 5 10

<210> 21
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain for urelumab

<400> 21

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile
35 40 45

```
Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
    210                 215                 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
225                 230                 235                 240
```

```
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430
```

```
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210>  22
<211>  216
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain for urelumab

<400>  22

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95


Ala Leu Thr Phe Cys Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val
            100                 105                 110


Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125
```

```
Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140


Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160


Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175


Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190


Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205


Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  23
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable heavy chain for urelumab

<400>  23

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15


Val Leu Ser Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys
            20                  25                  30


Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe
        35                  40                  45


Ser Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu
    50                  55                  60
```

```
Glu Trp Ile Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro
65                  70                  75                  80


Ser Leu Glu Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95


Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110


Tyr Cys Ala Arg Asp Tyr Gly Pro
        115                 120


<210>  24
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable light chain for urelumab

<400>  24

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15


Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45


Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60


Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80
```

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
100 105 110

<210> 25
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for urelumab

<400> 25

Gly Tyr Tyr Trp Ser
1 5

<210> 26
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for urelumab

<400> 26

Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu Ser
1 5 10 15

<210> 27
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for urelumab

<400> 27

Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu
1 5 10

<210> 28
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for urelumab

<400> 28

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 29
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for urelumab

<400> 29

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 30
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for urelumab

<400> 30

Gln Gln Arg Ser Asp Trp Pro Pro Ala Leu Thr
1 5 10

<210> 31
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc domain

<400> 31

```
Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
1               5                  10                  15


Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            20                  25                  30


Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        35                  40                  45


Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
    50                  55                  60


Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
65                  70                  75                  80


Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
                85                  90                  95


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
            100                 105                 110


Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
        115                 120                 125


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    130                 135                 140


Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
145                 150                 155                 160


Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                165                 170                 175
```

```
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            180                 185                 190


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        195                 200                 205


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    210                 215                 220


Ser Leu Ser Pro Gly Lys
225                 230


<210>  32
<211>  22
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  linker

<400>  32

Gly Gly Pro Gly Ser Ser Lys Ser Cys Asp Lys Thr His Thr Cys Pro
1               5                   10                  15


Pro Cys Pro Ala Pro Glu
            20


<210>  33
<211>  22
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  linker

<400>  33

Gly Gly Ser Gly Ser Ser Lys Ser Cys Asp Lys Thr His Thr Cys Pro
1               5                   10                  15
```

Pro Cys Pro Ala Pro Glu
            20

<210> 34
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 34

Gly Gly Pro Gly Ser Ser Ser Ser Ser Ser Ser Lys Ser Cys Asp Lys
1   5   10   15

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20   25

<210> 35
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 35

Gly Gly Ser Gly Ser Ser Ser Ser Ser Ser Ser Lys Ser Cys Asp Lys
1   5   10   15

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20   25

<210> 36
<211> 29
<212> PRT
<213> Artificial Sequence

<220>

<223> linker

<400> 36

Gly Gly Pro Gly Ser Ser Ser Ser Ser Ser Ser Ser Ser Lys Ser Cys
1 5 10 15

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
20 25

<210> 37
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 37

Gly Gly Ser Gly Ser Ser Ser Ser Ser Ser Ser Ser Ser Lys Ser Cys
1 5 10 15

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
20 25

<210> 38
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 38

Gly Gly Pro Gly Ser Ser Gly Ser Gly Ser Ser Asp Lys Thr His Thr
1 5 10 15

Cys Pro Pro Cys Pro Ala Pro Glu
20

<210> 39
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 39

Gly Gly Pro Gly Ser Ser Gly Ser Gly Ser Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu
20

<210> 40
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 40

Gly Gly Pro Ser Ser Ser Gly Ser Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Glu
20

<210> 41
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 41

Gly Gly Ser Ser Ser Ser Ser Ser Ser Ser Gly Ser Asp Lys Thr His
1 5 10 15

```
Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20                  25


<210>  42
<211>  246
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fc domain

<400>  42

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15


Ala Gly Asn Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            20                  25                  30


Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        35                  40                  45


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    50                  55                  60


Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
65                  70                  75                  80


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                85                  90                  95


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            100                 105                 110


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
        115                 120                 125
```

```
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    130                 135                 140

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
145                 150                 155                 160

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                165                 170                 175

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            180                 185                 190

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        195                 200                 205

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    210                 215                 220

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
225                 230                 235                 240

Leu Ser Leu Ser Pro Gly
                245
```

<210> 43
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 43

```
Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1               5                   10
```

<210> 44
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 44

Ser Ser Ser Ser Ser Ser Gly Ser Gly Ser Gly Ser
1 5 10

<210> 45
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 45

Ser Ser Ser Ser Ser Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

<210> 46
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> 4-1BBL

<400> 46

Met Glu Tyr Ala Ser Asp Ala Ser Leu Asp Pro Glu Ala Pro Trp Pro
1 5 10 15

Pro Ala Pro Arg Ala Arg Ala Cys Arg Val Leu Pro Trp Ala Leu Val
20 25 30

Ala Gly Leu Leu Leu Leu Leu Leu Leu Ala Ala Ala Cys Ala Val Phe
35 40 45

```
Leu Ala Cys Pro Trp Ala Val Ser Gly Ala Arg Ala Ser Pro Gly Ser
    50                  55                  60

Ala Ala Ser Pro Arg Leu Arg Glu Gly Pro Glu Leu Ser Pro Asp Asp
65                  70                  75                  80

Pro Ala Gly Leu Leu Asp Leu Arg Gln Gly Met Phe Ala Gln Leu Val
                85                  90                  95

Ala Gln Asn Val Leu Leu Ile Asp Gly Pro Leu Ser Trp Tyr Ser Asp
            100                 105                 110

Pro Gly Leu Ala Gly Val Ser Leu Thr Gly Gly Leu Ser Tyr Lys Glu
        115                 120                 125

Asp Thr Lys Glu Leu Val Val Ala Lys Ala Gly Val Tyr Tyr Val Phe
    130                 135                 140

Phe Gln Leu Glu Leu Arg Arg Val Val Ala Gly Glu Gly Ser Gly Ser
145                 150                 155                 160

Val Ser Leu Ala Leu His Leu Gln Pro Leu Arg Ser Ala Ala Gly Ala
                165                 170                 175

Ala Ala Leu Ala Leu Thr Val Asp Leu Pro Pro Ala Ser Ser Glu Ala
            180                 185                 190

Arg Asn Ser Ala Phe Gly Phe Gln Gly Arg Leu Leu His Leu Ser Ala
        195                 200                 205

Gly Gln Arg Leu Gly Val His Leu His Thr Glu Ala Arg Ala Arg His
    210                 215                 220

Ala Trp Gln Leu Thr Gln Gly Ala Thr Val Leu Gly Leu Phe Arg Val
225                 230                 235                 240
```

Thr Pro Glu Ile Pro Ala Gly Leu Pro Ser Pro Arg Ser Glu
245 250

<210> 47
<211> 168
<212> PRT
<213> Artificial Sequence

<220>
<223> 4-1BBL soluble domain

<400> 47

Leu Arg Gln Gly Met Phe Ala Gln Leu Val Ala Gln Asn Val Leu Leu
1 5 10 15

Ile Asp Gly Pro Leu Ser Trp Tyr Ser Asp Pro Gly Leu Ala Gly Val
20 25 30

Ser Leu Thr Gly Gly Leu Ser Tyr Lys Glu Asp Thr Lys Glu Leu Val
35 40 45

Val Ala Lys Ala Gly Val Tyr Tyr Val Phe Phe Gln Leu Glu Leu Arg
50 55 60

Arg Val Val Ala Gly Glu Gly Ser Gly Ser Val Ser Leu Ala Leu His
65 70 75 80

Leu Gln Pro Leu Arg Ser Ala Ala Gly Ala Ala Ala Leu Ala Leu Thr
85 90 95

Val Asp Leu Pro Pro Ala Ser Ser Glu Ala Arg Asn Ser Ala Phe Gly
100 105 110

Phe Gln Gly Arg Leu Leu His Leu Ser Ala Gly Gln Arg Leu Gly Val
115 120 125

His Leu His Thr Glu Ala Arg Ala Arg His Ala Trp Gln Leu Thr Gln
130 135 140

```
Gly Ala Thr Val Leu Gly Leu Phe Arg Val Thr Pro Glu Ile Pro Ala
145                 150                 155                 160


Gly Leu Pro Ser Pro Arg Ser Glu
                165


<210>  48
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable heavy chain for 4B4-1-1 version 1

<400>  48

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
            20                  25                  30


Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Val Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn Pro Gly Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ser Phe Thr Thr Ala Arg Gly Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110
```

Thr Leu Val Thr Val Ser
        115

<210> 49
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> variable light chain for 4B4-1-1 version 1

<400> 49

Asp Ile Val Met Thr Gln Ser Pro Ala Thr Gln Ser Val Thr Pro Gly
1   5   10   15

Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Asp Tyr
            20   25   30

Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro
65   70   75   80

Glu Asp Val Gly Val Tyr Tyr Cys Gln Asp Gly His Ser Phe Pro Pro
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 50
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<223> variable heavy chain for 4B4-1-1 version 2

<400> 50

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Val Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Gly Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Phe Thr Thr Ala Arg Gly Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 51
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> variable light chain for 4B4-1-1 version 2

<400> 51

Asp Ile Val Met Thr Gln Ser Pro Ala Thr Gln Ser Val Thr Pro Gly
1 5 10 15

```
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Asp Tyr
            20                  25                  30

Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro
65                  70                  75                  80

Glu Asp Val Gly Val Tyr Tyr Cys Gln Asp Gly His Ser Phe Pro Pro
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105


<210>  52
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable heavy chain for H39E3-2

<400>  52

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45
```

```
Ser Asp Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ala Asp Ile Lys Asn Asp Gly Ser Tyr Thr Asn Tyr Ala
65                  70                  75                  80


Pro Ser Leu Thr Asn Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95


Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Glu Leu Thr
        115                 120


<210>  53
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable light chain for H39E3-2

<400>  53

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15


Asp Thr Thr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
            20                  25                  30


Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
        35                  40                  45


Leu Leu Ser Ser Gly Asn Gln Lys Asn Tyr Leu Trp Tyr Gln Gln Lys
    50                  55                  60


Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Arg Gln
65                  70                  75                  80
```

```
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95


Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
            100                 105


<210>  54
<211>  277
<212>  PRT
<213>  Homo Sapiens

<400>  54

Met Cys Val Gly Ala Arg Arg Leu Gly Arg Gly Pro Cys Ala Ala Leu
1               5                   10                  15


Leu Leu Leu Gly Leu Gly Leu Ser Thr Val Thr Gly Leu His Cys Val
            20                  25                  30


Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His Glu Cys Arg Pro
        35                  40                  45


Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln Asn Thr Val Cys
    50                  55                  60


Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val Ser Ser Lys Pro
65                  70                  75                  80


Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly Ser Glu Arg Lys
                85                  90                  95


Gln Leu Cys Thr Ala Thr Gln Asp Thr Val Cys Arg Cys Arg Ala Gly
            100                 105                 110


Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp Cys Ala Pro Cys
        115                 120                 125
```

```
Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala Cys Lys Pro Trp
    130                 135                 140


Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln Pro Ala Ser Asn
145                 150                 155                 160


Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro Ala Thr Gln Pro
                165                 170                 175


Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr Val Gln Pro Thr
            180                 185                 190


Glu Ala Trp Pro Arg Thr Ser Gln Gly Pro Ser Thr Arg Pro Val Glu
        195                 200                 205


Val Pro Gly Gly Arg Ala Val Ala Ala Ile Leu Gly Leu Gly Leu Val
    210                 215                 220


Leu Gly Leu Leu Gly Pro Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu
225                 230                 235                 240


Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
                245                 250                 255


Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
            260                 265                 270


Thr Leu Ala Lys Ile
        275


<210>  55
<211>  272
<212>  PRT
<213>  Mus Musculus

<400>  55
```

```
Met Tyr Val Trp Val Gln Gln Pro Thr Ala Leu Leu Leu Leu Gly Leu
1               5                  10                  15

Thr Leu Gly Val Thr Ala Arg Arg Leu Asn Cys Val Lys His Thr Tyr
            20                  25                  30

Pro Ser Gly His Lys Cys Cys Arg Glu Cys Gln Pro Gly His Gly Met
        35                  40                  45

Val Ser Arg Cys Asp His Thr Arg Asp Thr Leu Cys His Pro Cys Glu
    50                  55                  60

Thr Gly Phe Tyr Asn Glu Ala Val Asn Tyr Asp Thr Cys Lys Gln Cys
65                  70                  75                  80

Thr Gln Cys Asn His Arg Ser Gly Ser Glu Leu Lys Gln Asn Cys Thr
                85                  90                  95

Pro Thr Gln Asp Thr Val Cys Arg Cys Arg Pro Gly Thr Gln Pro Arg
            100                 105                 110

Gln Asp Ser Gly Tyr Lys Leu Gly Val Asp Cys Val Pro Cys Pro Pro
        115                 120                 125

Gly His Phe Ser Pro Gly Asn Asn Gln Ala Cys Lys Pro Trp Thr Asn
    130                 135                 140

Cys Thr Leu Ser Gly Lys Gln Thr Arg His Pro Ala Ser Asp Ser Leu
145                 150                 155                 160

Asp Ala Val Cys Glu Asp Arg Ser Leu Leu Ala Thr Leu Leu Trp Glu
                165                 170                 175

Thr Gln Arg Pro Thr Phe Arg Pro Thr Thr Val Gln Ser Thr Thr Val
            180                 185                 190
```

```
Trp Pro Arg Thr Ser Glu Leu Pro Ser Pro Pro Thr Leu Val Thr Pro
        195                 200                 205


Glu Gly Pro Ala Phe Ala Val Leu Leu Gly Leu Gly Leu Gly Leu Leu
    210                 215                 220


Ala Pro Leu Thr Val Leu Leu Ala Leu Tyr Leu Leu Arg Lys Ala Trp
225                 230                 235                 240


Arg Leu Pro Asn Thr Pro Lys Pro Cys Trp Gly Asn Ser Phe Arg Thr
                245                 250                 255


Pro Ile Gln Glu Glu His Thr Asp Ala His Phe Thr Leu Ala Lys Ile
            260                 265                 270


<210>  56
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain for tavolixizumab

<400>  56

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Ser Gly
            20                  25                  30


Tyr Trp Asn Trp Ile Arg Lys His Pro Gly Lys Gly Leu Glu Tyr Ile
        35                  40                  45


Gly Tyr Ile Ser Tyr Asn Gly Ile Thr Tyr His Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Thr Ile Asn Arg Asp Thr Ser Lys Asn Gln Tyr Ser Leu
65                  70                  75                  80
```

```
Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Tyr Lys Tyr Asp Tyr Asp Gly Gly His Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270
```

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Lys
    450
```

<210> 57
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain for tavolixizumab

<400> 57

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Thr Ser Lys Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Trp
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140
```

```
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  58
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region for tavolixizumab

<400>  58

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Ser Gly
            20                  25                  30


Tyr Trp Asn Trp Ile Arg Lys His Pro Gly Lys Gly Leu Glu Tyr Ile
        35                  40                  45


Gly Tyr Ile Ser Tyr Asn Gly Ile Thr Tyr His Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Thr Ile Asn Arg Asp Thr Ser Lys Asn Gln Tyr Ser Leu
65                  70                  75                  80
```

```
Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Tyr Lys Tyr Asp Tyr Asp Gly Gly His Ala Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr
        115


<210>  59
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region for tavolixizumab

<400>  59

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Thr Ser Lys Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Trp
                85                  90                  95
```

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 60
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for tavolixizumab

<400> 60

Gly Ser Phe Ser Ser Gly Tyr Trp Asn
1 5

<210> 61
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for tavolixizumab

<400> 61

Tyr Ile Gly Tyr Ile Ser Tyr Asn Gly Ile Thr Tyr His
1 5 10

<210> 62
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for tavolixizumab

<400> 62

Arg Tyr Lys Tyr Asp Tyr Asp Gly Gly His Ala Met Asp Tyr
1 5 10

<210> 63
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for tavolixizumab

<400> 63

Gln Asp Ile Ser Asn Tyr Leu Asn
1 5

<210> 64
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for tavolixizumab

<400> 64

Leu Leu Ile Tyr Tyr Thr Ser Lys Leu His Ser
1 5 10

<210> 65
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for tavolixizumab

<400> 65

Gln Gln Gly Ser Ala Leu Pro Trp
1 5

<210> 66
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain for 11D4

<400> 66

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Asp Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ser Gly Trp Tyr Leu Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
```

```
Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
    210                 215                 220

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
            260                 265                 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
    290                 295                 300

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
            340                 345                 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380
```

```
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385                 390                 395                 400


Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
                405                 410                 415


Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            420                 425                 430


Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440


<210>  67
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain for 11D4

<400>  67

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  68
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region for 11D4

<400>  68

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Asp Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Ser Gly Trp Tyr Leu Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  69
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region for 11D4

<400>  69

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30
```

```
Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  70
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain CDR1 for 11D4

<400>  70

Ser Tyr Ser Met Asn
1               5


<210>  71
<211>  17
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain CDR2 for 11D4

<400>  71

Tyr Ile Ser Ser Ser Ser Ser Thr Ile Asp Tyr Ala Asp Ser Val Lys
1               5                   10                  15
```

Gly

<210> 72
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for 11D4

<400> 72

Glu Ser Gly Trp Tyr Leu Phe Asp Tyr
1 5

<210> 73
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for 11D4

<400> 73

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 74
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for 11D4

<400> 74

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 75
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for 11D4

<400> 75

Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1   5

<210> 76
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain for 18D8

<400> 76

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85   90   95

Ala Lys Asp Gln Ser Thr Ala Asp Tyr Tyr Phe Tyr Tyr Gly Met Asp
            100   105   110

```
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
    130                 135                 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
        195                 200                 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
    210                 215                 220

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
    290                 295                 300
```

```
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> 77
<211> 213
<212> PRT
<213> Artificial Sequence

<220>

<223> light chain for 18D8

<400> 77

```
Glu Ile Val Val Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
                85                  90                  95


Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175
```

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 78
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region for 18D8

<400> 78

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Gln Ser Thr Ala Asp Tyr Tyr Phe Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 79
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region for 18D8

<400> 79

Glu Ile Val Val Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
                85   90   95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 80
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for 18D8

<400> 80

Asp Tyr Ala Met His
1   5

<210> 81
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for 18D8

<400> 81

Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 82
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for 18D8

<400> 82

Asp Gln Ser Thr Ala Asp Tyr Tyr Phe Tyr Tyr Gly Met Asp Val
1   5   10   15

<210> 83
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<223> light chain CDR1 for 18D8

<400> 83

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 84
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for 18D8

<400> 84

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 85
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for 18D8

<400> 85

Gln Gln Arg Ser Asn Trp Pro Thr
1 5

<210> 86
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region for Hu119-122

<400> 86

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Tyr Glu Phe Pro Ser His
            20                  25                  30


Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu Val
        35                  40                  45


Ala Ala Ile Asn Ser Asp Gly Gly Ser Thr Tyr Tyr Pro Asp Thr Met
    50                  55                  60


Glu Arg Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Asp Asp Tyr Tyr Ala Trp Phe Ala Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  87
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region for Hu119-122

<400>  87

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
            20                  25                  30
```

```
Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45


Arg Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95


Glu Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  88
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain CDRl for Hu119-122

<400>  88

Ser His Asp Met Ser
1               5


<210>  89
<211>  17
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain CDR2 for Hu119-122

<400>  89

Ala Ile Asn Ser Asp Gly Gly Ser Thr Tyr Tyr Pro Asp Thr Met Glu
1               5                   10                  15
```

Arg

<210> 90
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for Hu119-122

<400> 90

His Tyr Asp Asp Tyr Tyr Ala Trp Phe Ala Tyr
1 5 10

<210> 91
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for Hu119-122

<400> 91

Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His
1 5 10 15

<210> 92
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for Hu119-122

<400> 92

Leu Ala Ser Asn Leu Glu Ser
1 5

<210> 93
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for Hu119-122

<400> 93

Gln His Ser Arg Glu Leu Pro Leu Thr
1 5

<210> 94
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region for Hu106-222

<400> 94

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Asn Pro Tyr Tyr Asp Tyr Val Ser Tyr Tyr Ala Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 95
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region for Hu106-222

<400> 95

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Tyr Leu Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Arg
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 96
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for Hu106-222

<400> 96

Asp Tyr Ser Met His
1   5

<210> 97
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for Hu106-222

<400> 97

Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
1   5   10   15

Gly

<210> 98
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for Hu106-222

<400> 98

Pro Tyr Tyr Asp Tyr Val Ser Tyr Tyr Ala Met Asp Tyr
1   5   10

<210> 99
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<223> light chain CDR1 for Hu106-222

<400> 99

Lys Ala Ser Gln Asp Val Ser Thr Ala Val Ala
1 5 10

<210> 100
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for Hu106-222

<400> 100

Ser Ala Ser Tyr Leu Tyr Thr
1 5

<210> 101
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for Hu106-222

<400> 101

Gln Gln His Tyr Ser Thr Pro Arg Thr
1 5

<210> 102
<211> 183
<212> PRT
<213> Artificial Sequence

<220>
<223> OX40L

<400> 102

Met Glu Arg Val Gln Pro Leu Glu Glu Asn Val Gly Asn Ala Ala Arg
1 5 10 15

```
Pro Arg Phe Glu Arg Asn Lys Leu Leu Leu Val Ala Ser Val Ile Gln
            20                  25                  30

Gly Leu Gly Leu Leu Leu Cys Phe Thr Tyr Ile Cys Leu His Phe Ser
        35                  40                  45

Ala Leu Gln Val Ser His Arg Tyr Pro Arg Ile Gln Ser Ile Lys Val
    50                  55                  60

Gln Phe Thr Glu Tyr Lys Lys Glu Lys Gly Phe Ile Leu Thr Ser Gln
65                  70                  75                  80

Lys Glu Asp Glu Ile Met Lys Val Gln Asn Asn Ser Val Ile Ile Asn
                85                  90                  95

Cys Asp Gly Phe Tyr Leu Ile Ser Leu Lys Gly Tyr Phe Ser Gln Glu
            100                 105                 110

Val Asn Ile Ser Leu His Tyr Gln Lys Asp Glu Glu Pro Leu Phe Gln
        115                 120                 125

Leu Lys Lys Val Arg Ser Val Asn Ser Leu Met Val Ala Ser Leu Thr
    130                 135                 140

Tyr Lys Asp Lys Val Tyr Leu Asn Val Thr Thr Asp Asn Thr Ser Leu
145                 150                 155                 160

Asp Asp Phe His Val Asn Gly Gly Glu Leu Ile Leu Ile His Gln Asn
                165                 170                 175

Pro Gly Glu Phe Cys Val Leu
            180
```

<210> 103
<211> 131

<212> PRT
<213> Artificial Sequence

<220>
<223> OX40L soluble domain

<400> 103

Ser His Arg Tyr Pro Arg Ile Gln Ser Ile Lys Val Gln Phe Thr Glu
1 5 10 15

Tyr Lys Lys Glu Lys Gly Phe Ile Leu Thr Ser Gln Lys Glu Asp Glu
20 25 30

Ile Met Lys Val Gln Asn Asn Ser Val Ile Ile Asn Cys Asp Gly Phe
35 40 45

Tyr Leu Ile Ser Leu Lys Gly Tyr Phe Ser Gln Glu Val Asn Ile Ser
50 55 60

Leu His Tyr Gln Lys Asp Glu Glu Pro Leu Phe Gln Leu Lys Lys Val
65 70 75 80

Arg Ser Val Asn Ser Leu Met Val Ala Ser Leu Thr Tyr Lys Asp Lys
85 90 95

Val Tyr Leu Asn Val Thr Thr Asp Asn Thr Ser Leu Asp Asp Phe His
100 105 110

Val Asn Gly Gly Glu Leu Ile Leu Ile His Gln Asn Pro Gly Glu Phe
115 120 125

Cys Val Leu
130

<210> 104
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> OX40L soluble domain (alternative)

<400> 104

Tyr Pro Arg Ile Gln Ser Ile Lys Val Gln Phe Thr Glu Tyr Lys Lys
1   5   10   15

Glu Lys Gly Phe Ile Leu Thr Ser Gln Lys Glu Asp Glu Ile Met Lys
            20   25   30

Val Gln Asn Asn Ser Val Ile Ile Asn Cys Asp Gly Phe Tyr Leu Ile
        35   40   45

Ser Leu Lys Gly Tyr Phe Ser Gln Glu Val Asn Ile Ser Leu His Tyr
    50   55   60

Gln Lys Asp Glu Glu Pro Leu Phe Gln Leu Lys Lys Val Arg Ser Val
65   70   75   80

Asn Ser Leu Met Val Ala Ser Leu Thr Tyr Lys Asp Lys Val Tyr Leu
                85   90   95

Asn Val Thr Thr Asp Asn Thr Ser Leu Asp Asp Phe His Val Asn Gly
            100   105   110

Gly Glu Leu Ile Leu Ile His Gln Asn Pro Gly Glu Phe Cys Val Leu
        115   120   125

<210> 105
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> variable heavy chain for 008

<400> 105

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Asp Arg Tyr Ser Gln Val His Tyr Ala Leu Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser
        115                 120


<210>  106
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable light chain for 008

<400>  106

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Pro Val Thr Pro Gly
1               5                  10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
```

```
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Ala Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
                85                  90                  95


Tyr Asn His Pro Thr Thr Phe Gly Gln Gly Thr Lys
            100                 105


<210>  107
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable heavy chain for 011

<400>  107

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30


Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Arg Lys Gly
    50                  55                  60
```

```
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65                  70                  75                  80


Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
                85                  90                  95


Asp Arg Tyr Phe Arg Gln Gln Asn Ala Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Ala
        115                 120


<210>  108
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  variable light chain for 011

<400>  108

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Ala Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
                85                  90                  95
```

Tyr Asn His Pro Thr Thr Phe Gly Gln Gly Thr Lys
100 105

<210> 109
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> variable heavy chain for 021

<400> 109

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Arg Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Tyr Ile Thr Leu Pro Asn Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser
115 120

<210> 110
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> variable light chain for 021

<400> 110

Asp Ile Gln Met Thr Gln Ser Pro Val Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
85 90 95

Lys Ser Asn Pro Pro Thr Phe Gly Gln Gly Thr Lys
100 105

<210> 111
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> variable heavy chain for 023

<400> 111

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Thr Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Met
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Tyr Asp Asn Val Met Gly Leu Tyr Trp Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 112
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> variable light chain for 023

<400> 112

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95


Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210>  113
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region

<400>  113

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60
```

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Asn Tyr Tyr Gly Ser Ser Leu Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 114
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region

<400> 114

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 115
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region

<400> 115

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Lys Asp Tyr
20 25 30

Thr Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Tyr Pro Asn Asn Gly Gly Ser Thr Tyr Asn Gln Asn Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Phe Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Met Gly Tyr His Gly Pro His Leu Asp Phe Asp Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Pro
115 120

<210> 116
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region

<400> 116

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Leu Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Ala Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Thr Asp Tyr Phe Cys Gln Gln Tyr Ile Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 117
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region of humanized antibody

<400> 117

```
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                  10                  15


Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30


Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95


Ala Asn Pro Tyr Tyr Asp Tyr Val Ser Tyr Tyr Ala Met Asp Tyr Trp
            100                 105                 110


Gly His Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  118
<211>  122
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region of humanized antibody

<400>  118

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                  10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
```

```
Ser Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Asn Pro Tyr Tyr Asp Tyr Val Ser Tyr Tyr Ala Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  119
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region of humanized antibody

<400>  119

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Arg
1               5                   10                  15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Ser Ala Ser Tyr Leu Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 120
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region of humanized antibody

<400> 120

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Arg
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Leu Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 121
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region of humanized antibody

<400> 121

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
1 5 10 15

Ser Leu Lys Leu Ser Cys Glu Ser Asn Glu Tyr Glu Phe Pro Ser His
20 25 30

Asp Met Ser Trp Val Arg Lys Thr Pro Glu Lys Arg Leu Glu Leu Val
35 40 45

Ala Ala Ile Asn Ser Asp Gly Gly Ser Thr Tyr Tyr Pro Asp Thr Met
50 55 60

Glu Arg Arg Phe Ile Ile Ser Arg Asp Asn Thr Lys Lys Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg His Tyr Asp Asp Tyr Tyr Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 122
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region of humanized antibody

<400> 122

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Tyr Glu Phe Pro Ser His
            20                  25                  30


Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu Val
        35                  40                  45


Ala Ala Ile Asn Ser Asp Gly Gly Ser Thr Tyr Tyr Pro Asp Thr Met
    50                  55                  60


Glu Arg Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Asp Asp Tyr Tyr Ala Trp Phe Ala Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Met Val Thr Val Ser Ser
        115                 120
```

<210> 123
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> light chain variable region of humanized antibody

<400> 123

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

Glu Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 124
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region of humanized antibody

<400> 124

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30

```
Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45


Arg Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95


Glu Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  125
<211>  138
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region

<400>  125

Met Tyr Leu Gly Leu Asn Tyr Val Phe Ile Val Phe Leu Leu Asn Gly
1               5                   10                  15


Val Gln Ser Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30


Pro Gly Gly Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ser Pro Glu Lys Gly Leu
    50                  55                  60
```

```
Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Tyr
65                  70                  75                  80


Tyr Ala Glu Ser Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
                85                  90                  95


Lys Ser Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110


Gly Ile Tyr Tyr Cys Thr Trp Gly Glu Val Phe Tyr Phe Asp Tyr Trp
        115                 120                 125


Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
    130                 135


<210>  126
<211>  126
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region

<400>  126

Met Arg Pro Ser Ile Gln Phe Leu Gly Leu Leu Leu Phe Trp Leu His
1               5                   10                  15


Gly Ala Gln Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
            20                  25                  30


Ala Ser Leu Gly Gly Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Asp
        35                  40                  45


Ile Asn Lys Tyr Ile Ala Trp Tyr Gln His Lys Pro Gly Lys Gly Pro
    50                  55                  60


Arg Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Pro Gly Ile Pro Ser
65                  70                  75                  80
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser
                85                  90                  95


Asn Leu Glu Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp
            100                 105                 110


Asn Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125


<210>  127
<211>  260
<212>  PRT
<213>  Homo Sapiens

<400>  127

Met Ala Arg Pro His Pro Trp Trp Leu Cys Val Leu Gly Thr Leu Val
1               5                   10                  15


Gly Leu Ser Ala Thr Pro Ala Pro Lys Ser Cys Pro Glu Arg His Tyr
            20                  25                  30


Trp Ala Gln Gly Lys Leu Cys Cys Gln Met Cys Glu Pro Gly Thr Phe
        35                  40                  45


Leu Val Lys Asp Cys Asp Gln His Arg Lys Ala Ala Gln Cys Asp Pro
    50                  55                  60


Cys Ile Pro Gly Val Ser Phe Ser Pro Asp His His Thr Arg Pro His
65                  70                  75                  80


Cys Glu Ser Cys Arg His Cys Asn Ser Gly Leu Leu Val Arg Asn Cys
                85                  90                  95


Thr Ile Thr Ala Asn Ala Glu Cys Ala Cys Arg Asn Gly Trp Gln Cys
            100                 105                 110
```

```
Arg Asp Lys Glu Cys Thr Glu Cys Asp Pro Leu Pro Asn Pro Ser Leu
        115                 120                 125


Thr Ala Arg Ser Ser Gln Ala Leu Ser Pro His Pro Gln Pro Thr His
    130                 135                 140


Leu Pro Tyr Val Ser Glu Met Leu Glu Ala Arg Thr Ala Gly His Met
145                 150                 155                 160


Gln Thr Leu Ala Asp Phe Arg Gln Leu Pro Ala Arg Thr Leu Ser Thr
                165                 170                 175


His Trp Pro Pro Gln Arg Ser Leu Cys Ser Ser Asp Phe Ile Arg Ile
            180                 185                 190


Leu Val Ile Phe Ser Gly Met Phe Leu Val Phe Thr Leu Ala Gly Ala
        195                 200                 205


Leu Phe Leu His Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser
    210                 215                 220


Pro Val Glu Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu
225                 230                 235                 240


Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro
                245                 250                 255


Ala Cys Ser Pro
            260
```

<210> 128
<211> 260
<212> PRT
<213> Macaca Nemestrina

<400> 128

```
Met Ala Arg Pro His Pro Trp Trp Leu Cys Phe Leu Gly Thr Leu Val
1               5                  10                  15

Gly Leu Ser Ala Thr Pro Ala Pro Lys Ser Cys Pro Glu Arg His Tyr
            20                  25                  30

Trp Ala Gln Gly Lys Leu Cys Cys Gln Met Cys Glu Pro Gly Thr Phe
        35                  40                  45

Leu Val Lys Asp Cys Asp Gln His Arg Lys Ala Ala Gln Cys His Pro
    50                  55                  60

Cys Ile Pro Gly Val Ser Phe Ser Pro Asp His His Thr Arg Pro His
65                  70                  75                  80

Cys Glu Ser Cys Arg His Cys Asn Ser Gly Leu Leu Ile Arg Asn Cys
                85                  90                  95

Thr Ile Thr Ala Asn Ala Val Cys Ala Cys Arg Asn Gly Trp Gln Cys
            100                 105                 110

Arg Asp Lys Glu Cys Thr Glu Cys Asp Pro Pro Pro Asn Pro Ser Leu
        115                 120                 125

Thr Thr Trp Pro Ser Gln Ala Leu Gly Pro His Pro Gln Pro Thr His
    130                 135                 140

Leu Pro Tyr Val Asn Glu Met Leu Glu Ala Arg Thr Ala Gly His Met
145                 150                 155                 160

Gln Thr Leu Ala Asp Phe Arg His Leu Pro Ala Arg Thr Leu Ser Thr
                165                 170                 175

His Trp Pro Pro Gln Arg Ser Leu Cys Ser Ser Asp Phe Ile Arg Ile
            180                 185                 190
```

```
Leu Val Ile Phe Ser Gly Met Phe Leu Val Phe Thr Leu Ala Gly Thr
        195                 200                 205


Leu Phe Leu His Gln Gln Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser
    210                 215                 220


Pro Met Glu Pro Ala Glu Pro Cys Pro Tyr Ser Cys Pro Arg Glu Glu
225                 230                 235                 240


Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro
                245                 250                 255


Ala Ser Ser Pro
            260


<210>  129
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain for varlilumab

<400>  129

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Ser Gly Asn Trp Gly Phe Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270
```

```
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys Gly Ser Ser
    450
```

<210> 130
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain for varlilumab

<400> 130

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Tyr Pro Arg
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140
```

```
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  131
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  heavy chain variable region for varlilumab

<400>  131

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Ser Gly Asn Trp Gly Phe Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115


<210>  132
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  light chain variable region for varlilumab

<400>  132

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Tyr Pro Arg
                85                  90                  95
```

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 133
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for varlilumab

<400> 133

Gly Phe Thr Phe Ser Ser Tyr Asp
1 5

<210> 134
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for varlilumab

<400> 134

Ile Trp Tyr Asp Gly Ser Asn Lys
1 5

<210> 135
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for varlilumab

<400> 135

Ala Arg Gly Ser Gly Asn Trp Gly Phe Phe Asp Tyr
1 5 10

<210> 136
<211> 6

<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for varlilumab

<400> 136

Gln Gly Ile Ser Arg Trp
1 5

<210> 137
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for varlilumab

<400> 137

Ala Ala Ser Gly
1

<210> 138
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for varlilumab

<400> 138

Gln Gln Tyr Asn Thr Tyr Pro Arg Thr
1 5

<210> 139
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> CD70 (CD27L)

<400> 139

```
Met Pro Glu Glu Gly Ser Gly Cys Ser Val Arg Arg Arg Pro Tyr Gly
1               5                  10                  15

Cys Val Leu Arg Ala Ala Leu Val Pro Leu Val Ala Gly Leu Val Ile
            20                  25                  30

Cys Leu Val Val Cys Ile Gln Arg Phe Ala Gln Ala Gln Gln Gln Leu
        35                  40                  45

Pro Leu Glu Ser Leu Gly Trp Asp Val Ala Glu Leu Gln Leu Asn His
    50                  55                  60

Thr Gly Pro Gln Gln Asp Pro Arg Leu Tyr Trp Gln Gly Gly Pro Ala
65                  70                  75                  80

Leu Gly Arg Ser Phe Leu His Gly Pro Glu Leu Asp Lys Gly Gln Leu
                85                  90                  95

Arg Ile His Arg Asp Gly Ile Tyr Met Val His Ile Gln Val Thr Leu
            100                 105                 110

Ala Ile Cys Ser Ser Thr Thr Ala Ser Arg His His Pro Thr Thr Leu
        115                 120                 125

Ala Val Gly Ile Cys Ser Pro Ala Ser Arg Ser Ile Ser Leu Leu Arg
    130                 135                 140

Leu Ser Phe His Gln Gly Cys Thr Ile Ala Ser Gln Arg Leu Thr Pro
145                 150                 155                 160

Leu Ala Arg Gly Asp Thr Leu Cys Thr Asn Leu Thr Gly Thr Leu Leu
                165                 170                 175

Pro Ser Arg Asn Thr Asp Glu Thr Phe Phe Gly Val Gln Trp Val Arg
            180                 185                 190
```

Pro

<210> 140
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> CD70 soluble domain

<400> 140

Ser Leu Gly Trp Asp Val Ala Glu Leu Gln Leu Asn His Thr Gly Pro
1 5 10 15

Gln Gln Asp Pro Arg Leu Tyr Trp Gln Gly Gly Pro Ala Leu Gly Arg
20 25 30

Ser Phe Leu His Gly Pro Glu Leu Asp Lys Gly Gln Leu Arg Ile His
35 40 45

Arg Asp Gly Ile Tyr Met Val His Ile Gln Val Thr Leu Ala Ile Cys
50 55 60

Ser Ser Thr Thr Ala Ser Arg His His Pro Thr Thr Leu Ala Val Gly
65 70 75 80

Ile Cys Ser Pro Ala Ser Arg Ser Ile Ser Leu Leu Arg Leu Ser Phe
85 90 95

His Gln Gly Cys Thr Ile Ala Ser Gln Arg Leu Thr Pro Leu Ala Arg
100 105 110

Gly Asp Thr Leu Cys Thr Asn Leu Thr Gly Thr Leu Leu Pro Ser Arg
115 120 125

Asn Thr Asp Glu Thr Phe Phe Gly Val Gln Trp Val Arg Pro
130 135 140

<210> 141
<211> 137
<212> PRT
<213> Artificial Sequence

<220>
<223> CD70 soluble domain (alternative)

<400> 141

Val Ala Glu Leu Gln Leu Asn His Thr Gly Pro Gln Gln Asp Pro Arg
1 5 10 15

Leu Tyr Trp Gln Gly Gly Pro Ala Leu Gly Arg Ser Phe Leu His Gly
20 25 30

Pro Glu Leu Asp Lys Gly Gln Leu Arg Ile His Arg Asp Gly Ile Tyr
35 40 45

Met Val His Ile Gln Val Thr Leu Ala Ile Cys Ser Ser Thr Thr Ala
50 55 60

Ser Arg His His Pro Thr Thr Leu Ala Val Gly Ile Cys Ser Pro Ala
65 70 75 80

Ser Arg Ser Ile Ser Leu Leu Arg Leu Ser Phe His Gln Gly Cys Thr
85 90 95

Ile Ala Ser Gln Arg Leu Thr Pro Leu Ala Arg Gly Asp Thr Leu Cys
100 105 110

Thr Asn Leu Thr Gly Thr Leu Leu Pro Ser Arg Asn Thr Asp Glu Thr
115 120 125

Phe Phe Gly Val Gln Trp Val Arg Pro
130 135

<210> 142
<211> 241
<212> PRT
<213> Homo Sapiens

<400> 142

```
Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1               5                  10                  15


Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
            20                  25                  30


Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
        35                  40                  45


Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
    50                  55                  60


Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65                  70                  75                  80


Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
                85                  90                  95


Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
            100                 105                 110


Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
        115                 120                 125


Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
    130                 135                 140


Gly Asn Lys Thr His Asn Ala Val Cys Val Pro Gly Ser Pro Pro Ala
145                 150                 155                 160
```

```
Glu Pro Leu Gly Trp Leu Thr Val Val Leu Leu Ala Val Ala Ala Cys
                165                 170                 175


Val Leu Leu Leu Thr Ser Ala Gln Leu Gly Leu His Ile Trp Gln Leu
            180                 185                 190


Arg Ser Gln Cys Met Trp Pro Arg Glu Thr Gln Leu Leu Leu Glu Val
        195                 200                 205


Pro Pro Ser Thr Glu Asp Ala Arg Ser Cys Gln Phe Pro Glu Glu Glu
    210                 215                 220


Arg Gly Glu Arg Ser Ala Glu Glu Lys Gly Arg Leu Gly Asp Leu Trp
225                 230                 235                 240


Val
```

<210> 143
<211> 228
<212> PRT
<213> Mus Musculus

<400> 143

```
Met Gly Ala Trp Ala Met Leu Tyr Gly Val Ser Met Leu Cys Val Leu
1               5                   10                  15


Asp Leu Gly Gln Pro Ser Val Val Glu Glu Pro Gly Cys Gly Pro Gly
            20                  25                  30


Lys Val Gln Asn Gly Ser Gly Asn Asn Thr Arg Cys Cys Ser Leu Tyr
        35                  40                  45


Ala Pro Gly Lys Glu Asp Cys Pro Lys Glu Arg Cys Ile Cys Val Thr
    50                  55                  60
```

```
Pro Glu Tyr His Cys Gly Asp Pro Gln Cys Lys Ile Cys Lys His Tyr
65                  70                  75                  80


Pro Cys Gln Pro Gly Gln Arg Val Glu Ser Gln Gly Asp Ile Val Phe
                85                  90                  95


Gly Phe Arg Cys Val Ala Cys Ala Met Gly Thr Phe Ser Ala Gly Arg
            100                 105                 110


Asp Gly His Cys Arg Leu Trp Thr Asn Cys Ser Gln Phe Gly Phe Leu
        115                 120                 125


Thr Met Phe Pro Gly Asn Lys Thr His Asn Ala Val Cys Ile Pro Glu
    130                 135                 140


Pro Leu Pro Thr Glu Gln Tyr Gly His Leu Thr Val Ile Phe Leu Val
145                 150                 155                 160


Met Ala Ala Cys Ile Phe Phe Leu Thr Thr Val Gln Leu Gly Leu His
                165                 170                 175


Ile Trp Gln Leu Arg Arg Gln His Met Cys Pro Arg Glu Thr Gln Pro
            180                 185                 190


Phe Ala Glu Val Gln Leu Ser Ala Glu Asp Ala Cys Ser Phe Gln Phe
        195                 200                 205


Pro Glu Glu Glu Arg Gly Glu Gln Thr Glu Glu Lys Cys His Leu Gly
    210                 215                 220


Gly Arg Trp Pro
225


<210>  144
<211>  449
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> humanized 6C8 heavy chain variant

<400> 144

```
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15


Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45


Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80


Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125


Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140


Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160


Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175
```

```
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365
```

```
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> 145
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6C8 heavy chain variant

<400> 145

```
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45
```

```
Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240
```

```
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430
```

```
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


Lys



<210>  146
<211>  449
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized 6C8 heavy chain variant

<400>  146

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15


Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45


Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Gln Pro Ser
    50                  55                  60


Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80


Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125
```

```
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320
```

```
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> 147
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6C8 heavy chain variant

<400> 147

```
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                  10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Gln Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190
```

```
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380
```

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 148
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6C8 light chain

<400> 148

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

```
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Thr Asp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 149
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 heavy chain leader

<400> 149

Met Asp Arg Leu Thr Phe Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
1 5 10 15

Val Leu Ser

<210> 150
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 light chain leader

<400> 150

Met Glu Thr Gln Ser Gln Val Phe Val Tyr Met Leu Leu Trp Leu Ser
1 5 10 15

Gly Val Asp Gly
20

<210> 151
<211> 138
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6C8 heavy chain variable region variant

<400> 151

Met Asp Arg Leu Thr Phe Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
1 5 10 15

Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
35 40 45

Ser Thr Ser Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys
    50   55   60

Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr
65   70   75   80

Asn Pro Ser Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg
                85   90   95

Asn Gln Val Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Ala Ala
            100   105   110

Thr Tyr Tyr Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp
        115   120   125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130   135

<210> 152
<211> 138
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6C8 heavy chain variable region variant

<400> 152

Met Asp Arg Leu Thr Phe Ser Phe Leu Leu Leu Ile Val Pro Ala Tyr
1   5   10   15

Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys
            20   25   30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
        35   40   45

Ser Thr Ser Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys
    50   55   60

```
Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr
65                  70                  75                  80


Gln Pro Ser Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg
                85                  90                  95


Asn Gln Val Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Ala Ala
            100                 105                 110


Thr Tyr Tyr Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp
        115                 120                 125


Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135


<210>  153
<211>  127
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized 6C8 light chain variable region

<400>  153

Met Glu Thr Gln Ser Gln Val Phe Val Tyr Met Leu Leu Trp Leu Ser
1               5                   10                  15


Gly Val Asp Gly Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser
            20                  25                  30


Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn
        35                  40                  45


Val Gly Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
    50                  55                  60
```

Lys Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp
65 70 75 80

Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
85 90 95

Asn Val His Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn
100 105 110

Thr Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
115 120 125

<210> 154
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 heavy chain CDR1

<400> 154

Gly Phe Ser Leu Ser Thr Ser Gly Met Gly Val Gly
1 5 10

<210> 155
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 heavy chain CDR2 variant

<400> 155

His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 156
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 heavy chain CDR2 variant

<400> 156

His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Gln Pro Ser Leu Lys Ser
1   5   10   15

<210> 157
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 heavy chain CDR3

<400> 157

Thr Arg Arg Tyr Phe Pro Phe Ala Tyr
1   5

<210> 158
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 light chain CDR1

<400> 158

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
1   5   10

<210> 159
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 light chain CDR2

<400> 159

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 6C8 light chain CDR3

<400> 160

Gln Gln Tyr Asn Thr Asp Pro Leu Thr
1 5

<210> 161
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> chimeric 6C8 heavy chain variant

<400> 161

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg Asn Gln Val
65 70 75 80

```
Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Ala Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270
```

```
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285


Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300


Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320


Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335


Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350


Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


Lys
```

<210> 162
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> chimeric 6C8 heavy chain variant

<400> 162

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45


Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg Asn Gln Val
65                  70                  75                  80


Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Ala Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Thr Arg Arg Tyr Phe Pro Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125


Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140


Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160
```

```
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350
```

```
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


Lys



<210>  163
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  chimeric 6C8 light chain variant

<400>  163

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15


Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30
```

```
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Val His Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Thr Asp Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 164
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 36E5 heavy chain variable region

<400> 164

```
Glu Val Asn Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Val Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45


Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65                  70                  75                  80


Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85                  90                  95


Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp Tyr Trp Gly Gln Gly Ile
            100                 105                 110


Ser Val Thr Asp Ser Ser
        115
```

<210> 165
<211> 113
<212> PRT
<213> Artificial Sequence

<220>

<223> 36E5 light chain variable region

<400> 165

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Val Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65 70 75 80

Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln Gln Thr Lys
85 90 95

Glu Val Thr Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Ala

<210> 166
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D6 heavy chain variable region

<400> 166

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

```
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile His Ala Asn Gly Gly Ser Thr Tyr Tyr Arg Asp Ser Val
    50                  55                  60

Arg Gly Arg Phe Ser Ile Ser Arg Asp Asn Gly Lys Ser Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Thr Thr Gly Ser Phe Met Tyr Ala Ala Asp Tyr Tyr Ile Met Asp Ala
            100                 105                 110

Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
        115                 120


<210>  167
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  3D6 light chain variable region

<400>  167

Asp Val Val Met Thr Gln Thr Pro Val Ser Leu Ser Val Ser Leu Gly
1               5                   10                  15

Asn Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
```

```
Asp Gly Asn Thr Phe Leu Ser Trp Tyr Phe Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Ala Ser Asn Arg Phe Ser Gly Val Ser
    50                  55                  60


Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Pro Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln His
                85                  90                  95


Thr His Leu Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


Arg



<210>  168
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  61G6 heavy chain variable region

<400>  168

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45


Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Arg Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80


Leu Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Ala Arg Gln Leu Gly Leu Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Leu Thr Val Ser Ser
        115


<210>  169
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  61G6 light chain variable region

<400>  169

Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Ser Ala Asn Ser Thr Val Asn Tyr Met
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Cys Ile Tyr
        35                  40                  45


Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65                  70                  75                  80
```

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Asn Ser Asn Pro Pro Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg Arg Ala
100 105

<210> 170
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 6H6 heavy chain variable region

<400> 170

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Arg Tyr
20 25 30

Trp Ile Glu Trp Ile Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Ser Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Phe Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Val Tyr Tyr Tyr Ala Met Asp Phe Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 171
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> 6H6 light chain variable region

<400> 171

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Val Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Val Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Phe His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Thr Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105 110

<210> 172
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> 61F6 heavy chain variable region

<400> 172

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Val Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Gly Gly Tyr Tyr Asp Thr Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 173
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> 61F6 light chain variable region

<400> 173

Asp Ile Val Val Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
            20   25   30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65   70   75   80

Pro Met Glu Glu Asp Asp Thr Ala Val Tyr Phe Cys Gln Gln Ser Lys
                85   90   95

Glu Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
            100   105   110

Ala

<210> 174
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D8 heavy chain variable region

<400> 174

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20   25   30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35   40   45

```
Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Ser Pro Ser
    50                  55                  60


Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg Asn Gln Val
65                  70                  75                  80


Phe Leu Lys Ile Thr Ser Leu Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Val Arg Ser Tyr Tyr Tyr Gly Ser Ser Gly Ala Met Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  175
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  1D8 light chain variable region

<400>  175

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                   10                  15


Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30


Asp Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Lys Leu Leu Ile Tyr Lys Val Ser Lys Arg Phe Ser Gly Val Pro
    50                  55                  60
```

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Ala Asp Ala Ala Pro
115

<210> 176
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> 17F10 heavy chain variable region

<400> 176

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Phe Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Arg Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Thr Gly Asp Arg Ser Tyr Leu Pro Asp Ser Met Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Gln
85 90 95

```
Arg Tyr Phe Asp Phe Asp Ser Phe Ala Phe Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ala
        115


<210>  177
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  17F10 light chain variable region

<400>  177

Asp Ile Gln Met Thr Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15


Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Asn Asn Phe
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Ser Leu Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Thr Ser Lys Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser Asn Leu Asp Gln
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Gly His Thr Leu Pro Pro
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Val Lys Arg Ala Asp Ala Ala
            100                 105                 110
```

Pro

<210> 178
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 35D8 heavy chain variable region

<400> 178

Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
            20   25   30

Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
        35   40   45

Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Arg
    50   55   60

Gly Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Ser Gln Tyr Tyr Leu
65   70   75   80

Gln Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ser
                85   90   95

Arg Arg His Leu Gly Ser Gly Tyr Gly Trp Phe Ala Tyr Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ala
        115   120

<210> 179
<211> 114

<212> PRT
<213> Artificial Sequence

<220>
<223> 35D8 light chain variable region

<400> 179

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ala Leu Thr Ile Asn Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Ser Tyr Thr Pro Pro
85 90 95

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg Arg Ala Asp Ala
100 105 110

Ala Pro

<210> 180
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 49A1 heavy chain variable region

<400> 180

Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
20 25 30

Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Phe Glu Tyr Met
35 40 45

Gly Phe Ile Ser Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Arg
50 55 60

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Phe Leu
65 70 75 80

His Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ser
85 90 95

Arg Arg His Leu Ile Ser Gly Tyr Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 181
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> 49A1 light chain variable region

<400> 181

Val Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Ile Gly
1 5 10 15

```
Asp Arg Val Asn Ile Thr Cys Lys Ala Ser Gln Asp Val Ile Ser Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Arg Ala Leu Tyr Tyr Cys Gln Gln His Ser Tyr Thr Pro Pro
                85                  90                  95

Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg Ala Asp Ala
            100                 105                 110

Ala Pro
```

<210> 182
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 9E5 heavy chain variable region

<400> 182

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Tyr
            20                  25                  30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45
```

```
Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Asn Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Ile His Arg Leu Thr Val Ser Lys Asp Thr Ser Asn Asn Gln Ala
65                  70                  75                  80

Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Glu Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Gln Ile Lys Glu Pro Arg Asp Trp Phe Phe Glu Phe Trp Gly
            100                 105                 110

Pro Gly Thr Met Val Ser Val Ser Ser
        115                 120


<210>  183
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  9E5 light chain variable region

<400>  183

Asp Ile Gln Met Thr Gln Thr Pro Ser Ser Met Pro Ala Ser Leu Gly
1               5                   10                  15

Glu Arg Val Thr Ile Phe Cys Arg Ala Ser Gln Gly Val Asn Asn Phe
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Asp Gly Thr Ile Lys Pro Leu Ile
        35                  40                  45

Phe Tyr Thr Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Ser Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln Tyr His Gly Phe Pro Asn
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
100 105 110

Pro

<210> 184
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 31H6 heavy chain variable region

<400> 184

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Tyr
20 25 30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn Asn Gln Ala
65 70 75 80

Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Glu Thr Ala Thr Tyr Tyr
85 90 95

```
Cys Ala Gln Ile Lys Glu Pro Arg Asp Trp Phe Phe Glu Phe Trp Gly
            100                 105                 110


Pro Gly Thr Met Val Ser Val Ser Ser
        115                 120


<210>  185
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  31H6 light chain variable region

<400>  185

Asp Ile Gln Met Thr Gln Thr Pro Ser Ser Met Pro Ala Ser Leu Gly
1               5                   10                  15


Glu Arg Val Thr Ile Phe Cys Arg Ala Ser Gln Gly Val Asn Asn Tyr
            20                  25                  30


Leu Thr Trp Tyr Gln Gln Lys Pro Asp Gly Thr Ile Lys Pro Leu Ile
        35                  40                  45


Phe Tyr Thr Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Ser Leu Ser Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln Tyr His Gly Phe Pro Asn
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110
```

Pro

<210> 186
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 36E5 heavy chain variable region

<400> 186

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 187
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 36E5 light chain variable region

<220>
<221> misc_feature
<222> (31)..(31)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (57)..(57)
<223> Xaa can be any naturally occurring amino acid

<400> 187

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Xaa Tyr
20 25 30

Gly Val Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Xaa Gln Gly Ser Gly Ile Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Lys
85 90 95

Glu Val Thr Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

<210> 188

<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 3D6 heavy chain variable region

<220>
<221> misc_feature
<222> (97)..(98)
<223> Xaa can be any naturally occurring amino acid

<400> 188

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile His Ala Asn Gly Gly Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Xaa Xaa Gly Ser Phe Met Tyr Ala Ala Asp Tyr Tyr Ile Met Asp Ala
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 189

<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 3D6 light chain variable region

<400> 189

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Asn Thr Phe Leu Ser Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Ala Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln His
85 90 95

Thr His Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 190
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 61G6 heavy chain variable region

<220>
<221> misc_feature
<222> (49)..(49)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (68)..(68)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (72)..(72)
<223> Xaa can be any naturally occurring amino acid

<400> 190

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Xaa Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Arg Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Xaa Thr Ile Ser Xaa Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Leu Gly Leu Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser

115

<210> 191
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 61G6 light chain variable region

<220>
<221> misc_feature
<222> (45)..(46)
<223> Xaa can be any naturally occurring amino acid

<400> 191

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ser Ala Asn Ser Thr Val Asn Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Xaa Xaa Ile Tyr
35 40 45

Leu Thr Ser Asn Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu
65 70 75 80

Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Asn Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 192

<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6H6 heavy chain variable region

<220>
<221> misc_feature
<222> (48)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (68)..(68)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (70)..(70)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (72)..(72)
<223> Xaa can be any naturally occurring amino acid

<400> 192

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Xaa
        35                  40                  45


Gly Glu Ile Leu Pro Gly Ser Gly Ser Ser Asn Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asp Arg Xaa Thr Xaa Thr Xaa Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Val Tyr Tyr Tyr Ala Met Asp Phe Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 193
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 6H6 light chain variable region

<220>
<221> misc_feature
<222> (48)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (72)..(72)
<223> Xaa can be any naturally occurring amino acid

<400> 193

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Phe His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Xaa
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser

50 55 60

Gly Ser Gly Ser Gly Thr Asp Xaa Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 194
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 61F6 heavy chain variable region

<220>
<221> misc_feature
<222> (48)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (68)..(68)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (70)..(70)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (72)..(72)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (74)..(74)
<223> Xaa can be any naturally occurring amino acid

<400> 194

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Xaa
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Val Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Xaa Thr Xaa Thr Xaa Asp Xaa Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Gly Gly Tyr Tyr Asp Thr Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 195
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 61F6 light chain variable region

<400> 195

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
            20                  25                  30


Gly Ile Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
                85                  90                  95


Glu Val Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110


<210>  196
<211>  122
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized 1D8 heavy chain variable region


<220>
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<222>  (24)..(24)
<223>  Xaa can be any naturally occurring amino acid

<220>
<221>  misc_feature
<222>  (69)..(69)
<223>  Xaa can be any naturally occurring amino acid

<220>
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<222>  (73)..(73)
<223>  Xaa can be any naturally occurring amino acid
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<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (98)..(98)
<223> Xaa can be any naturally occurring amino acid

<400> 196

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Xaa Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Gly Val Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Ser Pro Ser
    50                  55                  60


Leu Lys Ser Arg Xaa Thr Ile Ser Xaa Asp Xaa Ser Lys Asn Thr Xaa
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Xaa Arg Ser Tyr Tyr Tyr Gly Ser Ser Gly Ala Met Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 197
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 1D8 light chain variable region

<400> 197

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Lys Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Ser
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 198
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 17F10 heavy chain variable region

<220>
<221> misc_feature
<222> (96)..(96)
<223> Xaa can be any naturally occurring amino acid

<400> 198

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Arg Asn Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ser Ile Ser Thr Gly Asp Arg Ser Tyr Leu Pro Asp Ser Met Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Xaa
                85   90   95

Arg Tyr Phe Asp Phe Asp Ser Phe Ala Phe Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 199
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 17F10 light chain variable region

<400> 199

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Asn Phe
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Tyr Thr Ser Lys Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly His Thr Leu Pro Pro
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 200
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 35D8 heavy chain variable region

<220>
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<222> (47)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (71)..(71)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (96)..(96)
<223> Xaa can be any naturally occurring amino acid

<400> 200

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Thr Ser Gly
20 25 30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Xaa Xaa
35 40 45

Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Arg
50 55 60

Gly Arg Val Thr Ile Ser Xaa Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Xaa
85 90 95

Arg Arg His Leu Gly Ser Gly Tyr Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 201
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 35D8 light chain variable region

<220>
<221> misc_feature
<222> (71)..(71)
<223> Xaa can be any naturally occurring amino acid

<400> 201

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35   40   45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Xaa Thr Leu Thr Ile Ser Ser Leu Gln Ala
65   70   75   80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Ser Tyr Thr Pro Pro
                85   90   95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 202
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 49A1 heavy chain variable region

<220>
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<222> (47)..(48)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (67)..(67)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (71)..(71)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (78)..(78)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (96)..(96)
<223> Xaa can be any naturally occurring amino acid

<400> 202

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Thr Ser Gly
20 25 30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Xaa Xaa
35 40 45

Gly Phe Ile Ser Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Arg
50 55 60

Ser Arg Xaa Thr Ile Ser Xaa Asp Thr Ser Lys Asn Gln Xaa Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Xaa
85 90 95

Arg Arg His Leu Ile Ser Gly Tyr Gly Trp Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 203
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 49A1 light chain variable region

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<400> 203

Xaa Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Asp Val Ile Ser Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Ser Tyr Thr Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 204
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 9E5 heavy chain variable region

<220>
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<222> (24)..(24)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (50)..(51)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (69)..(69)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (71)..(71)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (80)..(80)
<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature
<222> (99)..(99)
<223> Xaa can be any naturally occurring amino acid

<400> 204

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Xaa Ser Gly Phe Ser Leu Ser Thr Tyr
20 25 30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Xaa Xaa Asn Ile Trp Trp Asp Asp Asp Asn Tyr Tyr Asn Pro Ser
50 55 60

Leu Ile His Arg Xaa Thr Xaa Ser Xaa Asp Thr Ser Lys Asn Gln Xaa
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Xaa Ile Lys Glu Pro Arg Asp Trp Phe Phe Glu Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 205
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 9E5 light chain variable region

<220>

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<222> (46)..(46)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (49)..(49)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (71)..(71)
<223> Xaa can be any naturally occurring amino acid

<400> 205

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Phe
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Xaa Leu Ile
35 40 45

Xaa Tyr Thr Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Xaa Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr His Gly Phe Pro Asn
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 206
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized 31H6 heavy chain variable region

<220>
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<222> (24)..(24)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (50)..(51)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (99)..(99)
<223> Xaa can be any naturally occurring amino acid

<400> 206

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Xaa Ser Gly Phe Ser Leu Ser Thr Tyr
            20   25   30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35   40   45

```
Trp Xaa Xaa Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Asn Arg Xaa Thr Ile Ser Xaa Asp Thr Ser Lys Asn Gln Xaa
65                  70                  75                  80


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Xaa Ile Lys Glu Pro Arg Asp Trp Phe Phe Glu Phe Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  207
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized 31H6 light chain variable region


<220>
<221>  misc_feature
<222>  (46)..(46)
<223>  Xaa can be any naturally occurring amino acid

<220>
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<222>  (49)..(49)
<223>  Xaa can be any naturally occurring amino acid

<220>
<221>  misc_feature
<222>  (71)..(71)
<223>  Xaa can be any naturally occurring amino acid

<400>  207

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Tyr
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Xaa Leu Ile
35 40 45

Xaa Tyr Thr Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Xaa Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr His Gly Phe Pro Asn
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 208
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 variable heavy chain

<400> 208

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Gly Ala Ser Gly Phe Thr Ile Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ser Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Arg
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ser Leu Tyr Leu
65   70   75   80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
            100   105   110

Ser Val Thr Val Ser Ser
        115

<210> 209
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 variable light chain

<400> 209

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
            20   25   30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro
        35   40   45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His

65 70 75 80

Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 210
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (HC1) heavy chain

<400> 210

Gln Val Thr Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Thr Leu Ser Cys Gly Ala Ser Gly Phe Thr Ile Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ser Pro Gly Lys Ala Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Arg
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Thr Met Ser Ser Leu Asp Ser Val Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr
        115

<210> 211
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (HC2) heavy chain

<400> 211

Gln Val Thr Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Thr Leu Ser Cys Gly Ala Ser Gly Phe Thr Ile Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ser Pro Gly Lys Ala Leu Glu Trp Val
        35   40   45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Arg
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65   70   75   80

Thr Met Ser Ser Leu Asp Ser Val Asp Thr Ala Thr Tyr Tyr Cys Ala
                85   90   95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
            100   105   110

Ser Val Thr
        115

<210> 212

<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (HC3a) heavy chain

<400> 212

Gln Val Thr Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Thr Leu Ser Cys Gly Ala Ser Gly Phe Thr Ile Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ser Pro Gly Lys Ala Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Lys Phe Arg
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Thr Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr
115

<210> 213
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized (HC3b) heavy chain

<400> 213

Gln Val Thr Leu Lys Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Thr Leu Ser Cys Gly Ala Ser Gly Phe Thr Ile Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ser Pro Gly Lys Ala Leu Glu Trp Val
35 40 45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Pro Asp Lys Phe Arg
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Thr Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr
115

<210> 214
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized (HC4) heavy chain

<400> 214

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ile Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Val Gly Gly Tyr Tyr Asp Ser Met Asp His Trp Gly Gln Gly Thr
            100   105   110

Ser Val Thr
        115

<210> 215
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (LC1) light chain

<400> 215

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Ala Ser Val Gly
1   5   10   15

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
            20   25   30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro

35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65 70 75 80

Pro Met Gln Pro Asp Asp Thr Ala Thr Tyr Phe Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
100 105

<210> 216
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (LC2a) light chain

<400> 216

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser
65 70 75 80

Pro Met Gln Pro Asp Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
100 105

<210> 217
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (LC2b) light chain

<400> 217

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
20 25 30

Gly Ile Ser Tyr Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser
65 70 75 80

Pro Met Gln Pro Asp Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
100 105

<210> 218

<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 humanized (LC3) light chain

<400> 218

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Pro Val Glu Ala Asp Asp Thr Ala Asn Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
100 105

<210> 219
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 variable heavy chain

<400> 219

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala

1 5 10 15

Ser Val Lys Met Ser Cys Glu Ala Ser Gly Tyr Ser Phe Thr Thr Tyr
20 25 30

Trp Met His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Gly Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asp Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Thr Ser Thr Tyr Pro His Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 220
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 variable light chain

<400> 220

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

```
Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile Asn Ser Val Glu Ser
65                  70                  75                  80


Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn Asn Trp Pro Leu
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105


<210>  221
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  706 variable heavy chain

<400>  221

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Glu Ala Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30


Trp Met His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Gly Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
```

65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Thr Ser Thr Tyr Pro His Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 222
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 706 variable light chain

<400> 222

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Thr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 223
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 827 variable heavy chain

<400> 223

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Glu Thr Ser Gly Tyr Ser Phe Thr Thr Tyr
20 25 30

Trp Ile His Trp Ile Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Ala Thr Ile Tyr Pro Gly Asn Ser Asp Ala Gly Tyr Asn Gln Lys Phe
50 55 60

Arg Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ser Ser Thr Tyr Pro His Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 224

<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 827 variable light chain

<400> 224

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Asp Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Thr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 225
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 variable heavy chain

<400> 225

Gln Val Gln Val Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala

1 5 10 15

Ser Val Arg Ile Ser Cys Lys Ala Ser Asp Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Leu
35 40 45

Gly Trp Ile Tyr Pro Gly Lys Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Phe Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Ser Gly Tyr Gly Asn Tyr Tyr Phe Pro Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 226
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 variable light chain

<400> 226

Ile Gln Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly Gly
1 5 10 15

Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Lys Asn Trp Leu
20 25 30

```
Ala Trp Tyr Gln Gln Lys Pro Gly Asn Val Pro Arg Leu Leu Met Ser
        35                  40                  45


Ala Ala Thr Ser Leu Glu Thr Gly Phe Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Lys Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Thr Glu
65                  70                  75                  80


Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Trp Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  227
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  2155 heavy chain CDR3

<400>  227

Val Gly Gly Tyr Tyr Asp Ser Met Asp His
1               5                   10


<210>  228
<211>  9
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  2155 heavy chain CDR2

<400>  228

Ile Ile Ser Thr Gly Gly Ser Thr Tyr
1               5
```

<210> 229
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 heavy chain CDR1

<400> 229

Gly Phe Thr Ile Ser Ser Tyr Ala Met Ser
1   5   10

<210> 230
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 light chain CDR3

<400> 230

Gln Gln Ser Lys Glu Val Pro Trp Thr
1   5

<210> 231
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 light chain CDR2

<400> 231

Ala Ala Ser Asn Gln Gly Ser
1   5

<210> 232
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> 2155 light chain CDR1

<400> 232

Arg Ala Ser Glu Thr Val Asp Asn Tyr Gly Ile Ser Phe Met Asn
1   5   10   15

<210> 233
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 and 706 heavy chain CDR3

<400> 233

Thr Ser Thr Tyr Pro His Phe Asp Tyr
1   5

<210> 234
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 and 706 heavy chain CDR2

<400> 234

Ala Ile Tyr Pro Gly Asn Ser Asp Thr Gly
1   5   10

<210> 235
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 and 706 heavy chain CDR1

<400> 235

Gly Tyr Ser Phe Thr Thr Tyr Trp Met His

1 5 10

<210> 236
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 698 light chain CDR3

<400> 236

Gln Gln Ser Asn Asn Trp Pro Leu Thr
1 5

<210> 237
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 698, 706, 827, and 1649 light chain CDR2

<400> 237

Lys Tyr Ala Ser Glu Ser Ile Ser
1 5

<210> 238
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 698, 706, 827, and 1649 light chain CDR1

<400> 238

Arg Ala Ser Gln Ser Ile Gly Thr Ser Ile His
1 5 10

<210> 239
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<223> 706, 827, and 1649 light chain CDR3

<400> 239

Gln Gln Thr Asn Asn Trp Pro Leu Thr
1 5

<210> 240
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 827 and 1649 heavy chain CDR3

<400> 240

Ser Ser Thr Tyr Pro His Phe Asp Tyr
1 5

<210> 241
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 827 heavy chain CDR2

<400> 241

Thr Ile Tyr Pro Gly Asn Ser Asp Ala Gly
1 5 10

<210> 242
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 1649 heavy chain CDR2

<400> 242

Ala Ile Tyr Pro Gly Asn Ser Asp Ala Gly
1 5 10

<210> 243
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 heavy chain CDR3

<400> 243

Gly Tyr Gly Asn Tyr Tyr Phe Pro Tyr
1 5

<210> 244
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 heavy chain CDR2

<400> 244

Trp Ile Tyr Pro Gly Lys Gly Tyr Thr Asn
1 5 10

<210> 245
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 heavy chain CDR1

<400> 245

Asp Tyr Thr Phe Thr Asn Tyr Tyr Ile
1 5

<210> 246

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 light chain CDR3

<400> 246

Gln Gln Thr Trp Ser Thr Pro Trp Thr
1 5

<210> 247
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 light chain CDR2

<400> 247

Ala Ala Thr Ser Leu Glu Thr
1 5

<210> 248
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 1718 light chain CDR1

<400> 248

Lys Ala Ser Asp His Ile Lys Asn Trp Leu Ala
1 5 10

<210> 249
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 827 and 1649 heavy chain CDR1

<400> 249

Gly Tyr Ser Phe Thr Thr Tyr Trp Ile His
1   5   10

<210> 250
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 heavy chain

<400> 250

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Thr Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Gly Gln Leu Gly Lys Tyr Tyr Tyr Tyr Gly Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115   120   125

```
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  251
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  1D7 light chain

<400>  251

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

```
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
```

195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 252
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 variable heavy chain

<400> 252

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gln Leu Gly Lys Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 253
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 variable light chain

<400> 253

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 254
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 heavy chain CDR1

<400> 254

Ser Tyr Gly Met His
1 5

<210> 255
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 heavy chain CDR2

<400> 255

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 256
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 heavy chain CDR3

<400> 256

Gly Gly Gln Leu Gly Lys Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 257
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 light chain CDR1

<400> 257

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly

1 5 10

<210> 258
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 light chain CDR2

<400> 258

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> 259
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 1D7 light chain CDR3

<400> 259

Leu Gln His Asn Asn Tyr Pro Trp Thr
1 5

<210> 260
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 heavy chain

<400> 260

Gln Val Gln Val Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Leu Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220
```

```
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
```

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 261
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 light chain

<400> 261

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His His Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 262
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 variable heavy chain

<400> 262

Gln Val Gln Val Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Leu Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  263
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  33C9 variable light chain

<400>  263

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His His Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 264
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 heavy chain CDR1

<400> 264

Ser Tyr Gly Met His
1 5

<210> 265
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 heavy chain CDR2

<400> 265

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 266

<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 heavy chain CDR3

<400> 266

Gly Gly Leu Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 267
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 light chain CDR1

<400> 267

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 268
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 light chain CDR2

<400> 268

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> 269
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 33C9 light chain CDR3

<400> 269

Leu Gln His His Ser Tyr Pro Trp Thr
1   5

<210> 270
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 heavy chain

<400> 270

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Gly Glu Leu Arg Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115   120   125

```
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  271
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  33F6 light chain

<400>  271

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

```
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
```

195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 272
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 variable heavy chain

<400> 272

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Glu Leu Arg Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 273
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 variable light chain

<400> 273

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 274
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 heavy chain CDR1

<400> 274

Asn Tyr Gly Met His
1 5

<210> 275
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 heavy chain CDR2

<400> 275

Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 276
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 heavy chain CDR3

<400> 276

Gly Gly Glu Leu Arg Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 277
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 light chain CDR1

<400> 277

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly

1 5 10

<210> 278
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 light chain CDR2

<400> 278

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 279
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 33F6 light chain CDR3

<400> 279

Leu Gln Leu Asn Ser Tyr Pro Trp Thr
1 5

<210> 280
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 heavy chain

<400> 280

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220
```

```
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
```

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 281
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 light chain

<400> 281

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 282
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 variable heavy chain

<400> 282

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  283
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  34G4 variable light chain

<400>  283

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 284
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 heavy chain CDR1

<400> 284

Ser Tyr Gly Met His
1 5

<210> 285
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 heavy chain CDR2

<400> 285

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 286

<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 heavy chain CDR3

<400> 286

Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 287
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 light chain CDR1

<400> 287

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 288
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 light chain CDR2

<400> 288

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> 289
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 34G4 light chain CDR3

<400> 289

Leu Gln Leu Asn Ser Tyr Pro Trp Thr
1 5

<210> 290
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 heavy chain

<400> 290

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Glu Leu Ser Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

```
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  291
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  35B10 light chain

<400>  291

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

```
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
```

195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 292
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 variable heavy chain

<400> 292

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Glu Leu Ser Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 293
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 variable light chain

<400> 293

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 294
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 heavy chain CDR1

<400> 294

Ser Tyr Gly Met His
1 5

<210> 295
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 heavy chain CDR2

<400> 295

Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 296
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 heavy chain CDR3

<400> 296

Gly Gly Glu Leu Ser Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 297
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 light chain CDR1

<400> 297

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly

1 5 10

<210> 298
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 light chain CDR2

<400> 298

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 299
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 35B10 light chain CDR3

<400> 299

Leu Gln His Asn Asn Tyr Pro Trp Thr
1 5

<210> 300
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 heavy chain

<400> 300

Gln Val Gln Val Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Gln Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220
```

```
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
```

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 301
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 light chain

<400> 301

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

```
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210>  302
<211>  123
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  41E11 variable heavy chain

<400>  302

Gln Val Gln Val Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
```

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gln Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 303
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 variable light chain

<400> 303

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 304
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 heavy chain CDR1

<400> 304

Ser Tyr Gly Met Tyr
1 5

<210> 305
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 heavy chain CDR2

<400> 305

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Arg
1 5 10 15

Gly

<210> 306

<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 heavy chain CDR3

<400> 306

Gly Gly Gln Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
1 5 10

<210> 307
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 light chain CDR1

<400> 307

Arg Ala Ser Gln Val Ile Arg Asn Asp Leu Gly
1 5 10

<210> 308
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 light chain CDR2

<400> 308

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 309
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 41E11 light chain CDR3

<400> 309

Leu Gln His Asn Ser Tyr Pro Leu Thr
1   5

<210> 310
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 heavy chain

<400> 310

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Pro Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Gly Glu Leu Gly Arg Tyr Tyr Tyr Tyr Gly Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115   120   125

```
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  311
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  41G5 light chain

<400>  311

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

```
1               5                   10                  15

Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
```

195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 312
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 variable heavy chain

<400> 312

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Pro Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Glu Leu Gly Arg Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 313
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 variable light chain

<400> 313

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 314
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 heavy chain CDR1

<400> 314

Ser Tyr Gly Met His
1 5

<210> 315
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 heavy chain CDR2

<400> 315

Val Ile Trp Tyr Pro Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 316
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 heavy chain CDR3

<400> 316

Gly Gly Glu Leu Gly Arg Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 317
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 light chain CDR1

<400> 317

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly

1 5 10

<210> 318
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 light chain CDR2

<400> 318

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 319
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 41G5 light chain CDR3

<400> 319

Leu Gln His Asn Asn Tyr Pro Trp Thr
1 5

<210> 320
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 heavy chain

<400> 320

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220
```

```
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
```

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 321
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 light chain

<400> 321

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Glu Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 322
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 variable heavy chain

<400> 322

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  323
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  42A11 variable light chain

<400>  323

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Glu Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 324
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 heavy chain CDR1

<400> 324

Ser Tyr Gly Met His
1 5

<210> 325
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 heavy chain CDR2

<400> 325

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 326

<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 heavy chain CDR3

<400> 326

Gly Gly Gln Leu Gly Tyr Tyr Tyr Tyr Ser Gly Met Asp Val
1 5 10

<210> 327
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 light chain CDR1

<400> 327

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 328
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 light chain CDR2

<400> 328

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> 329
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 42A11 light chain CDR3

<400> 329

Leu Gln His Asn Asn Tyr Pro Trp Thr
1   5

<210> 330
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 heavy chain

<400> 330

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Arg Gly Thr Val Thr Thr Pro Asp Phe Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115   120   125

```
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335


Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350


Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365


Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380


Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400


Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415


Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


Gly Lys
    450


<210>  331
<211>  216
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  44C1 light chain

<400>  331

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
```

```
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr
            20                  25                  30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Phe
                85                  90                  95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
```

195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 332
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 variable heavy chain

<400> 332

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Thr Val Thr Thr Pro Asp Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 333
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 variable light chain

<400> 333

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr
20 25 30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Phe
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 334
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 heavy chain CDR1

<400> 334

Ser Tyr Gly Met His
1 5

<210> 335
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 heavy chain CDR2

<400> 335

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 336
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 heavy chain CDR3

<400> 336

Arg Gly Thr Val Thr Thr Pro Asp Phe Asp Tyr
1 5 10

<210> 337
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 light chain CDR1

<400> 337

Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr Asn Leu Val Ser

1 5 10

<210> 338
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 light chain CDR2

<400> 338

Glu Val Ser Lys Arg Pro Ser
1 5

<210> 339
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 44C1 light chain CDR3

<400> 339

Cys Ser Tyr Ala Gly Phe Ser Thr Trp Val
1 5 10

<210> 340
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 heavy chain

<400> 340

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Tyr Gly Gly Asn Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220
```

```
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270


Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285


Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300


Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320


Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335


Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415
```

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 341
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 light chain

<400> 341

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr
20 25 30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Ile Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Tyr
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu

115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 342
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 variable heavy chain

<400> 342

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Tyr Gly Gly Asn Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  343
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  45A8 variable light chain

<400>  343

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr
            20                  25                  30


Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Ile Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
```

65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Tyr
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg
100 105 110

<210> 344
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 heavy chain CDR1

<400> 344

Ser Tyr Gly Met His
1 5

<210> 345
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 heavy chain CDR2

<400> 345

Val Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 346
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 heavy chain CDR3

<400> 346

Glu Tyr Gly Gly Asn Phe Asp Tyr
1   5

<210> 347
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 light chain CDR1

<400> 347

Thr Gly Thr Ser Ser Asp Val Gly Thr Tyr Asn Leu Val Ser
1   5   10

<210> 348
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 light chain CDR2

<400> 348

Glu Val Ser Lys Arg Pro Ser
1   5

<210> 349
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 45A8 light chain CDR3

<400> 349

Cys Ser Tyr Ala Gly Tyr Ser Thr Trp Val

1 5 10

<210> 350
<211> 454
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 heavy chain

<400> 350

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Ile Leu Thr Gly Tyr Ser Leu Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

```
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160


Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175


Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190


Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205


Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215                 220


Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240


Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255


Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270


Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285


Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    290                 295                 300


Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                325                 330                 335
```

```
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
        355                 360                 365


Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380


Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400


Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                405                 410                 415


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            420                 425                 430


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445


Ser Leu Ser Pro Gly Lys
    450


<210>  351
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  46E11 light chain

<400>  351

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
```

```
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Ala Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
```

210

<210> 352
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 variable heavy chain

<400> 352

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Ile Leu Thr Gly Tyr Ser Leu Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 353
<211> 108
<212> PRT

<213> Artificial Sequence

<220>
<223> 46E11 variable light chain

<400> 353

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ala Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 354
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 heavy chain CDR1

<400> 354

Ser Tyr Gly Met His
1 5

<210> 355
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 heavy chain CDR2

<400> 355

Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 356
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 heavy chain CDR3

<400> 356

Gly Asp Ile Leu Thr Gly Tyr Ser Leu Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 357
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 light chain CDR1

<400> 357

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 358

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 light chain CDR2

<400> 358

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 359
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 46E11 light chain CDR3

<400> 359

Leu Gln His Asn Ser Tyr Pro Trp Thr
1 5

<210> 360
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 heavy chain

<400> 360

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Gln Leu Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240
```

```
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430
```

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435   440   445

Leu Ser Pro Gly Lys
    450

<210> 361
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 light chain

<400> 361

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20   25   30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 362
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 variable heavy chain

<400> 362

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Gln Leu Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  363
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  48H12 variable light chain

<400>  363

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
```

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 364
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 heavy chain CDR1

<400> 364

Ser Tyr Gly Met His
1 5

<210> 365
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 heavy chain CDR2

<400> 365

Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 366
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 heavy chain CDR3

<400> 366

Gly Gly Gln Leu Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1   5   10

<210> 367
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 light chain CDR1

<400> 367

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1   5   10

<210> 368
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 light chain CDR2

<400> 368

Ala Ala Ser Ser Leu Gln Ser
1   5

<210> 369
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H12 light chain CDR3

<400> 369

Leu Gln His Asn Asn Tyr Pro Trp Thr

1 5

<210> 370
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 heavy chain

<400> 370

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

```
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160


Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175


Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190


Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205


Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220


Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335
```

```
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  371
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  48H7 light chain

<400>  371

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
```

```
            20                  25                  30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Ile
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
```

210

<210> 372
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 variable heavy chain

<400> 372

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 373
<211> 108
<212> PRT

<213> Artificial Sequence

<220>
<223> 48H7 variable light chain

<400> 373

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 374
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 heavy chain CDR1

<400> 374

Ser Tyr Gly Met Tyr
1 5

<210> 375
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 heavy chain CDR2

<400> 375

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 376
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 heavy chain CDR3

<400> 376

Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
1 5 10

<210> 377
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 light chain CDR1

<400> 377

Arg Ala Ser Gln Val Ile Arg Asn Asp Leu Gly
1 5 10

<210> 378

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 light chain CDR2

<400> 378

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 379
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 48H7 light chain CDR3

<400> 379

Leu Gln His Asn Ser Tyr Pro Ile Thr
1 5

<210> 380
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 heavy chain

<400> 380

Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Arg Leu Gly Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240
```

```
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430
```

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435   440   445

Leu Ser Pro Gly Lys
    450

<210> 381
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 light chain

<400> 381

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20   25   30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 382
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 variable heavy chain

<400> 382

Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ala Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Arg Leu Gly Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  383
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  49D9 variable light chain

<400>  383

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
```

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Leu Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 384
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 heavy chain CDR1

<400> 384

Ser Tyr Gly Met His
1 5

<210> 385
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 heavy chain CDR2

<400> 385

Val Ile Trp Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 386
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 heavy chain CDR3

<400> 386

Gly Gly Arg Leu Gly Phe Tyr Tyr Tyr Tyr Gly Met Asp Val
1   5   10

<210> 387
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 light chain CDR1

<400> 387

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1   5   10

<210> 388
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 light chain CDR2

<400> 388

Ala Ala Ser Ser Leu Gln Ser
1   5

<210> 389
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 49D9 light chain CDR3

<400> 389

Leu Gln Leu Asn Ser Tyr Pro Trp Thr

1 5

<210> 390
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 heavy chain

<400> 390

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Ser Asp Gly Asn Asn Lys Tyr Tyr Glu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Ala Thr Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

```
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160


Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175


Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190


Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205


Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220


Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270


Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285


Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300


Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320


Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335
```

```
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  391
<211>  216
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  49E2 light chain

<400>  391

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ile Tyr
            20                  25                  30


Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
```

```
        35                  40                  45

Met Ile His Glu Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ile
                85                  90                  95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 392

<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 variable heavy chain

<400> 392

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Ser Asp Gly Asn Asn Lys Tyr Tyr Glu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Ala Thr Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 393
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 variable light chain

<400> 393

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ile Tyr
20 25 30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile His Glu Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ile
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 394
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 heavy chain CDR1

<400> 394

Ser Tyr Gly Met His
1 5

<210> 395
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> 49E2 heavy chain CDR2

<400> 395

Val Ile Trp Ser Asp Gly Asn Asn Lys Tyr Tyr Glu Asp Ser Val Lys
1   5   10   15

Gly

<210> 396
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 heavy chain CDR3

<400> 396

Asp Thr Ala Thr Pro Phe Asp Tyr
1   5

<210> 397
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 light chain CDR1

<400> 397

Thr Gly Thr Ser Ser Asp Val Gly Ile Tyr Asn Leu Val Ser
1   5   10

<210> 398
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 light chain CDR2

<400> 398

Glu Val Ser Lys Arg Pro Ser
1   5

<210> 399
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 49E2 light chain CDR3

<400> 399

Cys Ser Tyr Ala Gly Ile Ser Thr Trp Val
1   5   10

<210> 400
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 heavy chain

<400> 400

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Cys
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Arg Tyr Asn Trp Asn Asp Gly Gly Val Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255
```

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445
```

Ser Pro Gly Lys
    450

<210> 401
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 light chain

<400> 401

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Ile Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20   25   30

Leu His Trp Tyr Lys Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Gly Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115   120   125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 402
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 variable heavy chain

<400> 402

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Cys
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Leu Arg Tyr Asn Trp Asn Asp Gly Gly Val Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  403
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  48A9 variable light chain

<400>  403

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Ile Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


Leu His Trp Tyr Lys Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Ser Thr Pro Leu
```

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 404
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 heavy chain CDR1

<400> 404

Ser Cys Gly Met His
1 5

<210> 405
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 heavy chain CDR2

<400> 405

Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 406
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 heavy chain CDR3

<400> 406

Asp Leu Arg Tyr Asn Trp Asn Asp Gly Gly Val Asp Tyr
1 5 10

<210> 407
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 light chain CDR1

<400> 407

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu His
1 5 10

<210> 408
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 light chain CDR2

<400> 408

Gly Ala Ser Arg Leu Gln Ser
1 5

<210> 409
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 48A9 light chain CDR3

<400> 409

Gln Gln Ser Ser Ser Thr Pro Leu Thr
1 5

<210> 410

<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 heavy chain

<400> 410

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                  10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30


Gly Tyr Phe Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn His Phe
65                  70                  75                  80


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Arg Asp Leu Phe Tyr Tyr Asp Ser Ser Gly Pro Arg Gly Phe
            100                 105                 110


Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125


Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140


Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160
```

```
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350
```

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445


Leu Ser Leu Ser Pro Gly Lys
    450                 455


<210>  411
<211>  215
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  5H7 light chain

<400>  411

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Val Ser Ser Asn
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
```

```
        35                  40                  45

Ile Tyr Gly Ser Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Pro
                85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 412

<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 variable heavy chain

<400> 412

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Phe Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn His Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Leu Phe Tyr Tyr Asp Ser Ser Gly Pro Arg Gly Phe
100 105 110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 413
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 variable light chain

<400> 413

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Val Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ser Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 414
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 heavy chain CDR1

<400> 414

Ser Gly Gly Tyr Phe Trp Ser
1 5

<210> 415
<211> 16
<212> PRT

<213> Artificial Sequence

<220>
<223> 5H7 heavy chain CDR2

<400> 415

Tyr Ile Tyr Tyr Ser Gly Thr Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 416
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 heavy chain CDR3

<400> 416

Asp Leu Phe Tyr Tyr Asp Ser Ser Gly Pro Arg Gly Phe Asp Pro
1 5 10 15

<210> 417
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 light chain CDR1

<400> 417

Arg Ala Ser Gln Thr Val Ser Ser Asn Tyr Leu Ala
1 5 10

<210> 418
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 light chain CDR2

<400> 418

Gly Ser Ser Thr Arg Ala Thr
1 5

<210> 419
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 5H7 light chain CDR3

<400> 419

Gln Gln Tyr Asp Ser Ser Pro Trp Thr
1 5

<210> 420
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 heavy chain

<400> 420

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

```
Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270
```

```
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450
```

<210> 421
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 light chain

<400> 421

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Ser Tyr Pro Trp
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
```

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 422
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 variable heavy chain

<400> 422

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

```
Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  423
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  7A10 variable light chain

<400>  423

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Ser Tyr Pro Trp
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
```

100 105

<210> 424
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 heavy chain CDR1

<400> 424

Ser Tyr Gly Met His
1 5

<210> 425
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 heavy chain CDR2

<400> 425

Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 426
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 heavy chain CDR3

<400> 426

Gly Gly Glu Leu Gly Arg Asp Tyr Tyr Ser Gly Met Asp Val
1 5 10

<210> 427
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 light chain CDR1

<400> 427

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 428
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 light chain CDR2

<400> 428

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 429
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7A10 light chain CDR3

<400> 429

Gln Gln His Asn Ser Tyr Pro Trp Thr
1 5

<210> 430
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 heavy chain

<400> 430

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Arg Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125


Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140


Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160


Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175
```

```
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190


Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205


Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
    210                 215                 220


Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350


Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365
```

```
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445


Leu Ser Pro Gly Lys
    450


<210>  431
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  9H6 light chain

<400>  431

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30


Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Arg Leu Ile
        35                  40                  45


Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

```
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Thr Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210>  432
<211>  123
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> 9H6 variable heavy chain

<400> 432

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Gly Arg Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 433
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 variable light chain

<400> 433

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Arg Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Thr Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 434
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 heavy chain CDR1

<400> 434

Ser Tyr Gly Met His
1 5

<210> 435
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 heavy chain CDR2

<400> 435

Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 436
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 heavy chain CDR3

<400> 436

Gly Gly Arg Leu Gly Lys Asp Tyr Tyr Ser Gly Met Asp Val
1 5 10

<210> 437
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 light chain CDR1

<400> 437

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 438
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 light chain CDR2

<400> 438

Ala Thr Ser Ser Leu Gln Ser
1 5

<210> 439
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 9H6 light chain CDR3

<400> 439

Leu Gln His Asn Thr Tyr Pro Trp Thr
1 5

<210> 440
<211> 177
<212> PRT
<213> Artificial Sequence

<220>
<223> GITRL

<400> 440

Met Cys Leu Ser His Leu Glu Asn Met Pro Leu Ser His Ser Arg Thr
1 5 10 15

Gln Gly Ala Gln Arg Ser Ser Trp Lys Leu Trp Leu Phe Cys Ser Ile
20 25 30

Val Met Leu Leu Phe Leu Cys Ser Phe Ser Trp Leu Ile Phe Ile Phe
35 40 45

Leu Gln Leu Glu Thr Ala Lys Glu Pro Cys Met Ala Lys Phe Gly Pro
50 55 60

Leu Pro Ser Lys Trp Gln Met Ala Ser Ser Glu Pro Pro Cys Val Asn
65 70 75 80

```
Lys Val Ser Asp Trp Lys Leu Glu Ile Leu Gln Asn Gly Leu Tyr Leu
                85                  90                  95


Ile Tyr Gly Gln Val Ala Pro Asn Ala Asn Tyr Asn Asp Val Ala Pro
            100                 105                 110


Phe Glu Val Arg Leu Tyr Lys Asn Lys Asp Met Ile Gln Thr Leu Thr
        115                 120                 125


Asn Lys Ser Lys Ile Gln Asn Val Gly Gly Thr Tyr Glu Leu His Val
    130                 135                 140


Gly Asp Thr Ile Asp Leu Ile Phe Asn Ser Glu His Gln Val Leu Lys
145                 150                 155                 160


Asn Asn Thr Tyr Trp Gly Ile Ile Leu Leu Ala Asn Pro Gln Phe Ile
                165                 170                 175


Ser



<210>  441
<211>  125
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  GITRL soluble domain

<400>  441

Thr Ala Lys Glu Pro Cys Met Ala Lys Phe Gly Pro Leu Pro Ser Lys
1               5                   10                  15


Trp Gln Met Ala Ser Ser Glu Pro Pro Cys Val Asn Lys Val Ser Asp
            20                  25                  30


Trp Lys Leu Glu Ile Leu Gln Asn Gly Leu Tyr Leu Ile Tyr Gly Gln
```

35 40 45

Val Ala Pro Asn Ala Asn Tyr Asn Asp Val Ala Pro Phe Glu Val Arg
50 55 60

Leu Tyr Lys Asn Lys Asp Met Ile Gln Thr Leu Thr Asn Lys Ser Lys
65 70 75 80

Ile Gln Asn Val Gly Gly Thr Tyr Glu Leu His Val Gly Asp Thr Ile
85 90 95

Asp Leu Ile Phe Asn Ser Glu His Gln Val Leu Lys Asn Asn Thr Tyr
100 105 110

Trp Gly Ile Ile Leu Leu Ala Asn Pro Gln Phe Ile Ser
115 120 125

<210> 442
<211> 283
<212> PRT
<213> Homo Sapiens

<400> 442

Met Glu Pro Pro Gly Asp Trp Gly Pro Pro Pro Trp Arg Ser Thr Pro
1 5 10 15

Arg Thr Asp Val Leu Arg Leu Val Leu Tyr Leu Thr Phe Leu Gly Ala
20 25 30

Pro Cys Tyr Ala Pro Ala Leu Pro Ser Cys Lys Glu Asp Glu Tyr Pro
35 40 45

Val Gly Ser Glu Cys Cys Pro Lys Cys Ser Pro Gly Tyr Arg Val Lys
50 55 60

Glu Ala Cys Gly Glu Leu Thr Gly Thr Val Cys Glu Pro Cys Pro Pro
65 70 75 80

```
Gly Thr Tyr Ile Ala His Leu Asn Gly Leu Ser Lys Cys Leu Gln Cys
                85                  90                  95

Gln Met Cys Asp Pro Ala Met Gly Leu Arg Ala Ser Arg Asn Cys Ser
            100                 105                 110

Arg Thr Glu Asn Ala Val Cys Gly Cys Ser Pro Gly His Phe Cys Ile
        115                 120                 125

Val Gln Asp Gly Asp His Cys Ala Ala Cys Arg Ala Tyr Ala Thr Ser
    130                 135                 140

Ser Pro Gly Gln Arg Val Gln Lys Gly Gly Thr Glu Ser Gln Asp Thr
145                 150                 155                 160

Leu Cys Gln Asn Cys Pro Pro Gly Thr Phe Ser Pro Asn Gly Thr Leu
                165                 170                 175

Glu Glu Cys Gln His Gln Thr Lys Cys Ser Trp Leu Val Thr Lys Ala
            180                 185                 190

Gly Ala Gly Thr Ser Ser Ser His Trp Val Trp Trp Phe Leu Ser Gly
        195                 200                 205

Ser Leu Val Ile Val Ile Val Cys Ser Thr Val Gly Leu Ile Ile Cys
    210                 215                 220

Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile Val Ser
225                 230                 235                 240

Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val Ile Glu
                245                 250                 255

Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu Glu Thr
            260                 265                 270
```

```
Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His
        275                 280


<210>  443
<211>  240
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  LIGHT (HVEM ligand)

<400>  443

Met Glu Glu Ser Val Val Arg Pro Ser Val Phe Val Val Asp Gly Gln
1               5                   10                  15


Thr Asp Ile Pro Phe Thr Arg Leu Gly Arg Ser His Arg Arg Gln Ser
            20                  25                  30


Cys Ser Val Ala Arg Val Gly Leu Gly Leu Leu Leu Leu Leu Met Gly
        35                  40                  45


Ala Gly Leu Ala Val Gln Gly Trp Phe Leu Leu Gln Leu His Trp Arg
    50                  55                  60


Leu Gly Glu Met Val Thr Arg Leu Pro Asp Gly Pro Ala Gly Ser Trp
65                  70                  75                  80


Glu Gln Leu Ile Gln Glu Arg Arg Ser His Glu Val Asn Pro Ala Ala
                85                  90                  95


His Leu Thr Gly Ala Asn Ser Ser Leu Thr Gly Ser Gly Gly Pro Leu
            100                 105                 110


Leu Trp Glu Thr Gln Leu Gly Leu Ala Phe Leu Arg Gly Leu Ser Tyr
        115                 120                 125
```

```
His Asp Gly Ala Leu Val Val Thr Lys Ala Gly Tyr Tyr Tyr Ile Tyr
    130                 135                 140


Ser Lys Val Gln Leu Gly Gly Val Gly Cys Pro Leu Gly Leu Ala Ser
145                 150                 155                 160


Thr Ile Thr His Gly Leu Tyr Lys Arg Thr Pro Arg Tyr Pro Glu Glu
                165                 170                 175


Leu Glu Leu Leu Val Ser Gln Gln Ser Pro Cys Gly Arg Ala Thr Ser
            180                 185                 190


Ser Ser Arg Val Trp Trp Asp Ser Ser Phe Leu Gly Gly Val Val His
        195                 200                 205


Leu Glu Ala Gly Glu Lys Val Val Val Arg Val Leu Asp Glu Arg Leu
    210                 215                 220


Val Arg Leu Arg Asp Gly Thr Arg Ser Tyr Phe Gly Ala Phe Met Val
225                 230                 235                 240


<210>  444
<211>  147
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  LIGHT soluble domain

<400>  444

Pro Ala Ala His Leu Thr Gly Ala Asn Ser Ser Leu Thr Gly Ser Gly
1               5                   10                  15


Gly Pro Leu Leu Trp Glu Thr Gln Leu Gly Leu Ala Phe Leu Arg Gly
            20                  25                  30


Leu Ser Tyr His Asp Gly Ala Leu Val Val Thr Lys Ala Gly Tyr Tyr
        35                  40                  45
```

```
Tyr Ile Tyr Ser Lys Val Gln Leu Gly Gly Val Gly Cys Pro Leu Gly
    50                  55                  60

Leu Ala Ser Thr Ile Thr His Gly Leu Tyr Lys Arg Thr Pro Arg Tyr
65                  70                  75                  80

Pro Glu Glu Leu Glu Leu Leu Val Ser Gln Gln Ser Pro Cys Gly Arg
                85                  90                  95

Ala Thr Ser Ser Ser Arg Val Trp Trp Asp Ser Ser Phe Leu Gly Gly
            100                 105                 110

Val Val His Leu Glu Ala Gly Glu Lys Val Val Val Arg Val Leu Asp
        115                 120                 125

Glu Arg Leu Val Arg Leu Arg Asp Gly Thr Arg Ser Tyr Phe Gly Ala
    130                 135                 140

Phe Met Val
145
```

<210> 445
<211> 146
<212> PRT
<213> Artificial Sequence

<220>
<223> LIGHT soluble domain (alternative)

<400> 445

```
Ala Ala His Leu Thr Gly Ala Asn Ser Ser Leu Thr Gly Ser Gly Gly
1               5                   10                  15

Pro Leu Leu Trp Glu Thr Gln Leu Gly Leu Ala Phe Leu Arg Gly Leu
            20                  25                  30
```

```
Ser Tyr His Asp Gly Ala Leu Val Val Thr Lys Ala Gly Tyr Tyr Tyr
        35                  40                  45


Ile Tyr Ser Lys Val Gln Leu Gly Gly Val Gly Cys Pro Leu Gly Leu
    50                  55                  60


Ala Ser Thr Ile Thr His Gly Leu Tyr Lys Arg Thr Pro Arg Tyr Pro
65                  70                  75                  80


Glu Glu Leu Glu Leu Leu Val Ser Gln Gln Ser Pro Cys Gly Arg Ala
                85                  90                  95


Thr Ser Ser Ser Arg Val Trp Trp Asp Ser Ser Phe Leu Gly Gly Val
            100                 105                 110


Val His Leu Glu Ala Gly Glu Lys Val Val Val Arg Val Leu Asp Glu
        115                 120                 125


Arg Leu Val Arg Leu Arg Asp Gly Thr Arg Ser Tyr Phe Gly Ala Phe
    130                 135                 140


Met Val
145


<210>  446
<211>  145
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  LIGHT soluble domain (alternative)

<400>  446

Ala His Leu Thr Gly Ala Asn Ser Ser Leu Thr Gly Ser Gly Gly Pro
1               5                   10                  15


Leu Leu Trp Glu Thr Gln Leu Gly Leu Ala Phe Leu Arg Gly Leu Ser
            20                  25                  30
```

```
Tyr His Asp Gly Ala Leu Val Val Thr Lys Ala Gly Tyr Tyr Tyr Ile
        35                  40                  45

Tyr Ser Lys Val Gln Leu Gly Gly Val Gly Cys Pro Leu Gly Leu Ala
    50                  55                  60

Ser Thr Ile Thr His Gly Leu Tyr Lys Arg Thr Pro Arg Tyr Pro Glu
65                  70                  75                  80

Glu Leu Glu Leu Leu Val Ser Gln Gln Ser Pro Cys Gly Arg Ala Thr
                85                  90                  95

Ser Ser Ser Arg Val Trp Trp Asp Ser Ser Phe Leu Gly Gly Val Val
            100                 105                 110

His Leu Glu Ala Gly Glu Lys Val Val Val Arg Val Leu Asp Glu Arg
        115                 120                 125

Leu Val Arg Leu Arg Asp Gly Thr Arg Ser Tyr Phe Gly Ala Phe Met
    130                 135                 140

Val
145


<210>  447
<211>  335
<212>  PRT
<213>  Homo Sapiens

<400>  447

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala
1               5                   10                  15

Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser
            20                  25                  30
```

```
Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn
        35                  40                  45

Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro
    50                  55                  60

Pro Gly Glu Arg Lys Ala Arg Asp Cys Thr Val Asn Gly Asp Glu Pro
65                  70                  75                  80

Asp Cys Val Pro Cys Gln Glu Gly Lys Glu Tyr Thr Asp Lys Ala His
                85                  90                  95

Phe Ser Ser Lys Cys Arg Arg Cys Arg Leu Cys Asp Glu Gly His Gly
            100                 105                 110

Leu Glu Val Glu Ile Asn Cys Thr Arg Thr Gln Asn Thr Lys Cys Arg
        115                 120                 125

Cys Lys Pro Asn Phe Phe Cys Asn Ser Thr Val Cys Glu His Cys Asp
    130                 135                 140

Pro Cys Thr Lys Cys Glu His Gly Ile Ile Lys Glu Cys Thr Leu Thr
145                 150                 155                 160

Ser Asn Thr Lys Cys Lys Glu Glu Gly Ser Arg Ser Asn Leu Gly Trp
                165                 170                 175

Leu Cys Leu Leu Leu Leu Pro Ile Pro Leu Ile Val Trp Val Lys Arg
            180                 185                 190

Lys Glu Val Gln Lys Thr Cys Arg Lys His Arg Lys Glu Asn Gln Gly
        195                 200                 205

Ser His Glu Ser Pro Thr Leu Asn Pro Glu Thr Val Ala Ile Asn Leu
    210                 215                 220
```

```
Ser Asp Val Asp Leu Ser Lys Tyr Ile Thr Thr Ile Ala Gly Val Met
225                 230                 235                 240


Thr Leu Ser Gln Val Lys Gly Phe Val Arg Lys Asn Gly Val Asn Glu
                245                 250                 255


Ala Lys Ile Asp Glu Ile Lys Asn Asp Asn Val Gln Asp Thr Ala Glu
            260                 265                 270


Gln Lys Val Gln Leu Leu Arg Asn Trp His Gln Leu His Gly Lys Lys
        275                 280                 285


Glu Ala Tyr Asp Thr Leu Ile Lys Asp Leu Lys Lys Ala Asn Leu Cys
    290                 295                 300


Thr Leu Ala Glu Lys Ile Gln Thr Ile Ile Leu Lys Asp Ile Thr Ser
305                 310                 315                 320


Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
                325                 330                 335


<210>  448
<211>  314
<212>  PRT
<213>  Homo Sapiens

<400>  448

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala
1               5                   10                  15


Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser
            20                  25                  30


Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn
        35                  40                  45
```

```
Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro
    50                  55                  60

Pro Gly Glu Arg Lys Ala Arg Asp Cys Thr Val Asn Gly Asp Glu Pro
65                  70                  75                  80

Asp Cys Val Pro Cys Gln Glu Gly Lys Glu Tyr Thr Asp Lys Ala His
                85                  90                  95

Phe Ser Ser Lys Cys Arg Arg Cys Arg Leu Cys Asp Glu Gly His Gly
            100                 105                 110

Leu Glu Val Glu Ile Asn Cys Thr Arg Thr Gln Asn Thr Lys Cys Arg
        115                 120                 125

Cys Lys Pro Asn Phe Phe Cys Asn Ser Thr Val Cys Glu His Cys Asp
    130                 135                 140

Pro Cys Thr Lys Cys Glu His Gly Ile Ile Lys Glu Cys Thr Leu Thr
145                 150                 155                 160

Ser Asn Thr Lys Cys Lys Glu Glu Val Lys Arg Lys Glu Val Gln Lys
                165                 170                 175

Thr Cys Arg Lys His Arg Lys Glu Asn Gln Gly Ser His Glu Ser Pro
            180                 185                 190

Thr Leu Asn Pro Glu Thr Val Ala Ile Asn Leu Ser Asp Val Asp Leu
        195                 200                 205

Ser Lys Tyr Ile Thr Thr Ile Ala Gly Val Met Thr Leu Ser Gln Val
    210                 215                 220

Lys Gly Phe Val Arg Lys Asn Gly Val Asn Glu Ala Lys Ile Asp Glu
225                 230                 235                 240
```

```
Ile Lys Asn Asp Asn Val Gln Asp Thr Ala Glu Gln Lys Val Gln Leu
                245                 250                 255


Leu Arg Asn Trp His Gln Leu His Gly Lys Lys Glu Ala Tyr Asp Thr
            260                 265                 270


Leu Ile Lys Asp Leu Lys Lys Ala Asn Leu Cys Thr Leu Ala Glu Lys
        275                 280                 285


Ile Gln Thr Ile Ile Leu Lys Asp Ile Thr Ser Asp Ser Glu Asn Ser
    290                 295                 300


Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
305                 310


<210>  449
<211>  220
<212>  PRT
<213>  Homo Sapiens

<400>  449

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala
1               5                   10                  15


Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser
            20                  25                  30


Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn
        35                  40                  45


Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro
    50                  55                  60


Pro Gly Glu Arg Lys Ala Arg Asp Cys Thr Val Asn Gly Asp Glu Pro
65                  70                  75                  80


Asp Cys Val Pro Cys Gln Glu Gly Lys Glu Tyr Thr Asp Lys Ala His
```

85 90 95

Phe Ser Ser Lys Cys Arg Arg Cys Arg Leu Cys Asp Glu Gly His Gly
100 105 110

Leu Glu Val Glu Ile Asn Cys Thr Arg Thr Gln Asn Thr Lys Cys Arg
115 120 125

Cys Lys Pro Asn Phe Phe Cys Asn Ser Thr Val Cys Glu His Cys Asp
130 135 140

Pro Cys Thr Lys Cys Glu His Gly Ile Ile Lys Glu Cys Thr Leu Thr
145 150 155 160

Ser Asn Thr Lys Cys Lys Glu Glu Gly Ser Arg Ser Asn Leu Gly Trp
165 170 175

Leu Cys Leu Leu Leu Leu Pro Ile Pro Leu Ile Val Trp Val Lys Arg
180 185 190

Lys Glu Val Gln Lys Thr Cys Arg Lys His Arg Lys Glu Asn Gln Gly
195 200 205

Ser His Glu Ser Pro Thr Leu Asn Pro Met Leu Thr
210 215 220

<210> 450
<211> 197
<212> PRT
<213> Homo Sapiens

<400> 450

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala
1 5 10 15

Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser
20 25 30

```
Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn
        35                  40                  45

Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro
    50                  55                  60

Pro Gly Glu Arg Lys Ala Arg Asp Cys Thr Val Asn Gly Asp Glu Pro
65                  70                  75                  80

Asp Cys Val Pro Cys Gln Glu Gly Lys Glu Tyr Thr Asp Lys Ala His
                85                  90                  95

Phe Ser Ser Lys Cys Arg Arg Cys Arg Leu Cys Asp Glu Gly His Gly
            100                 105                 110

Leu Glu Val Glu Ile Asn Cys Thr Arg Thr Gln Asn Thr Lys Cys Arg
        115                 120                 125

Cys Lys Pro Asn Phe Phe Cys Asn Ser Thr Val Cys Glu His Cys Asp
    130                 135                 140

Pro Cys Thr Lys Cys Glu His Gly Ile Ile Lys Glu Cys Thr Leu Thr
145                 150                 155                 160

Ser Asn Thr Lys Cys Lys Glu Glu Gly Ser Arg Ser Asn Leu Gly Trp
                165                 170                 175

Leu Cys Leu Leu Leu Leu Pro Ile Pro Leu Ile Val Trp Gly Asn Ser
            180                 185                 190

Gly Asn Lys Phe Ile
        195
```

<210> 451
<211> 132

<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain variable region for E09

<400> 451

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ala Ser Ile Ser Ala Asn
20 25 30

Ser Tyr Tyr Gly Val Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu
35 40 45

Trp Val Gly Ser Ile Ala Tyr Arg Gly Asn Ser Asn Ser Gly Ser Thr
50 55 60

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Ala Thr Val Ser Val Asp Thr
65 70 75 80

Ser Lys Asn Gln Val Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp
85 90 95

Thr Ala Leu Tyr Tyr Cys Ala Arg Arg Gln Leu Leu Asp Asp Gly Thr
100 105 110

Gly Tyr Gln Trp Ala Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
115 120 125

Thr Val Ser Ser
130

<210> 452
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain variable region for E09

<400> 452

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Glu Ala Pro Arg Gln
1   5   10   15

Thr Val Thr Ile Ser Cys Ser Gly Asn Ser Phe Asn Ile Gly Arg Tyr
            20   25   30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Lys Leu Leu
        35   40   45

Ile Tyr Tyr Asn Asn Leu Arg Phe Ser Gly Val Ser Asp Arg Phe Ser
    50   55   60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Arg Asp Leu Leu
65   70   75   80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Asp Thr Leu
                85   90   95

Lys Gly Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100   105   110

<210> 453
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 for E09

<400> 453

Ala Asn Ser Tyr Tyr Gly Val
1   5

<210> 454
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 for E09

<400> 454

Gly Ser Ile Ala Tyr Arg Gly Asn Ser Asn Ser Gly Ser Thr Tyr Tyr
1 5 10 15

Asn Pro Ser Leu Lys Ser
20

<210> 455
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 for E09

<400> 455

Arg Gln Leu Leu Asp Asp Gly Thr Gly Tyr Gln Trp Ala Ala Phe Asp
1 5 10 15

Val

<210> 456
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR1 for E09

<400> 456

Ser Gly Asn Ser Phe Asn Ile Gly Arg Tyr Pro Val Asn
1 5 10

<210> 457
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR2 for E09

<400> 457

Tyr Asn Asn Leu Arg Phe Ser
1 5

<210> 458
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 for E09

<400> 458

Ser Thr Trp Asp Asp Thr Leu Lys Gly Trp Val
1 5 10

<210> 459
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<223> CD95L (CD95 ligand)

<400> 459

Met Gln Gln Pro Phe Asn Tyr Pro Tyr Pro Gln Ile Tyr Trp Val Asp
1 5 10 15

Ser Ser Ala Ser Ser Pro Trp Ala Pro Pro Gly Thr Val Leu Pro Cys
20 25 30

```
Pro Thr Ser Val Pro Arg Arg Pro Gly Gln Arg Arg Pro Pro Pro Pro
        35                  40                  45

Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Pro Pro Pro Pro Leu Pro
    50                  55                  60

Pro Leu Pro Leu Pro Pro Leu Lys Lys Arg Gly Asn His Ser Thr Gly
65                  70                  75                  80

Leu Cys Leu Leu Val Met Phe Phe Met Val Leu Val Ala Leu Val Gly
                85                  90                  95

Leu Gly Leu Gly Met Phe Gln Leu Phe His Leu Gln Lys Glu Leu Ala
            100                 105                 110

Glu Leu Arg Glu Ser Thr Ser Gln Met His Thr Ala Ser Ser Leu Glu
        115                 120                 125

Lys Gln Ile Gly His Pro Ser Pro Pro Pro Glu Lys Lys Glu Leu Arg
    130                 135                 140

Lys Val Ala His Leu Thr Gly Lys Ser Asn Ser Arg Ser Met Pro Leu
145                 150                 155                 160

Glu Trp Glu Asp Thr Tyr Gly Ile Val Leu Leu Ser Gly Val Lys Tyr
                165                 170                 175

Lys Lys Gly Gly Leu Val Ile Asn Glu Thr Gly Leu Tyr Phe Val Tyr
            180                 185                 190

Ser Lys Val Tyr Phe Arg Gly Gln Ser Cys Asn Asn Leu Pro Leu Ser
        195                 200                 205

His Lys Val Tyr Met Arg Asn Ser Lys Tyr Pro Gln Asp Leu Val Met
    210                 215                 220
```

Met Glu Gly Lys Met Met Ser Tyr Cys Thr Thr Gly Gln Met Trp Ala
225 230 235 240

Arg Ser Ser Tyr Leu Gly Ala Val Phe Asn Leu Thr Ser Ala Asp His
245 250 255

Leu Tyr Val Asn Val Ser Glu Leu Ser Leu Val Asn Phe Glu Glu Ser
260 265 270

Gln Thr Phe Phe Gly Leu Tyr Lys Leu
275 280

<210> 460
<211> 136
<212> PRT
<213> Artificial Sequence

<220>
<223> CD95L soluble domain

<400> 460

Val Ala His Leu Thr Gly Lys Ser Asn Ser Arg Ser Met Pro Leu Glu
1 5 10 15

Trp Glu Asp Thr Tyr Gly Ile Val Leu Leu Ser Gly Val Lys Tyr Lys
20 25 30

Lys Gly Gly Leu Val Ile Asn Glu Thr Gly Leu Tyr Phe Val Tyr Ser
35 40 45

Lys Val Tyr Phe Arg Gly Gln Ser Cys Asn Asn Leu Pro Leu Ser His
50 55 60

Lys Val Tyr Met Arg Asn Ser Lys Tyr Pro Gln Asp Leu Val Met Met
65 70 75 80

Glu Gly Lys Met Met Ser Tyr Cys Thr Thr Gly Gln Met Trp Ala Arg
85 90 95

Ser Ser Tyr Leu Gly Ala Val Phe Asn Leu Thr Ser Ala Asp His Leu
100 105 110

Tyr Val Asn Val Ser Glu Leu Ser Leu Val Asn Phe Glu Glu Ser Gln
115 120 125

Thr Phe Phe Gly Leu Tyr Lys Leu
130 135

<210> 461
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> CD95L soluble domain (alternative)

<400> 461

Ala His Leu Thr Gly Lys Ser Asn Ser Arg Ser Met Pro Leu Glu Trp
1 5 10 15

Glu Asp Thr Tyr Gly Ile Val Leu Leu Ser Gly Val Lys Tyr Lys Lys
20 25 30

Gly Gly Leu Val Ile Asn Glu Thr Gly Leu Tyr Phe Val Tyr Ser Lys
35 40 45

Val Tyr Phe Arg Gly Gln Ser Cys Asn Asn Leu Pro Leu Ser His Lys
50 55 60

Val Tyr Met Arg Asn Ser Lys Tyr Pro Gln Asp Leu Val Met Met Glu
65 70 75 80

Gly Lys Met Met Ser Tyr Cys Thr Thr Gly Gln Met Trp Ala Arg Ser
85 90 95

Ser Tyr Leu Gly Ala Val Phe Asn Leu Thr Ser Ala Asp His Leu Tyr
100 105 110

Val Asn Val Ser Glu Leu Ser Leu Val Asn Phe Glu Glu Ser Gln Thr
115 120 125

Phe Phe Gly Leu Tyr Lys Leu
130 135

<210> 462
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> CD95L soluble domain (alternative)

<400> 462

His Leu Thr Gly Lys Ser Asn Ser Arg Ser Met Pro Leu Glu Trp Glu
1 5 10 15

Asp Thr Tyr Gly Ile Val Leu Leu Ser Gly Val Lys Tyr Lys Lys Gly
20 25 30

Gly Leu Val Ile Asn Glu Thr Gly Leu Tyr Phe Val Tyr Ser Lys Val
35 40 45

Tyr Phe Arg Gly Gln Ser Cys Asn Asn Leu Pro Leu Ser His Lys Val
50 55 60

Tyr Met Arg Asn Ser Lys Tyr Pro Gln Asp Leu Val Met Met Glu Gly
65 70 75 80

Lys Met Met Ser Tyr Cys Thr Thr Gly Gln Met Trp Ala Arg Ser Ser
85 90 95

Tyr Leu Gly Ala Val Phe Asn Leu Thr Ser Ala Asp His Leu Tyr Val
100 105 110

Asn Val Ser Glu Leu Ser Leu Val Asn Phe Glu Glu Ser Gln Thr Phe
        115   120   125

Phe Gly Leu Tyr Lys Leu
    130

<210> 463
<211> 440
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab heavy chain

<400> 463

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100   105   110

```
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
        115                 120                 125


Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140


Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160


Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175


Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
            180                 185                 190


Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205


Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
    210                 215                 220


Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225                 230                 235                 240


Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                245                 250                 255


Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
            260                 265                 270


Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        275                 280                 285


Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    290                 295                 300
```

```
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305                 310                 315                 320


Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                325                 330                 335


Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
            340                 345                 350


Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
        355                 360                 365


Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    370                 375                 380


Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385                 390                 395                 400


Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
                405                 410                 415


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
            420                 425                 430


Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440


<210>  464
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  nivolumab light chain

<400>  464

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15
```

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
```

Phe Asn Arg Gly Glu Cys
    210

<210> 465
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab variable heavy chain

<400> 465

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100   105   110

Ser

<210> 466
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab variable light chain

<400> 466

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 467
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab heavy chain CDR1

<400> 467

Asn Ser Gly Met His
1 5

<210> 468
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab heavy chain CDR2

<400> 468

Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 469
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab heavy chain CDR3

<400> 469

Asn Asp Asp Tyr
1

<210> 470
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab light chain CDR1

<400> 470

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 471
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab light chain CDR2

<400> 471

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 472
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> nivolumab light chain CDR3

<400> 472

Gln Gln Ser Ser Asn Trp Pro Arg Thr
1 5

<210> 473
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab heavy chain

<400> 473

Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

```
Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60

Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220
```

```
Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255


Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270


Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285


Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300


Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320


Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335


Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350


Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400


Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
                405                 410                 415
```

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 474
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab light chain

<400> 474

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

```
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  475
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  pembrolizumab variable heavy chain

<400>  475

Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 476
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab variable light chain

<400> 476

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 477
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab heavy chain CDR1

<400> 477

Asn Tyr Tyr Met Tyr
1 5

<210> 478
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab heavy chain CDR2

<400> 478

Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe Lys
1 5 10 15

<210> 479
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab heavy chain CDR3

<400> 479

Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr
1 5 10

<210> 480
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab light chain CDR1

<400> 480

Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
1 5 10 15

<210> 481
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab light chain CDR2

<400> 481

Leu Ala Ser Tyr Leu Glu Ser
1 5

<210> 482
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> pembrolizumab light chain CDR3

<400> 482

Gln His Ser Arg Asp Leu Pro Leu Thr
1 5

<210> 483
<211> 451

<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab heavy chain

<400> 483

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125


Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190


Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205


Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220


Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly
225                 230                 235                 240


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile
                325                 330                 335


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350
```

```
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445


Pro Gly Lys
    450


<210>  484
<211>  265
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  durvalumab light chain

<400>  484

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ala Asn Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser
    50                  55                  60

Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser
65                  70                  75                  80

Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
                85                  90                  95

Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg
            100                 105                 110

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
        115                 120                 125

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser
    130                 135                 140

Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
145                 150                 155                 160

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
                165                 170                 175

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
            180                 185                 190

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
        195                 200                 205

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
    210                 215                 220

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
225                 230                 235                 240
```

```
Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
                245                 250                 255


Thr Lys Ser Phe Asn Arg Gly Glu Cys
            260                 265


<210>  485
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  durvalumab variable heavy chain

<400>  485

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 486
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab variable light chain

<400> 486

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
                85   90   95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 487
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> durvalumab heavy chain CDR1

<400> 487

Arg Tyr Trp Met Ser
1 5

<210> 488
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab heavy chain CDR2

<400> 488

Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> 489
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab heavy chain CDR3

<400> 489

Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr
1 5 10

<210> 490
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab light chain CDR1

<400> 490

Arg Ala Ser Gln Arg Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 491
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab light chain CDR2

<400> 491

Asp Ala Ser Ser Arg Ala Thr
1 5

<210> 492
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> durvalumab light chain CDR3

<400> 492

Gln Gln Tyr Gly Ser Leu Pro Trp Thr
1 5

<210> 493
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

heavy chain

<400> 493

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
```

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400
```

```
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415


Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


Gly Lys
    450


<210>  494
<211>  216
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  avelumab

light chain

<400>  494

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
```

```
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210>  495
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  avelumab

variable heavy chain
```

<400> 495

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 496
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

variable light chain

<400> 496

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

```
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95


Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110


<210>  497
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  avelumab

heavy chain CDR1

<400>  497

Ser Tyr Ile Met Met
1               5


<210>  498
<211>  17
<212>  PRT
<213>  Artificial Sequence

<220>
```

<223> avelumab

heavy chain CDR2

<400> 498

Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val Lys
1   5   10   15

Gly

<210> 499
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

heavy chain CDR3

<400> 499

Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr
1   5   10

<210> 500
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

light chain CDR1

<400> 500

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1   5   10

<210> 501
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

light chain CDR2

<400> 501

Asp Val Ser Asn Arg Pro Ser
1   5

<210> 502
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> avelumab

light chain CDR3

<400> 502

Ser Ser Tyr Thr Ser Ser Ser Thr Arg Val
1   5   10

<210> 503
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> atezolizumab

heavy chain

<400> 503

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
            20   25   30

```
Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220
```

```
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415
```

```
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  504
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  atezolizumab

light chain

<400>  504

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
```

```
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  505
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  atezolizumab

variable heavy chain

<400>  505

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
            20                  25                  30
```

```
Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ala
        115


<210>  506
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  atezolizumab

variable light chain

<400>  506

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210>  507
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  atezolizumab

heavy chain CDR1

<400>  507

Gly Phe Thr Phe Ser Asp Ser Trp Ile His
1               5                   10


<210>  508
<211>  18
<212>  PRT
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<220>
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heavy chain CDR2

<400>  508

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
1               5                   10                  15
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Lys Gly

<210> 509
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> atezolizumab

heavy chain CDR3

<400> 509

Arg His Trp Pro Gly Gly Phe Asp Tyr
1 5

<210> 510
<211> 11
<212> PRT
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<220>
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light chain CDR1

<400> 510

Arg Ala Ser Gln Asp Val Ser Thr Ala Val Ala
1 5 10

<210> 511
<211> 7
<212> PRT
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<220>
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light chain CDR2

<400> 511

Ser Ala Ser Phe Leu Tyr Ser
1 5

<210> 512
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> atezolizumab

light chain CDR3

<400> 512

Gln Gln Tyr Leu Tyr His Pro Ala Thr
1 5