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(54) Title: COMBINATION THERAPY FOR CANCER

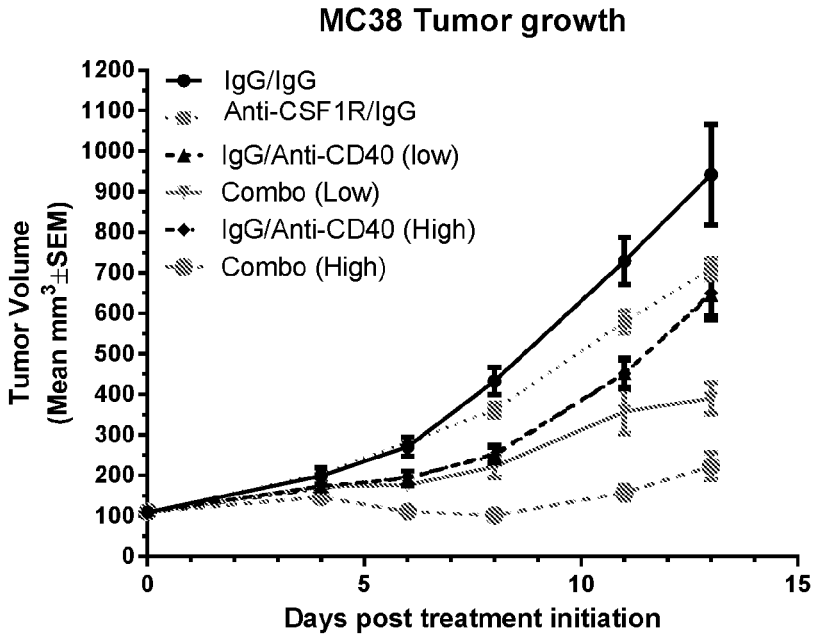

FIG. 3

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(57) Abstract: Methods of treating cancer with antibodies that bind colony stimulating factor 1 receptor (CSF1R) in combination with one or more immune stimulating agents are provided.

COMBINATION THERAPY FOR CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of priority of US Provisional Application No. 62/146,766, filed April 13, 2015; and US Provisional Application No. 62/190,945, filed July 10, 2015, each of which is incorporated by reference in its entirety for any purpose.

TECHNICAL FIELD

[002] Methods of treating cancer with antibodies that bind colony stimulating factor 1 receptor (CSF1R) in combination with one or more immune stimulating agents.

BACKGROUND

[003] Colony stimulating factor 1 receptor (referred to herein as CSF1R; also referred to in the art as FMS, FIM2, C-FMS, M-CSF receptor, and CDl15) is a single-pass transmembrane receptor with an N-terminal extracellular domain (ECD) and a C-terminal intracellular domain with tyrosine kinase activity. Ligand binding of CSF1 or the interleukin 34 ligand (referred to herein as IL-34; Lin et al., *Science* 320: 807-11 (2008)) to CSF1R leads to receptor dimerization, upregulation of CSF1R protein tyrosine kinase activity, phosphorylation of CSF1R tyrosine residues, and downstream signaling events. CSF1R activation by CSF1 or IL-34 leads to the trafficking, survival, proliferation, and differentiation of monocytes and macrophages, as well as other monocytic cell lineages such as osteoclasts, dendritic cells, and microglia.

[004] Many tumor cells or tumor stromal cells have been found to produce CSF1, which activates monocyte/macrophage cells through CSF1R. The level of CSF1 in tumors has been shown to correlate with the level of tumor-associated macrophages (TAMs) in the tumor. Higher levels of TAMs have been found to correlate with poorer patient prognoses in the majority of cancers. In addition, CSF1 has been found to promote tumor growth and progression to metastasis in, for example, human breast cancer xenografts in mice. See, e.g., Paulus et al., *Cancer Res.* 66: 4349-56 (2006). Further, CSF1R plays a role in osteolytic bone destruction in bone metastasis. *See, e.g.*, Ohno et al., *Mol. Cancer Ther.* 5: 2634-43 (2006). TAMs promote tumor growth, in part, by suppressing anti-tumor T cell effector function through the release of immunosuppressive cytokines and the expression of T cell inhibitory surface proteins. Thus, antibodies that bind to CSF1R may be useful in methods of treating cancer.

[005] Some tumor cells may escape detection by the immune system at least in part by suppressing the immune response, for instance by altering the expression of immune

modulatory genes. For example, the relative concentrations of both immune stimulatory and immune inhibitory molecules in the body may modulate the adaptive immune response. A relatively high level of expression of inhibitory molecules and/or reduced expression of certain stimulatory molecules may create a checkpoint or switch that down-regulates the adaptive immune response. Agents that counteract this effect by up-regulating the adaptive immune response or by stimulating the innate immune response are potential cancer therapies.

[006] A combination regimen of agents that modulate the immune response in cancer, such as immune stimulating agents, may increase the depth and durability of the response and may also broaden efficacy to patients who do not respond to a single agent alone.

[006a] It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in Australia or any other country.

SUMMARY

[006b] A first aspect provides a method of treating cancer in a subject comprising administering to the subject an anti-CSF1R antibody and at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

[006c] A second aspect provides use of an anti-CSF1R antibody in the manufacture of a medicament for treating cancer in a subject administered at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16,

and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

[006d] A third aspect provides use of at least one immune stimulating agent in the manufacture of a medicament for treating cancer in a subject administered an anti-CSF1R antibody, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

[006e] A fourth aspect provides a composition comprising an anti-CSF1R antibody and at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

[007] In some embodiments, methods of treating cancer in a subject aredisclosed, comprising administering to the subject an anti-CSF1R antibody and at least one immune stimulating agent. In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune-stimulatory molecule, including a co-stimulatory molecule, while in some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule. In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune-stimulatory molecule, including a co-stimulatory molecule, found on immune cells, such as T cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune-inhibitory molecule, including a co-inhibitory molecule, found on immune cells, such as T cells. In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune-stimulatory molecule, including a co-stimulatory molecule, found on cells involved in innate immunity, such as NK cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune-inhibitory molecule, including a co-inhibitory molecule, found on cells involved in innate immunity, such as NK cells. In some embodiments, the combination enhances the antigen-specific T cell response in the treated subject and/or enhances the innate immunity response in the subject. In some embodiments, the combination results in an improved anti-tumor response in an animal cancer model, such as a xenograft model, compared to administration of either the anti-CSF1R antibody or immune stimulating agent alone. In some embodiments, the combination results in a synergistic response in an animal cancer model, such as a xenograft model, compared to administration of either the anti-CSF1R antibody or immune stimulating agent alone.

[008] In some embodiments, the at least one immune stimulating agent comprises an antagonist of an inhibitor of the activation of T cells, while in some embodiments, the at least one immune stimulating agent comprises comprises an agonist of a stimulator of the activation of T cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of CTLA4, LAG-3, Galectin 1, Galectin 9, CEACAM-1, BTLA, CD25, CD69, TIGIT, CD113, GPR56, VISTA, B7-H3, B7-H4, 2B4, CD48, GARP, PD1H, LAIR1, TIM1, TIM3, TIM4, ILT4, IL-6, IL-10, TGFβ, VEGF, KIR, LAG-3, adenosine A2A receptor, PI3Kdelta, or IDO. In some embodiments, the at least one immune stimulating agent comprises an agonist of B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD27, CD40, CD40L, DR3, CD28H, IL-2, IL-7, IL-12, IL-15, IL-21, IFNα,

STING or a Toll-like receptor agonist such as a TLR2/4 agonist. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the B7 family of membrane-bound proteins such as B7-1, B7-2, B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the TNF receptor family or a co-stimulatory or co-inhibitory molecule binding to a member of the TNF receptor family such as CD40, CD40L, OX40, OX40L, GITR, GITRL, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, EDA1, EDA2, TACI, APRIL, BCMA, LTβR, LIGHT, DeR3, HVEM, VEGL/TL1A, TRAMP/DR3, TNFR1, TNFβ, TNFR2, TNFα, 1β2, FAS, FASL, RELT, DR6, TROY, or NGFβ. In some embodiments, the at least one immune stimulating agent comprises an agent that antagonizes or inhibits a cytokine that inhibits T cell activation such as IL-6, IL-10, TGFβ, VEGF. In some embodiments, the at least one immune stimulating agent comprises an antagonist of a chemokine, such as CXCR2, CXCR4, CCR2, or CCR4. In some embodiments, the at least one immune stimulating agent comprises an agonist of a cytokine that stimulates T cell activation such as IL-2, IL-7, IL-12, IL-15, IL-21, and IFNα. In some embodiments, the at least one immune stimulating agent comprises an antibody. In some embodiments, the at least one immune stimulating agent may comprise a vaccine, such as a mesothelin-targeting vaccine or attenuated listeria cancer vaccine such as CRS-207. Any one or more of the above antagonists, agonists, and binding agents may be combined with any one or more of the anti-CSF1R antibodies described herein.

[009] In some embodiments, the at least one immune stimulating agent comprises a CD40 agonist, optionally in combination with at least one other immune stimulating agent as listed above. In some embodiments, the CD40 agonist is an antibody. In some embodiments, the CD40 agonist is an anti-CD40 antibody. In some embodiments, the anti-CD40 antibody comprises the CDRs of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the anti-CD40 antibody comprises the heavy chain and light chain variable regions of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the anti-CD40 antibody is an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the CD40 agonist is recombinant CD40L. In some embodiments, the at least one immune stimulating agent comprises a CD40 agonist and at least one additional immune stimulating agent from any of those described above. For example, any one or more of the above immune stimulating

agents above may be combined with any one or more of the anti-CSF1R antibodies described herein as well as with a CD40 agonist, such as a CD40 agonist antibody or recombinant CD40L, such as any one of the anti-CD40 antibodies described above.

[010] In some embodiments, the anti-CSF1R antibody and the at least one immune stimulatory agent are administered concurrently or sequentially. In some embodiments, the anti-CSF1R antibody and the at least one immune stimulatory agent are administered concurrently. In some embodiments, one or more doses of the at least one immune stimulatory agent are administered prior to administering an anti-CSF1R antibody. In some embodiments, the subject received a complete course of therapy with the at least one immune stimulatory agent prior to administration of the anti-CSF1R antibody. In some embodiments, the anti-CSF1R antibody is administered during a second course of therapy with the at least one immune stimulatory agent. In some embodiments, the subject received at least one, at least two, at least three, or at least four doses of the at least one immune stimulatory agent prior to administration of the anti-CSF1R antibody. In some embodiments, at least one dose of the at least one immune stimulatory agent is administered concurrently with the anti-CSF1R inhibitor. In some embodiments, one or more doses of the anti-CSF1R antibody are administered prior to administering at least one immune stimulatory agent. In some embodiments, the subject received at least two, at least three, or at least four doses of the anti-CSF1R antibody prior to administration of at least one immune stimulatory agent. In some embodiments, at least one dose of the anti-CSF1R antibody is administered concurrently with the at least one immune stimulatory agent.

[011] In some embodiments, the cancer is selected from non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, endometrial cancer, Hodgkin's lymphoma, lung cancer, glioma, gioblastoma multiforme, colon cancer, breast cancer, bone cancer, skin cancer, uterince cancer, gastric cancer, stomach cancer, lymphoma, lymphocytic leukemia, multiple myeloma, prostate cancer, mesothelioma, and kidney cancer. In some embodiments, the cancer is recurrent or progressive after a therapy selected from surgery, chemotherapy, radiation therapy, or a combination thereof.

[012] In some embodiments, compositions are disclosed, comprising an anti-CSF1R antibody and at least one immune stimulatory agent. In some embodiments, the at least one immune stimulating agent comprises an antagonist of an inhibitor of the activation of T cells, while in some embodiments, the at least one immune stimulating agent comprises comprises an agonist of a stimulator of the activation of T cells. In some embodiments, the at least one

immune stimulating agent comprises an antagonist of CTLA4, LAG-3, Galectin 1, Galectin 9, CEACAM-1, BTLA, CD25, CD69, TIGIT, CD113, GPR56, VISTA, B7-H3, B7-H4, 2B4, CD48, GARP, PD1H, LAIR1, TIM1, TIM3, TIM4, ILT4, IL-6, IL-10, TGFβ, VEGF, KIR, LAG-3, adenosine A2A receptor, PI3Kdelta, or IDO. In some embodiments, the at least one immune stimulating agent comprises an agonist of B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD27, CD40, CD40L, DR3, CD28H, IL-2, IL-7, IL-12, IL-15, IL-21, IFNα, STING, or a Toll-like receptor agonist such as a TLR2/4 agonist. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the B7 family of membrane-bound proteins such as B7-1, B7-2, B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the TNF receptor family or a co-stimulatory or co-inhibitory molecule binding to a member of the TNF receptor family such as CD40, CD40L, OX40, OX40L, GITR, GITRL, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, EDA1, EDA2, TACI, APRIL, BCMA, LTβR, LIGHT, DeR3, HVEM, VEGL/TL1A, TRAMP/DR3, TNFR1, TNFβ, TNFR2, TNFα, 1β2, FAS, FASL, RELT, DR6, TROY, or NGFβ. In some embodiments, the at least one immune stimulating agent comprises an agent that antagonizes or inhibits a cytokine that inhibits T cell activation such as IL-6, IL-10, TGFβ, VEGF. In some embodiments, the at least one immune stimulating agent comprises an agonist of a cytokine that stimulates T cell activation such as IL-2, IL-7, IL-12, IL-15, IL-21, and IFNα. In some embodiments, the at least one immune stimulating agent comprises an antagonist of a chemokine, such as CXCR2, CXCR4, CCR2, or CCR4. In some embodiments, the at least one immune stimulating agent comprises an antibody. In some embodiments, the at least one immune stimulating agent may comprise a vaccine, such as a mesothelin-targeting vaccine or attenuated listeria cancer vaccine such as CRS-207.

[013] In some embodiments, the compositions comprise any one or more of the above antagonists, agonists, and binding agents combined with any one or more of the anti-CSF1R antibodies described herein. The compositions may include each therapeutic agent in a separate container or compartment or alternatively, may include two or more of the therapeutic agents mixed together.

[014] In some embodiments, the compositions comprise an anti-CSF1R antibody and a CD40 agonist, optionally along with at least one other immune stimulating agent as listed above. In some embodiments, the CD40 agonist is an anti-CD40 antibody. In some

embodiments, the anti-CD40 antibody comprises the CDRs of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the anti-CD40 antibody comprises the heavy chain and light chain variable regions of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the anti-CD40 antibody is an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4. In some embodiments, the CD40 agonist is recombinant CD40L. In some embodiments, the compositions comprise any one or more of the above immune stimulating agents above combined with both any one or more of the anti-CSF1R antibodies described herein as well as with a CD40 agonist, such as a CD40 agonist antibody or recombinant CD40L, such as any one of the anti-CD40 antibodies described above. The compositions may include each therapeutic agent in a separate container or compartment or alternatively, may include two or more of the therapeutic agents mixed together.

[015] In any of the compositions or methods described herein, the antibody heavy chain and/or the antibody light chain of the anti-CSF1R antibody may have the structure described below.

[016] In any of the compositions or methods described herein, the anti-CSF1R antibody heavy chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45. In any of the methods described herein, the anti-CSF1R antibody light chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52. In any of the compositions or methods described herein, the anti-CSF1R antibody heavy chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, and the anti-CSF1R antibody light chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52.

[017] In any of the compositions or methods described herein, the anti-CSF1R antibody HC CDR1, HC CDR2, and HC CDR3 may comprise a set of sequences selected from: (a) SEQ ID NOs: 15, 16, and 17; (b) SEQ ID NOs: 21, 22, and 23; and (c) SEQ ID NOs: 27, 28, and 29. In any of the compositions or methods described herein, the anti-CSF1R antibody LC CDR1, LC CDR2, and LC CDR3 may comprise a set of sequences selected from: (a) SEQ ID NOs: 18, 19, and 20; (b) SEQ ID NOs: 24, 25, and 26; and (c) SEQ ID NOs: 30, 31, and 32.

[018] In any of the compositions or methods described herein, the anti-CSF1R antibody heavy chain may comprise an HC CDR1, HC CDR2, and HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 comprise a set of sequences selected from: (a) SEQ ID NOs: 15, 16, and 17; (b) SEQ ID NOs: 21, 22, and 23; and (c) SEQ ID NOs: 27, 28, and 29; and the light chain may comprise an LC CDR1, LC CDR2, and LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 comprise a set of sequences selected from: (a) SEQ ID NOs: 18, 19, and 20; (b) SEQ ID NOs: 24, 25, and 26; and (c) SEQ ID NOs: 30, 31, and 32.

[019] In any of the compositions or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 9 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 10; (b) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 11 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 12; (c) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 13 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 14; (d) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 39 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (e) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 40 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (f) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 41 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (g) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 39 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; (h) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 40 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; (i) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 41 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; and (j) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light

chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (k) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (l) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (m) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (n) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (o) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (p) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; (q) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52; (r) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; or (s) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52.

[020] In any of the compositions or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; (b) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 21, an HC CDR2 having the sequence of SEQ ID NO: 22, and an HC CDR3 having the sequence of SEQ ID

NO: 23, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 24, a LC CDR2 having the sequence of SEQ ID NO: 25, and a LC CDR3 having the sequence of SEQ ID NO: 26; or (c) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 27, an HC CDR2 having the sequence of SEQ ID NO: 28, and an HC CDR3 having the sequence of SEQ ID NO: 29, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 30, a LC CDR2 having the sequence of SEQ ID NO: 31, and a LC CDR3 having the sequence of SEQ ID NO: 32.

[021] In any of the compositions or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a sequence of SEQ ID NO: 53 and a light chain comprising a sequence of SEQ ID NO: 60; (b) a heavy chain comprising a sequence of SEQ ID NO: 53 and a light chain comprising a sequence of SEQ ID NO: 61; or (c) a heavy chain comprising a sequence of SEQ ID NO: 58 and a light chain comprising a sequence of SEQ ID NO: 65. In some embodiments, an antibody comprises a heavy chain and a light chain, wherein the antibody comprises: (a) a heavy chain consisting of the sequence of SEQ ID NO: 53 and a light chain consisting of the sequence of SEQ ID NO: 60; (b) a heavy chain consisting of the sequence of SEQ ID NO: 53 and a light chain consisting of the sequence of SEQ ID NO: 61; or (c) a heavy chain consisting of the sequence of SEQ ID NO: 58 and a light chain consisting of the sequence of SEQ ID NO: 65.

[022] In any of the compositions or methods described herein, the anti-CSF1R antibody may be a humanized antibody. In any of the compositions or methods described herein, the anti-CSF1R antibody may be selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$. In any of the compositions or methods described herein, the anti-CSF1R antibody may be a chimeric antibody. In any of the compositions or methods described herein, the anti-CSF1R antibody may be selected from an IgA, an IgG, and an IgD. In any of the compositions or methods described herein, the anti-CSF1R antibody may be an IgG. In any of the methods described herein, the antibody may be an IgG1 or IgG2.

[023] In any of the compositions or methods described herein, the anti-CSF1R antibody may bind to human CSF1R and/or binds to cynomolgus CSF1R. In any of the compositions or methods described herein, the anti-CSF1R antibody may block ligand binding to CSF1R. In any of the compositions or methods described herein, the anti-CSF1R antibody may block binding of CSF1 and/or IL-34 to CSF1R. In any of the compositions or methods described herein, the anti-CSF1R antibody may block binding of both CSF1 and IL-34 to CSF1R. In any of the compositions or methods described herein, the anti-CSF1R antibody may inhibit ligand-induced CSF1R phosphorylation. In any of the compositions or methods

described herein, the anti-CSF1R antibody may inhibit CSF1- and/or IL-34-induced CSF1R phosphorylation. In any of the compositions or methods described herein, the anti-CSF1R antibody may bind to human CSF1R with an affinity (K_D) of less than 1 nM. In any of the compositions or methods described herein, the anti-CSF1R antibody may inhibit monocyte proliferation and/or survival responses in the presence of CSF1 or IL-34.

BRIEF DESCRIPTION OF THE FIGURES

[024] **FIG. 1A-C** show an alignment of the humanized heavy chain variable regions for each of humanized antibodies huAb1 to huAb16, as discussed in Example 1. Boxed residues are amino acids in the human acceptor sequence that were changed back to the corresponding mouse residue.

[025] **FIG. 2A-C** show an alignment of the humanized light chain variable regions for each of humanized antibodies huAb1 to huAb16, as discussed in Example 1. Boxed amino acids are residues in the human acceptor sequence that were changed back to the corresponding mouse residue.

[026] **FIG. 3** shows that the combination of anti-CSF1R antibody and anti-CD40 antibody demonstrate greater tumor growth suppression in an MC38 tumor mouse model than either therapy alone.

[027] **FIG. 4A-B** shows the tumor volume of individual mice at **(Fig. 4A)** day 11 and **(Fig. 4B)** day 13. The combination of anti-CSF1R antibody and anti-CD40 antibody performed significantly better than either therapy alone at both time points.

[028] **FIG. 5** shows body weight in mice used in the study.

DETAILED DESCRIPTION

[029] Tumor-associated macrophages (TAMs) are implicated in the pathogenesis of many cancers, and correlate with poor prognosis. TAMs can suppress an anti-tumor responses through multiple mechanisms. TAMs express anti-inflammatory cytokines such as TGFβ and IL-10 which acts to suppress the ability of intratumoral dendritic cells to stimulate cytotoxic T cell responses (Ruffell et al., 2014, *Cancer Cell*). TAMs also express chemokines which recruit immunosuppressive regulatory T cells into tumors (Curiel et al., 2004, *Nature Med.*; Mizukami et al., 2008, *Int. J. Cancer*), Moreover, TAMs express the ligands for the T cell inhibitor receptors PD-1 and CTLA-4 which act to directly inhibit T cell activation and funnction. Inhibition of CSF1R can reduce immunosuppressive TAMs in mouse models and human tumors. *See, e.g.*, Ries et al., 2014, *Cancer Cell*, 25: 846-859; Pyontech et al., 2013, *Nature Med.*, 19: 1264-1272; and Zhu et al., 2014, *Cancer Res.*, 74: 5057-5069. In contrast to

[035] The terms "**nucleic acid molecule**" and "**polynucleotide**" may be used interchangeably, and refer to a polymer of nucleotides. Such polymers of nucleotides may contain natural and/or non-natural nucleotides, and include, but are not limited to, DNA, RNA, and PNA. "**Nucleic acid sequence**" refers to the linear sequence of nucleotides that comprise the nucleic acid molecule or polynucleotide.

[036] The terms "**polypeptide**" and "**protein**" are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Such polymers of amino acid residues may contain natural or non-natural amino acid residues, and include, but are not limited to, peptides, oligopeptides, dimers, trimers, and multimers of amino acid residues. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. Furthermore, for purposes of the present invention, a "polypeptide" refers to a protein which includes modifications, such as deletions, additions, and substitutions (generally conservative in nature), to the native sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

[037] The term "**CSF1R**" refers herein to the full-length CSF1R, which includes the N-terminal ECD, the transmembrane domain, and the intracellular tyrosine kinase domain, with or without an N-terminal leader sequence. In some embodiments, the CSF1R is a human CSF1R having the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[038] The term "**immune stimulating agent**" as used herein refers to a molecule that stimulates the immune system by either acting as an agonist of an immune-stimulatory molecule, including a co-stimulatory molecule, or acting as an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule. An immune stimulating agent may be a biologic, such as an antibody or antibody fragment, other protein, or vaccine, or may be a small molecule drug. An "**immune stimulatory molecule**" includes a receptor or ligand that acts to enhance, stimulate, induce, or otherwise "turn-on" an immune response. Immune stimulatory molecules as defined herein include co-stimulatory molecules. An "**immune inhibitory molecule**" includes a receptor or ligand that acts to reduce, inhibit, suppress, or otherwise "turn-off" an immune response. Immune inhibitory molecules as defined herein include co-inhibitory molecules. Such immune stimulatory and immune inhibitory molecules may be, for example, receptors or ligands found on immune cells such as a T cells, or found on cells involved in innate immunity such as NK cells.

[039] The terms "**B-cell surface antigen CD40**" and "**CD40**" refer herein to the full-length CD40, which includes the N-terminal ECD, the transmembrane domain, and the intracellular domain, with or without an N-terminal leader sequence. In some embodiments, the CD40 is a human CD40 having the amino acid sequence of SEQ ID NO: 96 (precursor, with signal sequence) or SEQ ID NO: 97 (mature, without signal sequence).

[040] The term "**CD40 agonist**" refers to a moiety that interacts with CD40 and enhances CD40 activity. Nonlimiting exemplary CD40 activities include signaling through CD40, enhancement of antigen presenting activity, induction of proinflammatory cytokines, and induction of tumorcidal activity. In some embodiments, a CD40 agonist is an anti-CD40 antibody.

[041] The term "**anti-CD40 antibody**" refers to an antibody that specifically binds to CD40. Unless specifically indicated otherwise, the term "anti-CD40 antibody" as used herein refers to an anti-CD40 agonist antibody.

[042] With reference to anti-CSF1R antibodies the term "**blocks binding of**" a ligand, such as CSF1 and/or IL-34, and grammatical variants thereof, are used to refer to the ability to inhibit the interaction between CSF1R and a CSF1R ligand, such as CSF1 and/or IL-34. Such inhibition may occur through any mechanism, including direct interference with ligand binding, e.g., because of overlapping binding sites on CSF1R, and/or conformational changes in CSF1R induced by the antibody that alter ligand affinity, etc. Antibodies and antibody fragments referred to as "functional" are characterized by having such properties.

[043] The term "**antibody**" as used herein refers to a molecule comprising at least complementarity-determining region (CDR) 1, CDR2, and CDR3 of a heavy chain and at least CDR1, CDR2, and CDR3 of a light chain, wherein the molecule is capable of binding to antigen. The term antibody includes, but is not limited to, fragments that are capable of binding antigen, such as Fv, single-chain Fv (scFv), Fab, Fab', and $(Fab')_2$. The term antibody also includes, but is not limited to, chimeric antibodies, humanized antibodies, and antibodies of various species such as mouse, human, cynomolgus monkey, etc.

[044] In some embodiments, an antibody comprises a heavy chain variable region and a light chain variable region. In some embodiments, an antibody comprises at least one heavy chain comprising a heavy chain variable region and at least a portion of a heavy chain constant region, and at least one light chain comprising a light chain variable region and at least a portion of a light chain constant region. In some embodiments, an antibody comprises two heavy chains, wherein each heavy chain comprises a heavy chain variable region and at least a portion of a heavy chain constant region, and two light chains, wherein each light chain

comprises a light chain variable region and at least a portion of a light chain constant region. As used herein, a single-chain Fv (scFv), or any other antibody that comprises, for example, a single polypeptide chain comprising all six CDRs (three heavy chain CDRs and three light chain CDRs) is considered to have a heavy chain and a light chain. In some such embodiments, the heavy chain is the region of the antibody that comprises the three heavy chain CDRs and the light chain in the region of the antibody that comprises the three light chain CDRs.

[045] The term "**heavy chain variable region**" as used herein refers to a region comprising heavy chain CDR1, framework (FR) 2, CDR2, FR3, and CDR3. In some embodiments, a heavy chain variable region also comprises at least a portion of an FR1 and/or at least a portion of an FR4. In some embodiments, a heavy chain CDR1 corresponds to Kabat residues 26 to 35; a heavy chain CDR2 corresponds to Kabat residues 50 to 65; and a heavy chain CDR3 corresponds to Kabat residues 95 to 102. *See, e.g.*, Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, Md.); and Figure 1. In some embodiments, a heavy chain CDR1 corresponds to Kabat residues 31 to 35; a heavy chain CDR2 corresponds to Kabat residues 50 to 65; and a heavy chain CDR3 corresponds to Kabat residues 95 to 102. *See id.*

[046] The term "**heavy chain constant region**" as used herein refers to a region comprising at least three heavy chain constant domains, C_H1, C_H2, and C_H3. Nonlimiting exemplary heavy chain constant regions include γ, δ, and α. Nonlimiting exemplary heavy chain constant regions also include ε and μ. Each heavy constant region corresponds to an antibody isotype. For example, an antibody comprising a γ constant region is an IgG antibody, an antibody comprising a δ constant region is an IgD antibody, and an antibody comprising an α constant region is an IgA antibody. Further, an antibody comprising a μ constant region is an IgM antibody, and an antibody comprising an ε constant region is an IgE antibody. Certain isotypes can be further subdivided into subclasses. For example, IgG antibodies include, but are not limited to, IgG1 (comprising a γ_1 constant region), IgG2 (comprising a γ_2 constant region), IgG3 (comprising a γ_3 constant region), and IgG4 (comprising a γ_4 constant region) antibodies; IgA antibodies include, but are not limited to, IgA1 (comprising an α_1 constant region) and IgA2 (comprising an α_2 constant region) antibodies; and IgM antibodies include, but are not limited to, IgM1 and IgM2.

[047] In some embodiments, a heavy chain constant region comprises one or more mutations (or substitutions), additions, or deletions that confer a desired characteristic on the antibody. A nonlimiting exemplary mutation is the S241P mutation in the IgG4 hinge region (between constant domains C_H1 and C_H2), which alters the IgG4 motif CPSCP to CPPCP,

which is similar to the corresponding motif in IgG1. That mutation, in some embodiments, results in a more stable IgG4 antibody. See, e.g., Angal et al., *Mol. Immunol.* 30: 105-108 (1993); Bloom et al., *Prot. Sci.* 6: 407-415 (1997); Schuurman et al., *Mol. Immunol.* 38: 1-8 (2001).

[048] The term "**heavy chain**" as used herein refers to a polypeptide comprising at least a heavy chain variable region, with or without a leader sequence. In some embodiments, a heavy chain comprises at least a portion of a heavy chain constant region. The term "**full-length heavy chain**" as used herein refers to a polypeptide comprising a heavy chain variable region and a heavy chain constant region, with or without a leader sequence.

[049] The term "**light chain variable region**" as used herein refers to a region comprising light chain CDR1, framework (FR) 2, CDR2, FR3, and CDR3. In some embodiments, a light chain variable region also comprises an FR1 and/or an FR4. In some embodiments, a light chain CDR1 corresponds to Kabat residues 24 to 34; a light chain CDR2 corresponds to Kabat residues 50 to 56; and a light chain CDR3 corresponds to Kabat residues 89 to 97. *See, e.g.*, Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, Md.); and Figure 1.

[050] The term "**light chain constant region**" as used herein refers to a region comprising a light chain constant domain, C_L. Nonlimiting exemplary light chain constant regions include λ and κ.

[051] The term "**light chain**" as used herein refers to a polypeptide comprising at least a light chain variable region, with or without a leader sequence. In some embodiments, a light chain comprises at least a portion of a light chain constant region. The term "**full-length light chain**" as used herein refers to a polypeptide comprising a light chain variable region and a light chain constant region, with or without a leader sequence.

[052] A "**chimeric antibody**" as used herein refers to an antibody comprising at least one variable region from a first species (such as mouse, rat, cynomolgus monkey, etc.) and at least one constant region from a second species (such as human, cynomolgus monkey, etc.). In some embodiments, a chimeric antibody comprises at least one mouse variable region and at least one human constant region. In some embodiments, a chimeric antibody comprises at least one cynomolgus variable region and at least one human constant region. In some embodiments, a chimeric antibody comprises at least one rat variable region and at least one mouse constant region. In some embodiments, all of the variable regions of a chimeric antibody are from a first species and all of the constant regions of the chimeric antibody are from a second species.

[053] A "**humanized antibody**" as used herein refers to an antibody in which at least one amino acid in a framework region of a non-human variable region has been replaced with the corresponding amino acid from a human variable region. In some embodiments, a humanized antibody comprises at least one human constant region or fragment thereof. In some embodiments, a humanized antibody is a Fab, an scFv, a $(Fab')_2$, etc.

[054] A "**CDR-grafted antibody**" as used herein refers to a humanized antibody in which the complementarity determining regions (CDRs) of a first (non-human) species have been grafted onto the framework regions (FRs) of a second (human) species.

[055] A "**human antibody**" as used herein refers to antibodies produced in humans, antibodies produced in non-human animals that comprise human immunoglobulin genes, such as XenoMouse®, and antibodies selected using in vitro methods, such as phage display, wherein the antibody repertoire is based on a human immunoglobulin sequences.

[056] The term "**leader sequence**" refers to a sequence of amino acid residues located at the N terminus of a polypeptide that facilitates secretion of a polypeptide from a mammalian cell. A leader sequence may be cleaved upon export of the polypeptide from the mammalian cell, forming a mature protein. Leader sequences may be natural or synthetic, and they may be heterologous or homologous to the protein to which they are attached. Exemplary leader sequences include, but are not limited to, antibody leader sequences, such as, for example, the amino acid sequences of SEQ ID NOs: 3 and 4, which correspond to human light and heavy chain leader sequences, respectively. Nonlimiting exemplary leader sequences also include leader sequences from heterologous proteins. In some embodiments, an antibody lacks a leader sequence. In some embodiments, an antibody comprises at least one leader sequence, which may be selected from native antibody leader sequences and heterologous leader sequences.

[057] The term "**vector**" is used to describe a polynucleotide that may be engineered to contain a cloned polynucleotide or polynucleotides that may be propagated in a host cell. A vector may include one or more of the following elements: an origin of replication, one or more regulatory sequences (such as, for example, promoters and/or enhancers) that regulate the expression of the polypeptide of interest, and/or one or more selectable marker genes (such as, for example, antibiotic resistance genes and genes that may be used in colorimetric assays, e.g., β-galactosidase). The term "**expression vector**" refers to a vector that is used to express a polypeptide of interest in a host cell.

[058] A "**host cell**" refers to a cell that may be or has been a recipient of a vector or isolated polynucleotide. Host cells may be prokaryotic cells or eukaryotic cells. Exemplary eukaryotic cells include mammalian cells, such as primate or non-primate animal cells; fungal

cells, such as yeast; plant cells; and insect cells. Nonlimiting exemplary mammalian cells include, but are not limited to, NSO cells, PER.C6® cells (Crucell), and 293 and CHO cells, and their derivatives, such as 293-6E and DG44 cells, respectively.

[059] The term "**isolated**" as used herein refers to a molecule that has been separated from at least some of the components with which it is typically found in nature. For example, a polypeptide is referred to as "isolated" when it is separated from at least some of the components of the cell in which it was produced. Where a polypeptide is secreted by a cell after expression, physically separating the supernatant containing the polypeptide from the cell that produced it is considered to be "isolating" the polypeptide. Similarly, a polynucleotide is referred to as "isolated" when it is not part of the larger polynucleotide (such as, for example, genomic DNA or mitochondrial DNA, in the case of a DNA polynucleotide) in which it is typically found in nature, or is separated from at least some of the components of the cell in which it was produced, e.g., in the case of an RNA polynucleotide. Thus, a DNA polynucleotide that is contained in a vector inside a host cell may be referred to as "isolated" so long as that polynucleotide is not found in that vector in nature.

[060] The term "**elevated level**" means a higher level of a protein in a particular tissue of a subject relative to the same tissue in a control, such as an individual or individuals who are not suffering from cancer or other condition described herein. The elevated level may be the result of any mechanism, such as increased expression, increased stability, decreased degradation, increased secretion, decreased clearance, etc., of the protein.

[061] The term "**reduce**" or "**reduces**" means to lower the level of a protein in a particular tissue of a subject by at least 10%. In some embodiments, an agent, such as an antibody that binds CSF1R, reduces the level of a protein in a particular tissue of a subject by at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%. In some embodiments, the level of a protein is reduced relative to the level of the protein prior to contacting with an agent, such as an antibody that binds CSF1R.

[062] The term "**resistant**," when used in the context of resistance to a therapeutic agent, means a decreased response or lack of response to a standard dose of the therapeutic agent, relative to the subject's response to the standard dose of the therapeutic agent in the past, or relative to the expected response of a similar subject with a similar disorder to the standard dose of the therapeutic agent. Thus, in some embodiments, a subject may be resistant to therapeutic agent although the subject has not previously been given the therapeutic agent, or

the subject may develop resistance to the therapeutic agent after having responded to the agent on one or more previous occasions.

[063] The terms "**subject**" and "**patient**" are used interchangeably herein to refer to a human. In some embodiments, methods of treating other mammals, including, but not limited to, rodents, simians, felines, canines, equines, bovines, porcines, ovines, caprines, mammalian laboratory animals, mammalian farm animals, mammalian sport animals, and mammalian pets, are also provided.

[064] The term "**sample**," as used herein, refers to a composition that is obtained or derived from a subject that contains a cellular and/or other molecular entity that is to be characterized, quantitated, and/or identified, for example based on physical, biochemical, chemical and/or physiological characteristics. An exemplary sample is a tissue sample.

[065] The term "**tissue sample**" refers to a collection of similar cells obtained from a tissue of a subject. The source of the tissue sample may be solid tissue as from a fresh, frozen and/or preserved organ or tissue sample or biopsy or aspirate; blood or any blood constituents; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, synovial fluid, or interstitial fluid; cells from any time in gestation or development of the subject. In some embodiments, a tissue sample is a synovial biopsy tissue sample and/or a synovial fluid sample. In some embodiments, a tissue sample is a synovial fluid sample. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue sample is obtained from a disease tissue/organ. The tissue sample may contain compounds that are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like. A "control sample" or "control tissue", as used herein, refers to a sample, cell, or tissue obtained from a source known, or believed, not to be afflicted with the disease for which the subject is being treated.

[066] For the purposes herein a "**section**" of a tissue sample means a part or piece of a tissue sample, such as a thin slice of tissue or cells cut from a solid tissue sample.

[067] The term "**cancer**" is used herein to refer to a group of cells that exhibit abnormally high levels of proliferation and growth. A cancer may be benign (also referred to as a benign tumor), pre-malignant, or malignant. Cancer cells may be solid cancer cells or leukemic cancer cells. The term "**cancer growth**" is used herein to refer to proliferation or growth by a cell or cells that comprise a cancer that leads to a corresponding increase in the size or extent of the cancer.

[068] Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular nonlimiting examples of such cancers

include squamous cell cancer, small-cell lung cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non-small cell lung cancer (including squamous cell non-small cell lung cancer), adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, and various types of head and neck cancer (including squamous cell carcinoma of the head and neck).

[069] The term "**recurrent cancer**" refers to a cancer that has returned after a previous treatment regimen, following which there was a period of time during which the cancer could not be detected.

[070] The term "**progressive cancer**" is a cancer that has increased in size or tumor spread since the beginning of a treatment regimen. In certain embodiments, a progressive cancer is a cancer that has incrased in size or tumor spread by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50% since the beginning of a treatment regimen.

[071] A "**chemotherapeutic agent**" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and Cytoxan® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (*see, e.g.*, Agnew, *Chem Intl. Ed. Engl.*, 33: 183-186 (1994)); dynemicin, including dynemicin A;

bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, Adriamycin® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2- ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, Taxol® paclitaxel (Bristol- Myers Squibb Oncology, Princeton, N.J.), Abraxane® Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Illinois), and Taxotere® doxetaxel (Rhône- Poulenc Rorer, Antony, France); chloranbucil; Gemzar® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; Navelbine® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-11) (including the treatment regimen of irinotecan with 5-FU and leucovorin); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids such as

retinoic acid; capecitabine; combretastatin; leucovorin (LV); oxaliplatin, including the oxaliplatin treatment regimen (FOLFOX); inhibitors of PKC-alpha, Raf, H-Ras, EGFR (*e.g.*, erlotinib (Tarceva®)) and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[072] Further nonlimiting exemplary chemotherapeutic agents include anti-hormonal agents that act to regulate or inhibit hormone action on cancers such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including Nolvadex® tamoxifen), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and Fareston® toremifene; aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, Megase® megestrol acetate, Aromasin® exemestane, formestanie, fadrozole, Rivisor® vorozole, Femara® letrozole, and Arimidex® anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in abherant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; ribozymes such as a VEGF expression inhibitor (*e.g.*, Angiozyme® ribozyme) and a HER2 expression inhibitor; vaccines such as gene therapy vaccines, for example, Allovectin® vaccine, Leuvectin® vaccine, and Vaxid® vaccine; Proleukin® rIL-2; Lurtotecan® topoisomerase 1 inhibitor; Abarelix® rmRH; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[073] An "**anti-angiogenesis agent**" or "**angiogenesis inhibitor**" refers to a small molecular weight substance, a polynucleotide (including, *e.g.*, an inhibitory RNA (RNAi or siRNA)), a polypeptide, an isolated protein, a recombinant protein, an antibody, or conjugates or fusion proteins thereof, that inhibits angiogenesis, vasculogenesis, or undesirable vascular permeability, either directly or indirectly. It should be understood that the anti-angiogenesis agent includes those agents that bind and block the angiogenic activity of the angiogenic factor or its receptor. For example, an anti-angiogenesis agent is an antibody or other antagonist to an angiogenic agent, *e.g.*, antibodies to VEGF-A (*e.g.*, bevacizumab (Avastin®)) or to the VEGF-A receptor (*e.g.*, KDR receptor or Flt-1 receptor), anti-PDGFR inhibitors such as Gleevec® (Imatinib Mesylate), small molecules that block VEGF receptor signaling (*e.g.*, PTK787/ZK2284, SU6668, Sutent®/SU11248 (sunitinib malate), AMG706, or those described in, *e.g.*, international patent application WO 2004/113304). Anti-angiogensis agents also include native angiogenesis inhibitors , *e.g.*, angiostatin, endostatin, *etc.* *See, e.g.*, Klagsbrun

and D'Amore (1991) *Annu. Rev. Physiol.* 53:217-39; Streit and Detmar (2003) *Oncogene* 22:3172-3179 (*e.g.*, Table 3 listing anti-angiogenic therapy in malignant melanoma); Ferrara & Alitalo (1999) *Nature Medicine* 5(12):1359-1364; Tonini *et al.* (2003) *Oncogene* 22:6549-6556 (*e.g.*, Table 2 listing known anti-angiogenic factors); and, Sato (2003) *Int. J. Clin. Oncol.* 8:200-206 (*e.g.*, Table 1 listing anti-angiogenic agents used in clinical trials).

[074] A "**growth inhibitory agent**" as used herein refers to a compound or composition that inhibits growth of a cell (such as a cell expressing VEGF) either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one that significantly reduces the percentage of cells (such as a cell expressing VEGF) in S phase. Examples of growth inhibitory agents include, but are not limited to, agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in Mendelsohn and Israel, eds., *The Molecular Basis of Cancer*, Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami *et al.* (W.B. Saunders, Philadelphia, 1995), *e.g.*, p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (Taxotere®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (Taxol®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

[075] The term "**anti-neoplastic composition**" refers to a composition useful in treating cancer comprising at least one active therapeutic agent. Examples of therapeutic agents include, but are not limited to, *e.g.*, chemotherapeutic agents, growth inhibitory agents, cytotoxic agents, agents used in radiation therapy, anti-angiogenesis agents, cancer immunotherapeutic agents, apoptotic agents, anti-tubulin agents, and other-agents to treat cancer, such as anti-HER-2 antibodies, anti-CD20 antibodies, an epidermal growth factor receptor (EGFR) antagonist (*e.g.*, a tyrosine kinase inhibitor), HER1/EGFR inhibitor (*e.g.*, erlotinib (Tarceva®), platelet derived growth factor inhibitors (*e.g.*, Gleevec® (Imatinib Mesylate)), a COX-2 inhibitor (*e.g.*, celecoxib), interferons, CTLA4 inhibitors (*e.g.*, anti-CTLA antibody ipilimumab (YERVOY®)), TIM3 inhibitors (*e.g.*, anti-TIM3 antibodies), cytokines, antagonists (*e.g.*, neutralizing antibodies) that bind to one or more of the following

targets ErbB2, ErbB3, ErbB4, PDGFR-beta, BlyS, APRIL, BCMA, CTLA4, TIM3, or VEGF receptor(s), TRAIL/Apo2, and other bioactive and organic chemical agents, *etc.* Combinations thereof are also included in the invention.

[076] An agent "**antagonizes**" factor activity when the agent neutralizes, blocks, inhibits, abrogates, reduces, and/or interferes with the activity of the factor, including its binding to one or more receptors when the factor is a ligand.

[077] "**Treatment**," as used herein, refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. In certain embodiments, the term "**treatment**" covers any administration or application of a therapeutic for disease in a mammal, including a human, and includes inhibiting or slowing the disease or progression of the disease; partially or fully relieving the disease, for example, by causing regression, or restoring or repairing a lost, missing, or defective function; stimulating an inefficient process; or causing the disease plateau to have reduced severity. The term "**treatment**" also includes reducing the severity of any phenotypic characteristic and/or reducing the incidence, degree, or likelihood of that characteristic. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

[078] The term "**effective amount**" or "**therapeutically effective amount**" refers to an amount of a drug effective to treat a disease or disorder in a subject. In certain embodiments, an effective amount refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. A therapeutically effective amount of an anti-CSF1R antibody and/or an immune stimulating agent of the invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibodies to elicit a desired response in the individual. A therapeutically effective amount encompasses an amount in which any toxic or detrimental effects of the antibody or antibodies are outweighed by the therapeutically beneficial effects. In some embodiments, the expression "effective amount" refers to an amount of the antibody that is effective for treating the cancer.

[079] A "**prophylactically effective amount**" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount would be less than the therapeutically effective amount.

[080] Administration "**in combination with**" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive (sequential) administration in any order.

[081] A "**pharmaceutically acceptable carrier**" refers to a non-toxic solid, semisolid, or liquid filler, diluent, encapsulating material, formulation auxiliary, or carrier conventional in the art for use with a therapeutic agent that together comprise a "**pharmaceutical composition**" for administration to a subject. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. The pharmaceutically acceptable carrier is appropriate for the formulation employed. For example, if the therapeutic agent is to be administered orally, the carrier may be a gel capsule. If the therapeutic agent is to be administered subcutaneously, the carrier ideally is not irritable to the skin and does not cause injection site reaction.

Anti-CSF1R Antibodies

[082] Anti-CSF1R antibodies include, but are not limited to, humanized antibodies, chimeric antibodies, mouse antibodies, human antibodies, and antibodies comprising the heavy chain and/or light chain CDRs discussed herein.

Exemplary Humanized Antibodies

[083] In some embodiments, humanized antibodies that bind CSF1R are provided. Humanized antibodies are useful as therapeutic molecules because humanized antibodies reduce or eliminate the human immune response to non-human antibodies (such as the human anti-mouse antibody (HAMA) response), which can result in an immune response to an antibody therapeutic, and decreased effectiveness of the therapeutic.

[084] Nonlimiting exemplary humanized antibodies include huAb1 through huAb16, described herein. Nonlimiting exemplary humanized antibodies also include antibodies comprising a heavy chain variable region of an antibody selected from huAb1 to huAb16 and/or a light chain variable region of an antibody selected from huAb1 to huAb16. Nonlimiting exemplary humanized antibodies include antibodies comprising a heavy chain variable region selected from SEQ ID NOs: 39 to 45 and/or a light chain variable region selected from SEQ ID NOs: 46 to 52. Exemplary humanized antibodies also include, but are not limited to, humanized antibodies comprising heavy chain CDR1, CDR2, and CDR3, and/or light chain CDR1, CDR2, and CDR3 of an antibody selected from 0301, 0302, and 0311.

[085] In some embodiments, a humanized anti-CSF1R antibody comprises heavy chain CDR1, CDR2, and CDR3 and/or a light chain CDR1, CDR2, and CDR3 of an antibody selected from 0301, 0302, and 0311. Nonlimiting exemplary humanized anti-CSF1R

antibodies include antibodies comprising sets of heavy chain CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 15, 16, and 17; SEQ ID NOs: 21, 22, and 23; and SEQ ID NOs: 27, 28, and 29. Nonlimiting exemplary humanized anti-CSF1R antibodies also include antibodies comprising sets of light chain CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 18, 19, and 20; SEQ ID NOs: 24, 25, and 26; and SEQ ID NOs: 30, 31, and 32.

[086] Nonlimiting exemplary humanized anti-CSF1R antibodies include antibodies comprising the sets of heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3 in Table 1 (SEQ ID NOs shown; see Table 8 for sequences). Each row of Table 1 shows the heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3 of an exemplary antibody.

Table 1: Heavy chain and light chain CDRs

	Heavy chain			**Light chain**		
Ab	**CDR1 SEQ ID**	**CDR2 SEQ ID**	**CDR3 SEQ ID**	**CDR1 SEQ ID**	**CDR2 SEQ ID**	**CDR3 SEQ ID**
0301	15	16	17	18	19	20
0302	21	22	23	24	25	26
0311	27	28	29	30	31	32

Further exemplary humanized antibodies

[087] In some embodiments, a humanized anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, and wherein the antibody binds CSF1R. In some embodiments, a humanized anti-CSF1R antibody comprises a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52, wherein the antibody binds CSF1R. In some embodiments, a humanized anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45; and a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52; wherein the antibody binds CSF1R.

[088] As used herein, whether a particular polypeptide is, for example, at least 95% identical to an amino acid sequence can be determined using, e.g., a computer program. When determining whether a particular sequence is, for example, 95% identical to a reference sequence, the percentage of identity is calculated over the full length of the reference amino acid sequence.

[089] In some embodiments, a humanized anti-CSF1R antibody comprises at least one of the CDRs discussed herein. That is, in some embodiments, a humanized anti-CSF1R antibody comprises at least one CDR selected from a heavy chain CDR1 discussed herein, a heavy chain CDR2 discussed herein, a heavy chain CDR3 discussed herein, a light chain CDR1 discussed herein, a light chain CDR2 discussed herein, and a light chain CDR3 discussed herein. Further, in some embodiments, a humanized anti-CSF1R antibody comprises at least one mutated CDR based on a CDR discussed herein, wherein the mutated CDR comprises 1, 2, 3, or 4 amino acid substitutions relative to the CDR discussed herein. In some embodiments, one or more of the amino acid substitutions are conservative amino acid substitutions. One skilled in the art can select one or more suitable conservative amino acid substitutions for a particular CDR sequence, wherein the suitable conservative amino acid substitutions are not predicted to significantly alter the binding properties of the antibody comprising the mutated CDR.

[090] Exemplary humanized anti-CSF1R antibodies also include antibodies that compete for binding to CSF1R with an antibody described herein. Thus, in some embodiments, a humanized anti-CSF1R antibody is provided that competes for binding to CSF1R with an antibody selected from Fabs 0301, 0302, and 0311; and bivalent (i.e., having two heavy chains and two light chains) antibody versions of those Fabs.

Exemplary humanized antibody constant regions

[091] In some embodiments, a humanized antibody described herein comprises one or more human constant regions. In some embodiments, the human heavy chain constant region is of an isotype selected from IgA, IgG, and IgD. In some embodiments, the human light chain constant region is of an isotype selected from κ and λ. In some embodiments, a humanized antibody described herein comprises a human IgG constant region. In some embodiments, a humanized antibody described herein comprises a human IgG4 heavy chain constant region. In some such embodiments, a humanized antibody described herein comprises an S241P mutation in the human IgG4 constant region. In some embodiments, a humanized antibody described herein comprises a human IgG4 constant region and a human κ light chain.

[092] The choice of heavy chain constant region can determine whether or not an antibody will have effector function *in vivo*. Such effector function, in some embodiments, includes antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC), and can result in killing of the cell to which the antibody is bound. In some methods of treatment, including methods of treating some cancers, cell killing may be desirable, for example, when the antibody binds to a cell that supports the maintenance or growth of the tumor. Exemplary cells that may support the maintenance or growth of a tumor include, but are not limited to, tumor cells themselves, cells that aid in the recruitment of vasculature to the tumor, and cells that provide ligands, growth factors, or counter-receptors that support or promote tumor growth or tumor survival. In some embodiments, when effector function is desirable, an anti-CSF1R antibody comprising a human IgG1 heavy chain or a human IgG3 heavy chain is selected.

[093] An antibody may be humanized by any method. Nonlimiting exemplary methods of humanization include methods described, e.g., in U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,761; 5,693,762; 6,180,370; Jones et al., *Nature* 321: 522-525 (1986); Riechmann et al., *Nature* 332: 323-27 (1988); Verhoeyen et al., Science 239: 1534-36 (1988); and U.S. Publication No. US 2009/0136500.

[094] As noted above, a humanized antibody is an antibody in which at least one amino acid in a framework region of a non-human variable region has been replaced with the amino acid from the corresponding location in a human framework region. In some embodiments, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 15, or at least 20 amino acids in the framework regions of a non-human variable region are replaced with an amino acid from one or more corresponding locations in one or more human framework regions.

[095] In some embodiments, some of the corresponding human amino acids used for substitution are from the framework regions of different human immunoglobulin genes. That is, in some such embodiments, one or more of the non-human amino acids may be replaced with corresponding amino acids from a human framework region of a first human antibody or encoded by a first human immunoglobulin gene, one or more of the non-human amino acids may be replaced with corresponding amino acids from a human framework region of a second human antibody or encoded by a second human immunoglobulin gene, one or more of the non-human amino acids may be replaced with corresponding amino acids from a human framework region of a third human antibody or encoded by a third human immunoglobulin gene, etc. Further, in some embodiments, all of the corresponding human amino acids being used for

substitution in a single framework region, for example, FR2, need not be from the same human framework. In some embodiments, however, all of the corresponding human amino acids being used for substitution are from the same human antibody or encoded by the same human immunoglobulin gene.

[096] In some embodiments, an antibody is humanized by replacing one or more entire framework regions with corresponding human framework regions. In some embodiments, a human framework region is selected that has the highest level of homology to the non-human framework region being replaced. In some embodiments, such a humanized antibody is a CDR-grafted antibody.

[097] In some embodiments, following CDR-grafting, one or more framework amino acids are changed back to the corresponding amino acid in a mouse framework region. Such "back mutations" are made, in some embodiments, to retain one or more mouse framework amino acids that appear to contribute to the structure of one or more of the CDRs and/or that may be involved in antigen contacts and/or appear to be involved in the overall structural integrity of the antibody. In some embodiments, ten or fewer, nine or fewer, eight or fewer, seven or fewer, six or fewer, five or fewer, four or fewer, three or fewer, two or fewer, one, or zero back mutations are made to the framework regions of an antibody following CDR grafting.

[098] In some embodiments, a humanized antibody also comprises a human heavy chain constant region and/or a human light chain constant region.

Exemplary Chimeric Antibodies

[099] In some embodiments, an anti-CSF1R antibody is a chimeric antibody. In some embodiments, an anti-CSF1R antibody comprises at least one non-human variable region and at least one human constant region. In some such embodiments, all of the variable regions of an anti-CSF1R antibody are non-human variable regions, and all of the constant regions of an anti-CSF1R antibody are human constant regions. In some embodiments, one or more variable regions of a chimeric antibody are mouse variable regions. The human constant region of a chimeric antibody need not be of the same isotype as the non-human constant region, if any, it replaces. Chimeric antibodies are discussed, e.g., in U.S. Patent No. 4,816,567; and Morrison et al. *Proc. Natl. Acad. Sci. USA* 81: 6851-55 (1984).

[0100] Nonlimiting exemplary chimeric antibodies include chimeric antibodies comprising the heavy and/or light chain variable regions of an antibody selected from 0301, 0302, and 0311. Additional nonlimiting exemplary chimeric antibodies include chimeric

antibodies comprising heavy chain CDR1, CDR2, and CDR3, and/or light chain CDR1, CDR2, and CDR3 of an antibody selected from 0301, 0302, and 0311.

[0101] Nonlimiting exemplary chimeric anti-CSF1R antibodies include antibodies comprising the following pairs of heavy and light chain variable regions: SEQ ID NOs: 9 and 10; SEQ ID NOs: 11 and 12; and SEQ ID NOs: 13 and 14.

[0102] Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising a set of heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3 shown above in Table 1.

Further exemplary chimeric antibodies

[0103] In some embodiments, a chimeric anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, wherein the antibody binds CSF1R. In some embodiments, a chimeric anti-CSF1R antibody comprises a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52, wherein the antibody binds CSF1R. In some embodiments, a chimeric anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45; and a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52; wherein the antibody binds CSF1R.

[0104] In some embodiments, a chimeric anti-CSF1R antibody comprises at least one of the CDRs discussed herein. That is, in some embodiments, a chimeric anti-CSF1R antibody comprises at least one CDR selected from a heavy chain CDR1 discussed herein, a heavy chain CDR2 discussed herein, a heavy chain CDR3 discussed herein, a light chain CDR1 discussed herein, a light chain CDR2 discussed herein, and a light chain CDR3 discussed herein. Further, in some embodiments, a chimeric anti-CSF1R antibody comprises at least one mutated CDR based on a CDR discussed herein, wherein the mutated CDR comprises 1, 2, 3, or 4 amino acid substitutions relative to the CDR discussed herein. In some embodiments, one or more of the amino acid substitutions are conservative amino acid substitutions. One skilled in the art can

select one or more suitable conservative amino acid substitutions for a particular CDR sequence, wherein the suitable conservative amino acid substitutions are not predicted to significantly alter the binding properties of the antibody comprising the mutated CDR.

[0105] Exemplary chimeric anti-CSF1R antibodies also include chimeric antibodies that compete for binding to CSF1R with an antibody described herein. Thus, in some embodiments, a chimeric anti-CSF1R antibody is provided that competes for binding to CSF1R with an antibody selected from Fabs 0301, 0302, and 0311; and bivalent (i.e., having two heavy chains and two light chains) antibody versions of those Fabs.

Exemplary chimeric antibody constant regions

[0106] In some embodiments, a chimeric antibody described herein comprises one or more human constant regions. In some embodiments, the human heavy chain constant region is of an isotype selected from IgA, IgG, and IgD. In some embodiments, the human light chain constant region is of an isotype selected from κ and λ. In some embodiments, a chimeric antibody described herein comprises a human IgG constant region. In some embodiments, a chimeric antibody described herein comprises a human IgG4 heavy chain constant region. In some such embodiments, a chimeric antibody described herein comprises an S241P mutation in the human IgG4 constant region. In some embodiments, a chimeric antibody described herein comprises a human IgG4 constant region and a human κ light chain.

[0107] As noted above, whether or not effector function is desirable may depend on the particular method of treatment intended for an antibody. Thus, in some embodiments, when effector function is desirable, a chimeric anti-CSF1R antibody comprising a human IgG1 heavy chain constant region or a human IgG3 heavy chain constant region is selected. In some embodiments, when effector function is not desirable, a chimeric anti-CSF1R antibody comprising a human IgG4 or IgG2 heavy chain constant region is selected.

Exemplary Human Antibodies

[0108] Human antibodies can be made by any suitable method. Nonlimiting exemplary methods include making human antibodies in transgenic mice that comprise human immunoglobulin loci. See, e.g., Jakobovits et al., *Proc. Natl. Acad. Sci. USA* 90: 2551-55 (1993); Jakobovits et al., *Nature* 362: 255-8 (1993); Lonberg et al., *Nature* 368: 856-9 (1994); and U.S. Patent Nos. 5,545,807; 6,713,610; 6,673,986; 6,162,963; 5,545,807; 6,300,129; 6,255,458; 5,877,397; 5,874,299; and 5,545,806.

[0109] Nonlimiting exemplary methods also include making human antibodies using phage display libraries. See, e.g., Hoogenboom et al., *J. Mol. Biol.* 227: 381-8 (1992); Marks et al., *J. Mol. Biol.* 222: 581-97 (1991); and PCT Publication No. WO 99/10494.

[0110] In some embodiments, a human anti-CSF1R antibody binds to a polypeptide having the sequence of SEQ ID NO: 1. Exemplary human anti-CSF1R antibodies also include antibodies that compete for binding to CSF1R with an antibody described herein. Thus, in some embodiments, a human anti-CSF1R antibody is provided that competes for binding to CSF1R with an antibody selected from Fabs 0301, 0302, and 0311, and bivalent (i.e., having two heavy chains and two light chains) antibody versions of those Fabs.

[0111] In some embodiments, a human anti-CSF1R antibody comprises one or more human constant regions. In some embodiments, the human heavy chain constant region is of an isotype selected from IgA, IgG, and IgD. In some embodiments, the human light chain constant region is of an isotype selected from κ and λ. In some embodiments, a human antibody described herein comprises a human IgG constant region. In some embodiments, a human antibody described herein comprises a human IgG4 heavy chain constant region. In some such embodiments, a human antibody described herein comprises an S241P mutation in the human IgG4 constant region. In some embodiments, a human antibody described herein comprises a human IgG4 constant region and a human κ light chain.

[0112] In some embodiments, when effector function is desirable, a human anti-CSF1R antibody comprising a human IgG1 heavy chain constant region or a human IgG3 heavy chain constant region is selected. In some embodiments, when effector function is not desirable, a human anti-CSF1R antibody comprising a human IgG4 or IgG2 heavy chain constant region is selected.

Additional Exemplary Anti-CSF1R Antibodies

[0113] Exemplary anti-CSF1R antibodies also include, but are not limited to, mouse, humanized, human, chimeric, and engineered antibodies that comprise, for example, one or more of the CDR sequences described herein. In some embodiments, an anti-CSF1R antibody comprises a heavy chain variable region described herein. In some embodiments, an anti-CSF1R antibody comprises a light chain variable region described herein. In some embodiments, an anti-CSF1R antibody comprises a heavy chain variable region described herein and a light chain variable region described herein. In some embodiments, an anti-CSF1R antibody comprises heavy chain CDR1, CDR2, and CDR3 described herein. In some embodiments, an anti-CSF1R antibody comprises light chain CDR1, CDR2, and CDR3 described herein. In some embodiments, an anti-CSF1R antibody comprises heavy chain CDR1, CDR2, and CDR3 described herein and light chain CDR1, CDR2, and CDR3 described herein.

[0114] In some embodiments, an anti-CSF1R antibody comprises a heavy chain variable region of an antibody selected from Fabs 0301, 0302, and 0311. Nonlimiting exemplary anti-CSF1R antibodies also include antibodies comprising a heavy chain variable region of an antibody selected from humanized antibodies huAb1 to huAb16. Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45.

[0115] In some embodiments, an anti-CSF1R antibody comprises a light chain variable region of an antibody selected from Fabs 0301, 0302, and 0311. Nonlimiting exemplary anti-CSF1R antibodies also include antibodies comprising a light chain variable region of an antibody selected from humanized antibodies huAb1 to huAb16. Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising a light chain variable region comprising a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52.

[0116] In some embodiments, an anti-CSF1R antibody comprises a heavy chain variable region and a light chain variable region of an antibody selected from Fabs 0301, 0302, and 0311. Nonlimiting exemplary anti-CSF1R antibodies also include antibodies comprising a heavy chain variable region and a light chain variable region of an antibody selected from humanized antibodies huAb1 to huAb16. Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising the following pairs of heavy and light chain variable regions: SEQ ID NOs: 9 and 10; SEQ ID NOs: 11 and 12; and SEQ ID NOs: 13 and 14; SEQ ID NOs: 39 and 40; SEQ ID NOs: 41 and 42; SEQ ID NOs: 43 and 44; SEQ ID NOs: 45 and 46; SEQ ID NOs: 47 and 48; SEQ ID NOs: 49 and 50; and SEQ ID NOs: 51 and 52. Nonlimiting exemplary anti-CSF1R antibodies also include antibodies comprising the following pairs of heavy and light chains: SEQ ID NOs: 33 and 34; SEQ ID NOs: 35 and 36; and SEQ ID NOs: 37 and 38.

[0117] In some embodiments, an anti-CSF1R antibody comprises heavy chain CDR1, CDR2, and CDR3 of an antibody selected from Fabs 0301, 0302, and 0311. Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising sets of heavy chain CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 15, 16, and 17; SEQ ID NOs: 21, 22, and 23; and SEQ ID NOs: 27, 28,and 29.

[0118] In some embodiments, an anti-CSF1R antibody comprises light chain CDR1, CDR2, and CDR3 of an antibody selected from Fabs 0301, 0302, and 0311. Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising sets of light chain CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 18, 19, and 20; SEQ ID NOs: 24, 25, and 26; and SEQ ID NOs: 30, 31, and 32.

[0119] In some embodiments, an anti-CSF1R antibody comprises heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3 of an antibody selected from Fabs 0301, 0302, and 0311.

[0120] Nonlimiting exemplary anti-CSF1R antibodies include antibodies comprising the sets of heavy chain CDR1, CDR2, and CDR3, and light chain CDR1, CDR2, and CDR3 shown above in Table 1.

Further exemplary antibodies

[0121] In some embodiments, an anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, wherein the antibody binds CSF1R. In some embodiments, an anti-CSF1R antibody comprises a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52, wherein the antibody binds CSF1R. In some embodiments, an anti-CSF1R antibody comprises a heavy chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45; and a light chain comprising a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52; wherein the antibody binds CSF1R.

[0122] In some embodiments, an anti-CSF1R antibody comprises at least one of the CDRs discussed herein. That is, in some embodiments, an anti-CSF1R antibody comprises at least one CDR selected from a heavy chain CDR1 discussed herein, a heavy chain CDR2 discussed herein, a heavy chain CDR3 discussed herein, a light chain CDR1 discussed herein, a light chain CDR2 discussed herein, and a light chain CDR3 discussed herein. Further, in some embodiments, an anti-CSF1R antibody comprises at least one mutated CDR based on a CDR discussed herein, wherein the mutated CDR comprises 1, 2, 3, or 4 amino acid substitutions relative to the CDR discussed herein. In some embodiments, one or more of the amino acid substitutions are conservative amino acid substitutions. One skilled in the art can select one or more suitable conservative amino acid substitutions for a particular CDR

sequence, wherein the suitable conservative amino acid substitutions are not predicted to significantly alter the binding properties of the antibody comprising the mutated CDR.

[0123] Exemplary anti-CSF1R antibodies also include antibodies that compete for binding to CSF1R with an antibody described herein. Thus, in some embodiments, an anti-CSF1R antibody is provided that competes for binding to CSF1R with an antibody selected from Fabs 0301, 0302, and 0311, and bivalent (i.e., having two heavy chains and two light chains) antibody versions of those Fabs.

Exemplary antibody constant regions

[0124] In some embodiments, an antibody described herein comprises one or more human constant regions. In some embodiments, the human heavy chain constant region is of an isotype selected from IgA, IgG, and IgD. In some embodiments, the human light chain constant region is of an isotype selected from κ and λ. In some embodiments, an antibody described herein comprises a human IgG constant region. In some embodiments, an antibody described herein comprises a human IgG4 heavy chain constant region. In some such embodiments, an antibody described herein comprises an S241P mutation in the human IgG4 constant region. In some embodiments, an antibody described herein comprises a human IgG4 constant region and a human κ light chain.

[0125] As noted above, whether or not effector function is desirable may depend on the particular method of treatment intended for an antibody. Thus, in some embodiments, when effector function is desirable, an anti-CSF1R antibody comprising a human IgG1 heavy chain constant region or a human IgG3 heavy chain constant region is selected. In some embodiments, when effector function is not desirable, an anti-CSF1R antibody comprising a human IgG4 or IgG2 heavy chain constant region is selected.

Exemplary Anti-CSF1R Heavy Chain Variable Regions

[0126] In some embodiments, anti-CSF1R antibody heavy chain variable regions are provided. In some embodiments, an anti-CSF1R antibody heavy chain variable region is a mouse variable region, a human variable region, or a humanized variable region.

[0127] An anti-CSF1R antibody heavy chain variable region comprises a heavy chain CDR1, FR2, CDR2, FR3, and CDR3. In some embodiments, an anti-CSF1R antibody heavy chain variable region further comprises a heavy chain FR1 and/or FR4. Nonlimiting exemplary heavy chain variable regions include, but are not limited to, heavy chain variable regions having an amino acid sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45.

[0128] In some embodiments, an anti-CSF1R antibody heavy chain variable region comprises a CDR1 comprising a sequence selected from SEQ ID NOs: 15, 21, and 27.

[0129] In some embodiments, an anti-CSF1R antibody heavy chain variable region comprises a CDR2 comprising a sequence selected from SEQ ID NOs: 16, 22, and 28.

[0130] In some embodiments, an anti-CSF1R antibody heavy chain variable region comprises a CDR3 comprising a sequence selected from SEQ ID NOs: 17, 23, and 29.

[0131] Nonlimiting exemplary heavy chain variable regions include, but are not limited to, heavy chain variable regions comprising sets of CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 15, 16, and 17; SEQ ID NOs: 21, 22, and 23; and SEQ ID NOs: 27, 28, and 29.

[0132] In some embodiments, an anti-CSF1R antibody heavy chain comprises a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, wherein the heavy chain, together with a light chain, is capable of forming an antibody that binds CSF1R.

[0133] In some embodiments, an anti-CSF1R antibody heavy chain comprises at least one of the CDRs discussed herein. That is, in some embodiments, an anti-CSF1R antibody heavy chain comprises at least one CDR selected from a heavy chain CDR1 discussed herein, a heavy chain CDR2 discussed herein, and a heavy chain CDR3 discussed herein. Further, in some embodiments, an anti-CSF1R antibody heavy chain comprises at least one mutated CDR based on a CDR discussed herein, wherein the mutated CDR comprises 1, 2, 3, or 4 amino acid substitutions relative to the CDR discussed herein. In some embodiments, one or more of the amino acid substitutions are conservative amino acid substitutions. One skilled in the art can select one or more suitable conservative amino acid substitutions for a particular CDR sequence, wherein the suitable conservative amino acid substitutions are not predicted to significantly alter the binding properties of the heavy chain comprising the mutated CDR.

[0134] In some embodiments, a heavy chain comprises a heavy chain constant region. In some embodiments, a heavy chain comprises a human heavy chain constant region. In some embodiments, the human heavy chain constant region is of an isotype selected from IgA, IgG, and IgD. In some embodiments, the human heavy chain constant region is an IgG constant region. In some embodiments, a heavy chain comprises a human igG4 heavy chain constant region. In some such embodiments, the human IgG4 heavy chain constant region comprises an S241P mutation.

[0135] In some embodiments, when effector function is desirable, a heavy chain comprises a human IgG1 or IgG3 heavy chain constant region. In some embodiments, when effector function is less desirable, a heavy chain comprises a human IgG4 or IgG2 heavy chain constant region.

Exemplary Anti-CSF1R Light Chain Variable Regions

[0136] In some embodiments, anti-CSF1R antibody light chain variable regions are provided. In some embodiments, an anti-CSF1R antibody light chain variable region is a mouse variable region, a human variable region, or a humanized variable region.

[0137] An anti-CSF1R antibody light chain variable region comprises a light chain CDR1, FR2, CDR2, FR3, and CDR3. In some embodiments, an anti-CSF1R antibody light chain variable region further comprises a light chain FR1 and/or FR4. Nonlimiting exemplary light chain variable regions include light chain variable regions having an amino acid sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52.

[0138] In some embodiments, an anti-CSF1R antibody light chain variable region comprises a CDR1 comprising a sequence selected from SEQ ID NOs: 18, 24 and 30.

[0139] In some embodiments, an anti-CSF1R antibody light chain variable region comprises a CDR2 comprising a sequence selected from SEQ ID NOs: 19, 25, and 31.

[0140] In some embodiments, an anti-CSF1R antibody light chain variable region comprises a CDR3 comprising a sequence selected from SEQ ID NOs: 20, 26, and 32.

[0141] Nonlimiting exemplary light chain variable regions include, but are not limited to, light chain variable regions comprising sets of CDR1, CDR2, and CDR3 selected from: SEQ ID NOs: 18, 19, and 20; SEQ ID NOs: 24, 25, and 26; and SEQ ID NOs: 30, 31, and 32.

[0142] In some embodiments, an anti-CSF1R antibody light chain comprises a variable region sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52, wherein the light chain, together with a heavy chain, is capable of forming an antibody that binds CSF1R.

[0143] In some embodiments, an anti-CSF1R antibody light chain comprises at least one of the CDRs discussed herein. That is, in some embodiments, an anti-CSF1R antibody light chain comprises at least one CDR selected from a light chain CDR1 discussed herein, a light chain CDR2 discussed herein, and a light chain CDR3 discussed herein. Further, in some embodiments, an anti-CSF1R antibody light chain comprises at least one mutated CDR based on a CDR discussed herein, wherein the mutated CDR comprises 1, 2, 3, or 4 amino acid substitutions relative to the CDR discussed herein. In some embodiments, one or more of the amino acid substitutions are conservative amino acid substitutions. One skilled in the art can select one or more suitable conservative amino acid substitutions for a particular CDR sequence, wherein the suitable conservative amino acid substitutions are not predicted to significantly alter the binding properties of the light chain comprising the mutated CDR.

[0144] In some embodiments, a light chain comprises a human light chain constant region. In some embodiments, a human light chain constant region is selected from a human κ and a human λ light chain constant region.

Exemplary Additional CSF1R Binding Molecules

[0145] In some embodiments, additional molecules that bind CSF1R are provided. Such molecules include, but are not limited to, non-canonical scaffolds, such as anti-calins, adnectins, ankyrin repeats, etc. See, e.g., Hosse et al., *Prot. Sci.* 15:14 (2006); Fiedler, M. and Skerra, A., "Non-Antibody Scaffolds," pp.467-499 in Handbook of Therapeutic Antibodies, Dubel, S., ed., Wiley-VCH, Weinheim, Germany, 2007.

Exemplary Properties of anti-CSF1R antibodies

[0146] In some embodiments, an antibody having a structure described above binds to the CSF1R with a binding affinity (K_D) of less than 1 nM, blocks binding of CSF1 and/or IL-34 to CSF1R, and inhibits CSF1R phosphorylation induced by CSF1 and/or IL-34.

[0147] In some embodiments, an anti-CSF1R antibody binds to the extracellular domain of CSF1R (CSF1R-ECD). In some embodiments, an anti-CSF1R antibody has a binding affinity (K_D) for CSF1R of less than 1 nM, less than 0.5 nM, less than 0.1 nM, or less than 0.05 nM. In some embodiments, an anti-CSF1R antibody has a K_D of between 0.01 and 1 nM, between 0.01 and 0.5 nM, between 0.01 and 0.1 nM, between 0.01 and 0.05 nM, or between 0.02 and 0.05 nM.

[0148] In some embodiments, an anti-CSF1R antibody blocks ligand binding to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of CSF1 to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of IL-34 to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of both CSF1 and IL-34 to CSF1R. In some embodiments, an antibody that blocks ligand binding binds to the extracellular domain of CSF1R. In some embodiments, an antibody blocks ligand binding to CSF1R when it reduces the amount of detectable binding of a ligand to CSF1R by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 7, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of detectable binding of a ligand to CSF1R by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the antibody is said to block ligand binding by at least 50%, at least 60%, at least 70%, etc.

[0149] In some embodiments, an anti-CSF1R antibody inhibits ligand-induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits CSF1-induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits IL-34-

induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits both CSF1-induced and IL-34-induced CSF1R phosphorylation. In some embodiments, an antibody is considered to "inhibit ligand-induced CSF1R phosphorylation" when it reduces the amount of detectable ligand-induced CSF1R phosphorylation by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 6, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of detectable ligand-induced CSF1R phosphorylation by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the antibody is said to inhibit ligand-induced CSF1R phosphorylation by at least at least 50%, at least 60%, at least 70%, etc.

[0150] In some embodiments, an antibody inhibits monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34. In some embodiments, an antibody is considered to "inhibit monocyte proliferation and/or survival responses" when it reduces the amount of monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34 by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 10, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34 by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the antibody is said to inhibit monocyte proliferation and/or survival responses by at least at least 50%, at least 60%, at least 70%, etc.

Exemplary Immune Stimulating Agents

[0151] Immune stimulating agents may include, for example, a small molecule drug, antibody or fragment thereof, or other biologic or small molecule. Examples of biologic immune stimulating agents include, but are not limited to, antibodies, antibody fragments, fragments of receptor or ligand polypeptides, for example that block receptor-ligand binding, vaccines and cytokines. In one aspect, the antibody is a monoclonal antibody. In certain aspects, the monoclonal antibody is humanized or human antibody.

[0152] In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune stimulatory molecule, including a co-stimulatory molecule, while in some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule. In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune-stimulatory molecule, including a co-stimulatory molecule, found on immune cells, such as T cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule, found on immune cells, such as T

cells. In some embodiments, the at least one immune stimulating agent comprises an agonist of an immune stimulatory molecule, including a co-stimulatory molecule, found on cells involved in innate immunity, such as NK cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule, found on cells involved in innate immunity, such as NK cells. In some embodiments, the combination enhances the antigen-specific T cell response in the treated subject and/or enhances the innate immunity response in the subject. In some embodiments, the combination results in an improved anti-tumor response in an animal cancer model, such as a xenograft model, compared to administration of either the anti-CSF1R antibody or immune stimulating agent alone. In some embodiments, the combination results in a synergistic response in an animal cancer model, such as a xenograft model, compared to administration of either the anti-CSF1R antibody or immune stimulating agent alone.

[0153] In certain embodiments, an immune stimulating agent targets a stimulatory or inhibitory molecule that is a member of the immunoglobulin super family (IgSF). For example, an immune stimulating agent may be an agent that targets (or binds specifically to) a member of the B7 family of membrane-bound ligands, which includes B7-1, B7-2, B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6, or a co-stimulatory or co-inhibitory receptor binding specifically to a B7 family member. An immune stimulating agent may be an agent that targets a member of the TNF family of membrane bound ligands or a co-stimulatory or co-inhibitory receptor binding specifically to a member of the TNF family. Exemplary TNF and TNFR family members that may be targeted by immune stimulating agents include CD40 and CD40L, OX-40, OX-40L, GITR, GITRL, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α 1β2, FAS, FASL, RELT, DR6, TROY and NGFR. An immune stimulating agent may be an agent, e.g., an antibody, targeting an IgSF member, such as a B7 family member, a B7 receptor family member, a TNF family member or a TNFR family member, such as those described above.

[0154] In some embodiments, an immune stimulating agent may comprise (i) an antagonist of a protein that inhibits T cell activation (e.g., immune checkpoint inhibitor) such as CTLA-4, LAG-3, TIM3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, B7-H3, B7-H4, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, TIM-4, and ILT4 and/or may comprise (ii)an agonist of a protein that stimulates T cell activation such

as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, CD40L, DR3 and CD28H.

[0155] In some embodiments, an immune stimulating agent may comprise an agent that inhibit or is an antagonist of a cytokine that inhibits T cell activation (e.g., IL-6, IL-10, TGF-ß, VEGF, and other immunosuppressive cytokines), and it some embodiments an immune stimulating agent may comprise an agent that is an agonist of a cytokine, such as IL-2, IL-7, IL-12, IL-15, IL-21 and IFNα (e.g., the cytokine itself) that stimulates T cell activation. In some embodiments, immune stimulating agents may comprise an antagonist of a chemokine, such as CXCR2 (e.g., MK-7123), CXCR4 (e.g. AMD3100), CCR2, or CCR4 (mogamulizumab).

[0156] In some embodiments, immune stimulating agents may include antagonists of inhibitory receptors on NK cells or agonists of activating receptors on NK cells. For example, an anti-CSF1R antibody can be combined with an antagonist of KIR, optionally along with at least one other immune stimulating agent such as an agonist of CD40.

[0157] Immune stimulating agents may also include agents that inhibit TGF-β signaling, agents that enhance tumor antigen presentation, e.g., dendritic cell vaccines, GM-CSF secreting cellular vaccines, CpG oligonucleotides,and imiquimod, or therapies that enhance the immunogenicity of tumor cells (e.g., anthracyclines).

[0158] Immune stimulating agents may also include certain vaccines such as mesothelin-targeting vaccines or attenuated listeria cancer vaccines, such as CRS-207.

[0159] Immune stimulating agents may also comprise agents that deplete or block Treg cells, such as agents that specifically bind to CD25.

[0160] Immune stimulating agents may also comprise agents that inhibit a metabolic enzyme such as indoleamine dioxigenase (IDO), dioxigenase, arginase, or nitric oxide synthetase.

[0161] Immune stimulating agents may also comprise agents that inhibit the formation of adenosine or inhibit the adenosine A2A receptor.

[0162] Immune stimulating agents may also comprise agents that reverse/prevent T cell anergy or exhaustion and agents that trigger an innate immune activation and/or inflammation at a tumor site.

[0163] An anti-CSF1R antibody may be combined with more than one immune stimulating agent, such as a CD40 agonist and at least one additional immune stimulating agent. The anti-CSF1R antibody, optionally along with a CD40 agonist, may be combined with a combinatorial approach that targets multiple elements of the immune pathway, such as

one or more of the following: at least one agent that enhances tumor antigen presentation (e.g., dendritic cell vaccine, GM-CSF secreting cellular vaccines, CpG oligonucleotides, imiquimod); at least one agent that inhibits negative immune regulation e.g., by inhibiting CTLA-4 pathway and/or depleting or blocking Treg or other immune suppressing cells; a therapy that stimulates positive immune regulation, e.g., with agonists that stimulate the CD-137, OX-40 and/or GITR pathway and/or stimulate T cell effector function; at least one agent that increases systemically the frequency of anti-tumor T cells; a therapy that depletes or inhibits Tregs, such as Tregs in the tumor, e.g., using an antagonist of CD25 (e.g., daclizumab) or by ex vivo anti-CD25 bead depletion; at least one agent that impacts the function of suppressor myeloid cells in the tumor; a therapy that enhances immunogenicity of tumor cells (e.g., anthracyclines); adoptive T cell or NK cell transfer including genetically modified cells, e.g., cells modified by chimeric antigen receptors (CAR-T therapy); at least one agent that inhibits a metabolic enzyme such as indoleamine dioxigenase (IDO), dioxigenase, arginase or nitric oxide synthetase; at least one agent that reverses/prevents T cell anergy or exhaustion; a therapy that triggers an innate immune activation and/or inflammation at a tumor site; administration of immune stimulatory cytokines or blocking of immuno repressive cytokines.

[0164] For example, an anti-CSF1R antibody, optionally with a CD40 agonist, can be used with one or more agonistic agents that ligate positive costimulatory receptors; one or more antagonists (blocking agents) that attenuate signaling through inhibitory receptors, such as antagonists that overcome distinct immune suppressive pathways within the tumor microenvironment; one or more agents that increase systemically the frequency of anti-tumor immune cells, such as T cells, deplete or inhibit Tregs (e.g., by inhibiting CD25); one or more agents that inhibit metabolic enzymes such as IDO; one or more agents that reverse/prevent T cell anergy or exhaustion; and one or more agents that trigger innate immune activation and/or inflammation at tumor sites.

[0165] In one embodiment, the at least one immune stimulating agent comprises a CTLA-4 antagonist, such as an antagonistic CTLA-4 antibody. Suitable CTLA-4 antibodies include, for example, YERVOY (ipilimumab) or tremelimumab.

[0166] In some embodiments, the at least one immune stimulating agent comprises a LAG-3 antagonist, such as an antagonistic LAG-3 antibody. Suitable LAG3 antibodies include, for example, BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO09/44273).

[0167] In some embodiments, the at least one immune stimulating agent comprises a CD137 (4-1BB) agonist, such as an agonistic CD137 antibody. Suitable CD137 antibodies include, for example, urelumab or PF-05082566 (WO12/32433).

[0168] In some embodiments, the at least one immune stimulating agent comprises a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, TRX-518 (WO06/105021, WO09/009116), MK-4166 (WO11/028683) or a GITR antibody disclosed in WO2015/031667.

[0169] In some embodiments, the at least one immune stimulating agent comprises an OX40 agonist, such as an agonistic OX40 antibody. Suitable OX40 antibodies include, for example, MEDI-6383, MEDI-6469 or MOXR0916 (RG7888; WO06/029879).

[0170] In some embodiments, the at least one immune stimulating agent comprises a CD27 agonist, such as an agonistic CD27 antibody. Suitable CD27 antibodies include, for example, varlilumab (CDX-1127).

[0171] In some embodiments, the at least one immune stimulating agent comprises MGA271, which targets B7H3 (WO11/109400).

[0172] In some embodiments, the at least one immune stimulating agent comprises a KIR antagonist, such as lirilumab.

[0173] In some embodiments, the at least one immune stimulating agent comprises an IDO antagonist. IDO antagonists include, for example, INCB-024360 (WO2006/122150, WO07/75598, WO08/36653, WO08/36642), indoximod, NLG-919 (WO09/73620, WO09/1156652, WO11/56652, WO12/142237) or F001287.

[0174] In some embodiments, the at least one immune stimulating agent comprises a Toll-like receptor agonist, e.g., a TLR2/4 agonist (e.g., Bacillus Calmette-Guerin); a TLR7 agonist (e.g., Hiltonol or Imiquimod); a TLR7/8 agonist (e.g., Resiquimod); or a TLR9 agonist (e.g., CpG7909).

[0175] In some embodiments, the at least one immune stimulating agent comprises a TGF-β inhibitor, e.g., GC1008, LY2157299, TEW7197 or IMC-TR1.

CD40 Agonists and Exemplary CD40 Agonist Molecules

[0176] In some embodiments, the at least one immune stimulating agent comprises a CD40 agonist, optionally together with at least one additional immune stimulating agent as described herein. The cell surface molecule CD40 is a member of the tumor necrosis factor receptor superfamily and is expressed by antigen presenting cells such as dentritic cells, B cells, macrophages and monocytes and is also expressed on other cell types, including immune, hematopoietic, vascular, and epithelial cells, as well as on various tumor cells. In antigen

presenting cells CD40 signaling results in activation and upregulation of T cell costimulatory molecules and other critical immune mediators required for the induction of an immune response. Agonists of CD40 are potential cancer therapies, causing tumor regression through both anti-tumor immune activation and direct cytotoxic effect on tumor cells. CD40-targeting therapies have undergone phase 1 clinical evaluation in advanced-stage cancer patients, and initial findings have shown efficacy in the absence of major toxicity.

[0177] With regard to CD40, for example, animal models have shown that ligation of CD40 on dendritic cells results in activation of cytotoxic T lymphocytes that mediate tumor killing (Marzo et al., 2000, *J. Immunol.*; Todryk et al., 2001, *J. Immunol. Methods*.) Activation of CD40 on macrophages results in tumoralcidal activity (Beatty et al., 2011, *Science*), and cytokines produced from CD40 stimulated antigen presenting cells leads to the activation of natural killer cells important for tumor eradication. Given the complex nature of an anti-tumor immune response, effective cancer therapy may require combining multiple immunotherapy agents. Consistent with this, small molecule inhibition of CSF1R was shown to synergize with anti-PD1 immune checkpoint blockade in a pancreatic tumor model. *See* Zhu et al., 2014, *Cancer Res.*, 74: 5057-5069. Thus, tumors that have CSF1R-expressing TAMs may be sensitive to combination therapy with an anti-CSF1R antibody and a CD40 agonist.

[0178] Exemplary CD40 agonists of the compositions and methods of this invention include, for example, anti-CD40 antibodies that enhance CD40 activity. Such antibodies may be humanized antibodies, chimeric antibodies, mouse antibodies, human antibodies, and antibodies comprising the heavy chain and/or light chain CDRs of an anti-CD40 antibody iscussed herein.

[0179] Various agonist anti-CD40 antibodies are known in the art. Nonlimiting exemplary agonist anti-CD40 antibodies include, but are not limited to, CP-870,893 (Pfizer and VLST; antibody 21.4.1 in EP 1 476 185 B1 and US Patent No. 7,338,660; *see also* clinicaltrials.gov/ct2/show/NCT02225002); dacetuzumab (Seattle Genetics; SEQ ID NOs: 98 and 99 herein; see also US Patent No. 6,946,129 and US Patent No. 8,303,955); RO7009789 (Roche; *see, e.g.*, clinicaltrials.gov/ct2/show/NCT02304393); ADC-1013 (Alligator Bioscience; US Publication No. 2014/0348836; *see also* clinicaltrials.gov/ct2/show/NCT02379741); SEA-CD40 (Seattle Genetics; afucosylated form of antibody comprising SEQ ID NOs: 98 and 99; *see also* clinicaltrials.gov/ct2/show/NCT02376699); and Chi Lob 7/4 (Univ. Southampton; US Publication No. 2009/0074711; *see also* clinicaltrials.gov/ct2/show/NCT01561911). *See, e.g.*, Vonderheide et al., 2013, *Clin Cancer Res* 19:1035.

[0180] Exemplary CD40 agonists also include recombinant CD40L.

Exemplary Antibody Conjugates

[0181] In some embodiments, an antibody is conjugated to a label and/or a cytotoxic agent. As used herein, a label is a moiety that facilitates detection of the antibody and/or facilitates detection of a molecule to which the antibody binds. Nonlimiting exemplary labels include, but are not limited to, radioisotopes, fluorescent groups, enzymatic groups, chemiluminescent groups, biotin, epitope tags, metal-binding tags, etc. One skilled in the art can select a suitable label according to the intended application.

[0182] As used herein, a cytotoxic agent is a moiety that reduces the proliferative capacity of one or more cells. A cell has reduced proliferative capacity when the cell becomes less able to proliferate, for example, because the cell undergoes apoptosis or otherwise dies, the cell fails to proceed through the cell cycle and/or fails to divide, the cell differentiates, etc. Nonlimiting exemplary cytotoxic agents include, but are not limited to, radioisotopes, toxins, and chemotherapeutic agents. One skilled in the art can select a suitable cytotoxic according to the intended application.

[0183] In some embodiments, a label and/or a cytotoxic agent is conjugated to an antibody using chemical methods *in vitro*. Nonlimiting exemplary chemical methods of conjugation are known in the art, and include services, methods and/or reagents commercially available from, e.g., Thermo Scientific Life Science Research Produces (formerly Pierce; Rockford, IL), Prozyme (Hayward, CA), SACRI Antibody Services (Calgary, Canada), AbD Serotec (Raleigh, NC), etc. In some embodiments, when a label and/or cytotoxic agent is a polypeptide, the label and/or cytotoxic agent can be expressed from the same expression vector with at least one antibody chain to produce a polypeptide comprising the label and/or cytotoxic agent fused to an antibody chain. One skilled in the art can select a suitable method for conjugating a label and/or cytotoxic agent to an antibody according to the intended application.

Exemplary Leader Sequences

[0184] In order for some secreted proteins to express and secrete in large quantities, a leader sequence from a heterologous protein may be desirable. In some embodiments, a leader sequence is selected from SEQ ID NOs: 3 and 4, which are light chain and heavy chain leader sequences, respectively. In some embodiments, employing heterologous leader sequences may be advantageous in that a resulting mature polypeptide may remain unaltered as the leader sequence is removed in the ER during the secretion process. The addition of a heterologous leader sequence may be required to express and secrete some proteins.

[0185] Certain exemplary leader sequence sequences are described, e.g., in the online Leader sequence Database maintained by the Department of Biochemistry, National University of Singapore. *See* Choo et al., *BMC* Bioinformatics, 6: 249 (2005); and PCT Publication No. WO 2006/081430.

Nucleic Acid Molecules Encoding Antibodies

[0186] Nucleic acid molecules comprising polynucleotides that encode one or more chains of an antibody are provided. In some embodiments, a nucleic acid molecule comprises a polynucleotide that encodes a heavy chain or a light chain of an antibody. In some embodiments, a nucleic acid molecule comprises both a polynucleotide that encodes a heavy chain and a polynucleotide that encodes a light chain, of an antibody. In some embodiments, a first nucleic acid molecule comprises a first polynucleotide that encodes a heavy chain and a second nucleic acid molecule comprises a second polynucleotide that encodes a light chain.

[0187] In some such embodiments, the heavy chain and the light chain are expressed from one nucleic acid molecule, or from two separate nucleic acid molecules, as two separate polypeptides. In some embodiments, such as when an antibody is an scFv, a single polynucleotide encodes a single polypeptide comprising both a heavy chain and a light chain linked together.

[0188] In some embodiments, a polynucleotide encoding a heavy chain or light chain of an antibody comprises a nucleotide sequence that encodes a leader sequence, which, when translated, is located at the N terminus of the heavy chain or light chain. As discussed above, the leader sequence may be the native heavy or light chain leader sequence, or may be another heterologous leader sequence.

[0189] Nucleic acid molecules may be constructed using recombinant DNA techniques conventional in the art. In some embodiments, a nucleic acid molecule is an expression vector that is suitable for expression in a selected host cell.

Antibody Expression and Production

Vectors

[0190] Vectors comprising polynucleotides that encode antibody heavy chains and/or light chains are provided. Vectors comprising polynucleotides that encode antibody heavy chains and/or light chains are also provided. Such vectors include, but are not limited to, DNA vectors, phage vectors, viral vectors, retroviral vectors, etc. In some embodiments, a vector comprises a first polynucleotide sequence encoding a heavy chain and a second polynucleotide sequence encoding a light chain. In some embodiments, the heavy chain and light chain are expressed from the vector as two separate polypeptides. In some embodiments, the heavy chain

and light chain are expressed as part of a single polypeptide, such as, for example, when the antibody is an scFv.

[0191] In some embodiments, a first vector comprises a polynucleotide that encodes a heavy chain and a second vector comprises a polynucleotide that encodes a light chain. In some embodiments, the first vector and second vector are transfected into host cells in similar amounts (such as similar molar amounts or similar mass amounts). In some embodiments, a mole- or mass-ratio of between 5:1 and 1:5 of the first vector and the second vector is transfected into host cells. In some embodiments, a mass ratio of between 1:1 and 1:5 for the vector encoding the heavy chain and the vector encoding the light chain is used. In some embodiments, a mass ratio of 1:2 for the vector encoding the heavy chain and the vector encoding the light chain is used.

[0192] In some embodiments, a vector is selected that is optimized for expression of polypeptides in CHO or CHO-derived cells, or in NSO cells. Exemplary such vectors are described, e.g., in Running Deer et al., *Biotechnol. Prog.* 20:880-889 (2004).

[0193] In some embodiments, a vector is chosen for *in vivo* expression of antibody heavy chains and/or antibody light chains in animals, including humans. In some such embodiments, expression of the polypeptide is under the control of a promoter that functions in a tissue-specific manner. For example, liver-specific promoters are described, e.g., in PCT Publication No. WO 2006/076288.

Host Cells

[0194] In various embodiments, antibody heavy chains and/or light chains may be expressed in prokaryotic cells, such as bacterial cells; or in eukaryotic cells, such as fungal cells (such as yeast), plant cells, insect cells, and mammalian cells. Such expression may be carried out, for example, according to procedures known in the art. Exemplary eukaryotic cells that may be used to express polypeptides include, but are not limited to, COS cells, including COS 7 cells; 293 cells, including 293-6E cells; CHO cells, including CHO-S and DG44 cells; PER.C6® cells (Crucell); and NSO cells. In some embodiments, antibody heavy chains and/or light chains may be expressed in yeast. See, e.g., U.S. Publication No. US 2006/0270045 A1. In some embodiments, a particular eukaryotic host cell is selected based on its ability to make desired post-translational modifications to the antibody heavy chains and/or light chains. For example, in some embodiments, CHO cells produce polypeptides that have a higher level of sialylation than the same polypeptide produced in 293 cells.

[0195] Introduction of one or more nucleic acids into a desired host cell may be accomplished by any method, including but not limited to, calcium phosphate transfection,

DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, etc. Nonlimiting exemplary methods are described, e.g., in Sambrook et al., *Molecular Cloning, A Laboratory Manual,* 3rd ed. Cold Spring Harbor Laboratory Press (2001). Nucleic acids may be transiently or stably transfected in the desired host cells, according to any suitable method.

[0196] In some embodiments, one or more polypeptides may be produced *in vivo* in an animal that has been engineered or transfected with one or more nucleic acid molecules encoding the polypeptides, according to any suitable method.

Purification of Antibodies

[0197] Antibodies may be purified by any suitable method. Such methods include, but are not limited to, the use of affinity matrices or hydrophobic interaction chromatography. Suitable affinity ligands include the antigen and ligands that bind antibody constant regions. For example, a Protein A, Protein G, Protein A/G, or an antibody affinity column may be used to bind the constant region and to purify an antibody. Hydrophobic interactive chromatography, for example, a butyl or phenyl column, may also suitable for purifying some polypeptides. Many methods of purifying polypeptides are known in the art.

Cell-free Production of Antibodies

[0198] In some embodiments, an antibody is produced in a cell-free system. Nonlimiting exemplary cell-free systems are described, e.g., in Sitaraman et al., *Methods Mol. Biol.* 498: 229-44 (2009); Spirin, *Trends Biotechnol.* 22: 538-45 (2004); Endo et al., *Biotechnol. Adv.* 21: 695-713 (2003).

Therapeutic Compositions and Methods

Methods of Treating Cancer

[0199] In some embodiments, methods for treating cancer are provided, comprising administering an effective amount of an anti-CSF1R antibody and an effective amount of at least one immune stimulating agent. In some embodiments, the anti-CSF1R antibody and the at least one immune stimulating agent are administered concurrently. For example, the therapeutics may be infused together or injected at roughly the same time. In some embodiments, the anti-CSF1R antibody and the at least one immune stimulating agent administered sequentially. For example, in some embodiments the anti-CSF1R antibody is administered sequentially before or after at least one immune stimulating agent such that the two therapeutics are administered 30 minutes, 60 minutes, 90 minutes, 120 minutes, 3 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 3 days, 5 days, 7 days, or two weeks apart.

[0200] In some embodiments, at least one, at least two, at least three doses, at least five doses, or at least ten doses of an anti-CSF1R antibody is administered prior to administration of at least one immune stimulating agent. In some embodiments, at least one, at least two, at least three doses, at least five doses, or at least ten doses of at least one immune stimulating agent is administered prior to administration of an anti-CSF1R antibody. In some embodiments, the last dose of immune stimulating agent is administered at least one, two, three, five, days or ten, or one, two, three, five, twelve, or twenty four weeks prior to the first dose of CSFR1 inhibitor. In some other embodiment, the last dose of CSFR1 inhibitor is administered at least one, two, three, five, days or ten, or one, two, three, five, twelve, or twenty four weeks prior to the first dose of at least one immune stimulating agent. In some embodiments, a subject has received, or is receiving, therapy with at least one immune stimulating agent, and an anti-CSF1R antibody is added to the therapeutic regimen.

[0201] In some embodiments, a method of selecting a patient for combination therapy with an anti-CSF1R antibody and a at least one immune stimulating agent, such as a CD40 agonist is provided, comprising determining the levels of TAMs and/or CD8+ T cells in the patient. In some embodiments, if a patient's TAM levels are high, the patient is selected for combination therapy. In some embodiments, if a patient's TAM and CD8+ T cell levels are high, the patient is selected for combination therapy. The level of TAMs or CD8+ T cells is considered "high" if it is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 75%, or at least 100% higher than the level in an individual who does not have cancer. In some embodiments, the level of TAMs or CD8+ T cells is considered "high" if it is above the median level found in individuals with cancer. In some embodiments, if a patient's TAM levels are high and CD8+ T cell levels are low, the patient is selected for combination therapy with an anti-CSF1R antibody and at least one immune stimulating agent, such as a CD40 agonist. The level of CD8+ T cells is considered "low" if it is at or below the median level found in individuals with cancer. In some embodiment, the level of CD8+ T cells is considered "low" if it is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 75%, or at least 100% lower than the level in an individual who does not have cancer. In some embodiments, expression of CSF1R on the patient's TAMs is determined. In some embodiments, if the patient's TAMs express CSF1R, the patient is selected for combination therapy. In some embodiments, if the patient's TAMs express elevated levels of CSF1R, the patient is selected for combination therapy. In some embodiments, a patient's TAMs are considered to express "elevated" levels of CSF1R if the level of CSF1R is at or above the median level of CSF1R found expressed on TAMS in individuals with cancer. In some

embodiments, if the patient's CSF1R expression shows a high correlation with the level of CD8+ T cells, the patient is selected for combination therapy. The correlation of the expressions is considered "high" if it is at or above the median level found in individuals with cancer.

[0202] Levels of TAMs, CSF1R expression, CD8+ T cells, and/or regulatory T cells may be measured by methods in the art. Nonexemplary methods include immunohistochemistry (IHC), fluorescence-activated cell sorting (FACS), protein arrays, and gene expression assays, such as RNA sequencing, gene arrays, and quantitative PCR. In some embodiments, one or more markers selected from CSF1R, CD68, CD163, CD8, and FoxP3 may be detected by IHC, FACS, or gene expression assay on tumor sections, or dissociated cells from tumor sections.

[0203] In some embodiments, the cancer is selected from squamous cell cancer, small-cell lung cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, and various types of head and neck cancer. In some embodiments, lung cancer is non-small cell lung cancer or lung squamous cell carcinoma. In some embodiments, leukemia is acute myeloid leukemia or chronic lymphocytic leukemia. In some embodiments, breast cancer is breast invasive carcinoma. In some embodiments, ovarian cancer is ovarian serous cystadenocarcinoma. In some embodiments, kidney cancer is kidney renal clear cell carcinoma. In some embodiments, colon cancer is colon adenocarcinoma. In some embodiments, bladder cancer is bladder urothelial carcinoma. In some embodiments, the cancer is selected from bladder cancer, cervical cancer (such as squamous cell cervical cancer), head and neck squamous cell carcinoma, rectal adenocarcinoma, non-small cell lung cancer, endometrial cancer, prostate adenocarcinoma, colon cancer, ovarian cancer (such as serous epithelial ovarian cancer), and melanoma.

[0204] In some embodiments, the anti-CSF1R antibody blocks binding of CSF1 and/or IL-34 to CSF1R and/or inhibits CSF1R phosphorylation induced by CSF1 and/or IL-34. In some embodiments, the anti-CSF1R antibody locks binding of CSF1 and IL-34 to CSF1R and/or inhibits CSF1R phosphorylation induced by CSF1 and/or IL-34. In some embodiments,

the anti-CSF1R antibody comprises the CDRs of, or the variable regions of, an antibody selected from huAb1 to huAb16, described herein. In some embodiments, the anti-CSF1R antibody comprises the CDRs of, or the variable regions of, huAb1.

[0205] In some embodiments, the at least one immune stimulating agent comprises an antagonist of an inhibitor of the activation of T cells, while in some embodiments, the at least one immune stimulating agent comprises comprises an agonist of a stimulator of the activation of T cells. In some embodiments, the at least one immune stimulating agent comprises an antagonist of CTLA4, LAG-3, Galectin 1, Galectin 9, CEACAM-1, BTLA, CD25, CD69, TIGIT, CD113, GPR56, VISTA, B7-H3, B7-H4, 2B4, CD48, GARP, PD1H, LAIR1, TIM1, TIM3, TIM4, ILT4, IL-6, IL-10, TGFβ, VEGF, KIR, LAG-3, adenosine A2A receptor, PI3Kdelta, or IDO. In some embodiments, the at least one immune stimulating agent comprises an agonist of B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD27, CD40, CD40L, DR3, CD28H, IL-2, IL-7, IL-12, IL-15, IL-21, IFNα, STING, or a Toll-like receptor agonist such as a TLR2/4 agonist. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the B7 family of membrane-bound proteins such as B7-1, B7-2, B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. In some embodiments, the at least one immune stimulating agent comprises an agent that binds to a member of the TNF receptor family or a co-stimulatory or co-inhibitory molecule binding to a member of the TNF receptor family such as CD40, CD40L, OX40, OX40L, GITR, GITRL, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, EDA1, EDA2, TACI, APRIL, BCMA, LTβR, LIGHT, DeR3, HVEM, VEGL/TL1A, TRAMP/DR3, TNFR1, TNFβ, TNFR2, TNFα, 1β2, FAS, FASL, RELT, DR6, TROY, or NGFβ. In some embodiments, the at least one immune stimulating agent comprises an agent that antagonizes or inhibits a cytokine that inhibits T cell activation such as IL-6, IL-10, TGFβ, VEGF. In some embodiments, the at least one immune stimulating agent comprises an agonist of a cytokine that stimulates T cell activation such as IL-2, IL-7, IL-12, IL-15, IL-21, and IFNα. In some embodiments, the at least one immune stimulating agent comprises an antagonist of a chemokine, such as CXCR2, CXCR4, CCR2, or CCR4. In some embodiments, the at least one immune stimulating agent comprises an antibody. In some embodiments, the at least one immune stimulating agent may comprise a vaccine, such as a mesothelin-targeting vaccine or attenuated listeria cancer vaccine such as CRS-207.

[0206] In some embodiments, the at least one immune stimulating agent comprises a CD40 agonist, for example, an anti-CD40 antibody. Nonlimiting exemplary agonist anti-CD40 antibodies include CP-870,893 (Pfizer and VLST); dacetuzumab (Seattle Genetics); RO7009789 (Roche); ACD-1013 (Alligator Bioscience); SEA-CD40 (Seattle Genetics); and Chi Lob 7/4 (Univ. Southampton). In some embodiments, a CD40 agonist is recombinant CD40L.

Routes of Administration and Carriers

[0207] In various embodiments, antibodies may be administered *in vivo* by various routes, including, but not limited to, oral, intra-arterial, parenteral, intranasal, intramuscular, intracardiac, intraventricular, intratracheal, buccal, rectal, intraperitoneal, intradermal, topical, transdermal, and intrathecal, or otherwise by implantation or inhalation. The subject compositions may be formulated into preparations in solid, semi-solid, liquid, or gaseous forms; including, but not limited to, tablets, capsules, powders, granules, ointments, solutions, suppositories, enemas, injections, inhalants, and aerosols. A nucleic acid molecule encoding an antibody may be coated onto gold microparticles and delivered intradermally by a particle bombardment device, or "gene gun," as described in the literature (see, e.g., Tang et al., *Nature* 356:152-154 (1992)). The appropriate formulation and route of administration may be selected according to the intended application.

[0208] In various embodiments, compositions comprising antibodies are provided in formulations with a wide variety of pharmaceutically acceptable carriers (see, e.g., Gennaro, *Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus*, 20th ed. (2003); Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems,* 7th ed., Lippencott Williams and Wilkins (2004); Kibbe et al., *Handbook of Pharmaceutical Excipients,* 3rd ed., Pharmaceutical Press (2000)). Various pharmaceutically acceptable carriers, which include vehicles, adjuvants, and diluents, are available. Moreover, various pharmaceutically acceptable auxiliary substances, such as Ph adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are also available. Non-limiting exemplary carriers include saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof.

[0209] In various embodiments, compositions comprising antibodies may be formulated for injection, including subcutaneous administration, by dissolving, suspending, or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids, or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents,

emulsifying agents, stabilizers and preservatives. In various embodiments, the compositions may be formulated for inhalation, for example, using pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen, and the like. The compositions may also be formulated, in various embodiments, into sustained release microcapsules, such as with biodegradable or non-biodegradable polymers. A non-limiting exemplary biodegradable formulation includes poly lactic acid-glycolic acid polymer. A non-limiting exemplary non-biodegradable formulation includes a polyglycerin fatty acid ester. Certain methods of making such formulations are described, for example, in EP 1 125 584 A1.

[0210] Pharmaceutical packs and kits comprising one or more containers, each containing one or more doses of an antibody or combination of antibodiesare also provided. In some embodiments, a unit dosage is provided wherein the unit dosage contains a predetermined amount of a composition comprising an antibody or combination of antibodies, with or without one or more additional agents. In some embodiments, such a unit dosage is supplied in single-use prefilled syringe for injection. In various embodiments, the composition contained in the unit dosage may comprise saline, sucrose, or the like; a buffer, such as phosphate, or the like; and/or be formulated within a stable and effective Ph range. Alternatively, in some embodiments, the composition may be provided as a lyophilized powder that may be reconstituted upon addition of an appropriate liquid, for example, sterile water. In some embodiments, the composition comprises one or more substances that inhibit protein aggregation, including, but not limited to, sucrose and arginine. In some embodiments, a composition of the invention comprises heparin and/or a proteoglycan.

[0211] Pharmaceutical compositions are administered in an amount effective for treatment or prophylaxis of the specific indication. The therapeutically effective amount is typically dependent on the weight of the subject being treated, his or her physical or health condition, the extensiveness of the condition to be treated, or the age of the subject being treated. In general, antibodies may be administered in an amount in the range of about 10 μg/kg body weight to about 100 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 50 μg/kg body weight to about 5 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 100 μg/kg body weight to about 10 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 100 μg/kg body weight to about 20 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose.

[0212] The antibody compositions may be administered as needed to subjects. Determination of the frequency of administration may be made by persons skilled in the art, such as an attending physician based on considerations of the condition being treated, age of the subject being treated, severity of the condition being treated, general state of health of the subject being treated and the like. In some embodiments, an effective dose of an antibody is administered to a subject one or more times. In various embodiments, an effective dose of an antibody is administered to the subject once a month, less than once a month, such as, for example, every two months or every three months. In other embodiments, an effective dose of an antibody is administered more than once a month, such as, for example, every three weeks, every two weeks or every week. In some embodiments, an effective dose of an antibody is administered once per 1, 2, 3, 4, or 5 weeks. In some embodiments, an effective dose of an antibody is administered twice or three times per week. An effective dose of an antibody is administered to the subject at least once. In some embodiments, the effective dose of an antibody may be administered multiple times, including for periods of at least a month, at least six months, or at least a year.

Additional Combination Therapy

[0213] The above therapeutic combinations may be administered alone or with other modes of treatment. They may be provided before, substantially contemporaneous with, or after other modes of treatment, for example, surgery, chemotherapy, radiation therapy, or the administration of a biologic, such as another therapeutic antibody. In some embodiments, the cancer has recurred or progressed following a therapy selected from surgery, chemotherapy, and radiation therapy, or a combination thereof.

[0214] For treatment of cancer, the combinations may be administered in conjunction with one or more additional anti-cancer agents, such as a chemotherapeutic agent, growth inhibitory agent, anti-cancer vaccine such as a gene therapy vaccine, anti-angiogenesis agent and/or anti-neoplastic composition. Nonlimiting examples of chemotherapeutic agent, growth inhibitory agent, anti-cancer vaccine, anti-angiogenesis agent and anti-neoplastic composition that can be used in combination with the antibodies of the present invention are provided herein under “Definitions.”

[0215] In some embodiments, an anti-inflammatory drug may be administered with the combination, such as a steroid or a non-steroidal anti-inflammatory drug (NSAID).

EXAMPLES

[0216] The examples discussed below are intended to be purely exemplary of the invention and should not be considered to limit the invention in any way. The examples are not intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Humanized anti-CSF1R antibodies

[0217] Various humanized anti-CSF1R antibodies were developed previously. *See, e.g.*, PCT Publication No. WO 2011/140249.

[0218] The sequences for each of the humanized heavy chain variable regions and humanized light chain variable regions, aligned with the sequences of the parental chimeric antibody variable regions and the sequences of the human acceptor variable framework regions are shown in Figures 1 (heavy chains) and 2 (light chains). The changes in humanized variable region sequences relative to the human acceptor variable framework region sequences are boxed. Each of the CDRs for each of the variable regions is shown in a boxed region, and labeled as "CDR" above the boxed sequences.

[0219] Table 8, below, shows the full sequences for the humanized heavy chains and humanized light chains of antibodies huAb1 to huAb16. The name and SEQ ID Nos of the humanized heavy chain and humanized light chain of each of those antibodies is shown in Table 3.

Table 3: Humanized heavy chains and light chains of huAb1 to huAb16

Humanized antibody	Humanized HC	SEQ ID NO	Humanized LC	SEQ ID NO
huAb1	h0301-H0	53	h0301-L0	60
huAb2	h0301-H1	54	h0301-L0	60
huAb3	h0301-H2	55	h0301-L0	60
huAb4	h0301-H0	53	h0301-L1	61
huAb5	h0301-H1	54	h0301-L1	61
huAb6	h0301-H2	55	h0301-L1	61
huAb7	h0302-H1	56	h0302-L0	62
huAb8	h0302-H1	56	h0302-L1	63
huAb9	h0302-H1	56	h0302-L2	64

huAb10	h0302-H2	57	h0302-L0	62
huAb11	h0302-H2	57	h0302-L1	63
huAb12	h0302-H2	57	h0302-L2	64
huAb13	h0311-H1	58	h0311-L0	65
huAb14	h0311-H1	58	h0311-L1	66
huAb15	h0311-H2	59	h0311-L0	65
huAb16	h0311-H2	59	h0311-L1	66

[0220] The 16 humanized antibodies were tested for binding to human, cynomolgus monkey, and mouse CSF1R ECD, as described previously. *See, e.g.*, PCT Publication No. WO 2011/140249. The antibodies were found to bind to both human and cynomolgus monkey CSF1R ECD, but not to mouse CSF1R ECD. The humanized antibodies were also found to block binding of CSF1 and IL-34 to both human and cynomolgus CSF1R and to inhibit CSF1-induced and IL-34-induced phosphorylation of human CSF1R expressed in CHO cells. *See, e.g.*, PCT Publication No. WO 2011/140249.

[0221] The k_a, k_d, and K_D for binding to human CSF1R ECD were previously determined and are shown in Table 4. *See, e.g.*, PCT Publication No. WO 2011/140249.

Table 4: Humanized antibody binding affinity for human CSF1R

huAb	**k_a ($M^{-1}s^{-1}$)**	**K_d (s^{-1})**	**K_D (Nm)**
huAb 0301-L0H0	3.22 x 10^6	1.11 x 10^{-03}	0.35
huAb 0301-L0H1	3.56 x 10^6	1.22 x 10^{-03}	0.34
huAb 0301-L0H2	2.32 x 10^6	6.60 x 10^{-04}	0.28
huAb 0301-L1H0	3.29 x 10^6	1.15 x 10^{-03}	0.35
huAb 0301-L1H1	2.87 x 10^6	9.21 x 10^{-04}	0.32
huAb 0301-L1H2	2.95 x 10^6	7.42 x 10^{-04}	0.25
huAb 0302-L0H1	3.54 x 10^6	3.69 x 10^{-03}	1.04
huAb 0302-L1H1	3.47 x 10^6	4.04 x 10^{-03}	1.17
huAb 0302-L2H1	1.60 x 10^6	9.14 x 10^{-04}	0.57
huAb 0302-L0H2	3.40 x 10^6	1.79 x 10^{-03}	0.53
huAb 0302-L1H2	2.71 x 10^6	1.53 x 10^{-03}	0.56
huAb 0302-L2H2	1.84 x 10^6	8.40 x 10^{-04}	0.46
huAb 0311-L0H1	1.22 x 10^6	5.40 x 10^{-04}	0.44
huAb 0311-L1H1	1.32 x 10^6	6.64 x 10^{-04}	0.50
huAb 0311-L0H2	1.34 x 10^6	4.73 x 10^{-04}	0.35
huAb 0311-L1H2	1.51 x 10^6	6.09 x 10^{-04}	0.40

Example 2: Enhancement of Anti-Tumor Activity with Combination Therapy

[0222] 6-8 week old female C57BL/6 mice are housed 5 animals per cage with access to food and water *ad libitum*. Mice are acclimated for at least 3 days after arrival in the vivarium. Mice are weighed and their flanks shaved prior to tumor cell line inoculation.

[0223] Murine colon adenocarcinoma cell ine MC38 is cultured in RPMI + 10 % FBS + 2 mM L-glutamine + antibiotic/antimycotic at 37°C with 5% CO_2. Cells are suspended in a solution of 50%/v of DPBS and 50%/v of Matrigel at a concentration of 5 million cells/ml. 100 µl of cell solution (0.5 million cells) are implanted on the right flank of the each mouse using a 27G1/2 needle. Cells are kept from settling to the bottom of the tube by using an 18G needle and syringe and by slight vortex. Mice are anesthetized using isofluorane to reduce stress and to allow for more precise tumor cell implantation. Length (L) and Width (W) of each tumor is measured using an electronic caliper and the Volume (V) of the tumor will be calculated using $V= (L \times W^2)/2$. Once the mean tumor volume reaches approximately 105 mm^3, mice are grouped and dosed as discussed below.

Groups and dosing

[0224] Mice were separated into the following groups and administered chimeric rat anti-mouse CSF1R antibody (mouse IgG1; referred to as "cmFPA008") and/or anti-CD40 antibody FGK45 (Bio X Cell; *see* Rolink et al., 1996, *Immunity* 5:319-330) according to the dosing schedules described below.

- **Control**: Murine IgG, 30 mg/kg, i.p. 1x/wk, starting on day 0. Rat IgG 100 µg i.p. day 0.
- **huAb1**: anti-CSF1R antibody, 30 mg/kg, i.p. 1x/wk, starting on day 0. Rat IgG 100 µg i.p. day 0.
- **Anti-CD40 (High):** anti-CD40 antibody, 100 µg i.p. on day 0. Murine IgG, 30 mg/kg, i.p. 1x/wk, starting day 0.
- **Combo (High):** anti-CSF1R antibody, 30 mg/kg, i.p. 1x/wk, starting on day 0, Anti-CD40, 100 µg i.p. day 0.
- **Anti-CD40 (Low):** anti-CD40 antibody, 30 µg i.p. on day 0. Murine IgG, 30 mg/kg, i.p. 1x/wk, starting day 0.
- **Combo (Low):** anti-CSF1R antibody, 30 mg/kg, i.p. 1x/wk, starting on day 0, anti-CD40 antibody, 30 µg i.p. day 0.

[0225] The dosing schedule and groupings are shown in Table 5:

Table 5: Study dosing and grouping

Group	Treatment #1: chimeric Ab1	Dosing (mg/kg, schedule)	Treatment #2: Anti-CD40	Dosing (mg/kg, schedule)	Mice (n)
1	Murine IgG	30, 1x week (qw)	Rat IgG	100 µg on Day 0	10
2	anti-CSF1R antibody				10
3	Murine IgG		anti-CD40 antibody	100 µg on Day 0	10
4	anti-CSF1R antibody				10
5	Murine IgG			30 µg on Day 0	10
6	anti-CSF1R antibody				10

[0226] Animals are euthanized prior to the end of the study if any of the following signs are observed:

- Body weight loss of equal or greater than 15% of initial body weight.
- Tumor ulceration is observed.
- Mice appear moribund.
- Individual tumor volume is equal or larger than 10% of initial body weight

[0227] Plasma is collected for pharmacokinetic (PK) analysis. On the final day of the study, whole blood is collected via intra-cardiac bleeds, and plasma is isolated for PK analysis (bioanalytical group). At least five (5) tumors from each group are collected for the following analyses. Single-cell isolates of the tumors are generated by collagenase treatment, and FACS is used to examine the infiltration of immune cells into the tumor(s). Tumor sections are also snap frozen in liquid nitrogen and stored at -80ºC for protein and mRNA extraction. Tumor sections are embedded in Optimum Cutting Temperature compound (OCT) and stored in -80ºC. Tumor sections are also placed in 10% buffered formalin overnight, and then transferred to 70% ethanol the following day.

[0228] The results of this experiment are shown in Figures 3 and 4. As shown in Figure 3, the combination of anti-CSF1R antibody and anti-CD40 antibody (high) resulted in early tumor regression followed by tumor stasis. The combination of anti-CSF1R antibody and anti-CD40 antibody (low) also demonstrated greater efficacy than either treatment alone. Figure 4 shows individual tumor volumes at (A) day 11 and (B) day 13. Table 6 shows the tumor volume statistics at day 11 and day 13 using one-way ANOVA. The combination of

anti-CSF1R antibody and anti-CD40 antibody (high) showed significantly better efficacy than either treatment alone.

Table 6: Tumor volume statistics

	Day 11			Day 13		
Group	**Mean TV±SD**	**%TGI**	**p-value**	**Mean TV±SD**	**%TGI**	**p-value**
IgG/IgG	729.3 ± 183.8	0.00	-	942.4 ± 278.3	0.00	-
anti-CSF1R antibody/IgG vs Combo(Low)	579.2 ± 87.87	20.58	0.0037	710.0 ± 80.05	24.66	0.0004
IgG/anti-CD40 antibody (low) vs Combo(Low)	452.5 ± 111.9	37.95	0.5888 ns	645.2 ± 162.0	31.53	0.0139
IgG/anti-CD40 antibody (High) vs Combo(High)	450.8 ± 105.6	38.18	< 0.0001	650.6 ± 151.5	30.96	< 0.0001
Combo (High) vs anti-CSF1R antibody/IgG	157.4 ± 55.00	78.41	< 0.0001	223.3 ± 98.32	76.31	< 0.0001

[0229] Figure 5 shows body weight for all animals in the study, measured at least twice per week. No significant different in weight was observed for any group relative to control.

TABLE OF SEQUENCES

Table 10 provides certain sequences discussed herein. All polypeptide and antibody sequences are shown without leader sequences, unless otherwise indicated.

Table 10: Sequences and Descriptions

SEQ ID NO	Description	Sequence
1	hCSF1R (full-length, no leader sequence)	IPVIEPSVPE LVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPARPWN VLAQEVVVFE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMSI SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTLNLDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSEQNL IQEVTVGEGL NLKVMVEAYP GLQGFNWTYL GPFSDHQPEP KLANATTKDT YRHTFTLSLP RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ SLLTVETLEH NQTYECRAHN SVGSGSWAFI PISAGAHTHP PDEFLFTPVV VACMSIMALL LLLLLLLLYK YKQKPKYQVR WKIIESYEGN SYTFIDPTQL PYNEKWEFPR NNLQFGKTLG AGAFGKVVEA TAFGLGKEDA VLKVAVKMLK STAHADEKEA LMSELKIMSH LGQHENIVNL LGACTHGGPV LVITEYCCYG DLLNFLRRKA EAMLGPSLSP GQDPEGGVDY KNIHLEKKYV RRDSGFSSQG VDTYVEMRPV STSSNDSFSE QDLDKEDGRP LELRDLLHFS SQVAQGMAFL ASKNCIHRDV AARNVLLTNG HVAKIGDFGL ARDIMNDSNY IVKGNARLPV KWMAPESIFD CVYTVQSDVW SYGILLWEIF SLGLNPYPGI LVNSKFYKLV KDGYQMAQPA FAPKNIYSIM QACWALEPTH RPTFQQICSF LQEQAQEDRR ERDYTNLPSS SRSGGSGSSS SELEEESSSE HLTCCEQGDI AQPLLQPNNY QFC
2	hCSF1R (full-length, + leader sequence)	MGPGVLLLLL VATAWHGQGI PVIEPSVPEL VVKPGATVTL RCVGNGSVEW DGPPSPHWTL YSDGSSSILS TNNATFQNTG TYRCTEPGDP LGGSAAIHLY VKDPARPWNV LAQEVVVFED QDALLPCLLT DPVLEAGVSL VRVRGRPLMR HTNYSFSPWH GFTIHRAKFI QSQDYQCSAL MGGRKVMSIS IRLKVQKVIP GPPALTLVPA ELVRIRGEAA QIVCSASSVD VNFDVFLQHN NTKLAIPQQS DFHNNRYQKV LTLNLDQVDF QHAGNYSCVA SNVQGKHSTS MFFRVVESAY LNLSSEQNLI QEVTVGEGLN LKVMVEAYPG LQGFNWTYLG PFSDHQPEPK LANATTKDTY RHTFTLSLPR LKPSEAGRYS FLARNPGGWR ALTFELTLRY PPEVSVIWTF INGSGTLLCA ASGYPQPNVT WLQCSGHTDR CDEAQVLQVW DDPYPEVLSQ EPFHKVTVQS LLTVETLEHN QTYECRAHNS VGSGSWAFIP ISAGAHTHPP DEFLFTPVVV ACMSIMALLL LLLLLLLYKY KQKPKYQVRW KIIESYEGNS YTFIDPTQLP YNEKWEFPRN NLQFGKTLGA GAFGKVVEAT AFGLGKEDAV LKVAVKMLKS TAHADEKEAL MSELKIMSHL GQHENIVNLL GACTHGGPVL VITEYCCYGD LLNFLRRKAE AMLGPSLSPG QDPEGGVDYK NIHLEKKYVR RDSGFSSQGV DTYVEMRPVS TSSNDSFSEQ DLDKEDGRPL ELRDLLHFSS QVAQGMAFLA SKNCIHRDVA ARNVLLTNGH VAKIGDFGLA RDIMNDSNYI VKGNARLPVK WMAPESIFDC VYTVQSDVWS YGILLWEIFS LGLNPYPGIL VNSKFYKLVK DGYQMAQPAF APKNIYSIMQ ACWALEPTHR PTFQQICSFL QEQAQEDRRE RDYTNLPSSS RSGGSGSSSS ELEEESSSEH LTCCEQGDIA QPLLQPNNYQ FC
5	hCSF1R ECD.506	IPVIEPSVPE LVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPARPWN VLAQEVVVFE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMSI SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTLNLDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSEQNL IQEVTVGEGL NLKVMVEAYP GLQGFNWTYL GPFSDHQPEP KLANATTKDT YRHTFTLSLP RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ

		SLLTVETLEH NQTYECRAHN SVGSGSWAFI PISAGAH
6	hCSF1R ECD.506-Fc	IPVIEPSVPE LVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPARPWN VLAQEVVVFE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMSI SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTLNLDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSEQNL IQEVTVGEGL NLKVMVEAYP GLQGFNWTYL GPFSDHQPEP KLANATTKDT YRHTFTLSLP RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ SLLTVETLEH NQTYECRAHN SVGSGSWAFI PISAGAHEPK SSDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK
7	cynoCSF1R ECD (with leader sequence)	MGPGVLLLLL VVTAWHGQGI PVIEPSGPEL VVKPGETVTL RCVGNGSVEW DGPISPHWTL YSDGPSSVLT TTNATFQNTR TYRCTEPGDP LGGSAAIHLY VKDPARPWNV LAKEVVVFED QDALLPCLLT DPVLEAGVSL VRLRGRPLLR HTNYSFSPWH GFTIHRAKFI QGQDYQCSAL MGSRKVMSIS IRLKVQKVIP GPPALTLVPA ELVRIRGEAA QIVCSASNID VDFDVFLQHN TTKLAIPQRS DFHDNRYQKV LTLSLGQVDF QHAGNYSCVA SNVQGKHSTS MFFRVVESAY LDLSSEQNLI QEVTVGEGLN LKVMVEAYPG LQGFNWTYLG PFSDHQPEPK LANATTKDTY RHTFTLSLPR LKPSEAGRYS FLARNPGGWR ALTFELTLRY PPEVSVIWTS INGSGTLLCA ASGYPQPNVT WLQCAGHTDR CDEAQVLQVW VDPHPEVLSQ EPFQKVTVQS LLTAETLEHN QTYECRAHNS VGSGSWAFIP ISAGAR
8	cynoCSF1R ECD-Fc (with leader sequence)	MGPGVLLLLL VVTAWHGQGI PVIEPSGPEL VVKPGETVTL RCVGNGSVEW DGPISPHWTL YSDGPSSVLT TTNATFQNTR TYRCTEPGDP LGGSAAIHLY VKDPARPWNV LAKEVVVFED QDALLPCLLT DPVLEAGVSL VRLRGRPLLR HTNYSFSPWH GFTIHRAKFI QGQDYQCSAL MGSRKVMSIS IRLKVQKVIP GPPALTLVPA ELVRIRGEAA QIVCSASNID VDFDVFLQHN TTKLAIPQRS DFHDNRYQKV LTLSLGQVDF QHAGNYSCVA SNVQGKHSTS MFFRVVESAY LDLSSEQNLI QEVTVGEGLN LKVMVEAYPG LQGFNWTYLG PFSDHQPEPK LANATTKDTY RHTFTLSLPR LKPSEAGRYS FLARNPGGWR ALTFELTLRY PPEVSVIWTS INGSGTLLCA ASGYPQPNVT WLQCAGHTDR CDEAQVLQVW VDPHPEVLSQ EPFQKVTVQS LLTAETLEHN QTYECRAHNS VGSGSWAFIP ISAGARGSEP KSSDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
3	Light chain leader sequence	METDTLLLWV LLLWVPGSTG
4	Heavy chain leader sequence	MAVLGLLLCL VTFPSCVLS
9	Fab 0301 heavy chain variable region	EVQLQQSGPE LVRPGASVKM SCKASGYTFT DNYMIWVKQS HGKSLEWIGD INPYNGGTTF NQKFKGKATL TVEKSSSTAY MQLNSLTSED SAVYYCARES PYFSNLYVMD YWGQGTSVTV SS
10	Fab 0301 light chain variable region	NIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDNYMNWY QQKPGQPPKL LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCHLSNEDLS TFGGGTKLEI K

11	Fab 0302 heavy chain variable region	EIQLQQSGPE LVKPGASVKM SCKASGYTFS DFNIHWVKQK PGQGLEWIGY INPYTDVTVY NEKFKGKATL TSDRSSSTAY MDLSSLTSED SAVYYCASYF DGTFDYALDY WGQGTSITVS S
12	Fab 0302 light chain variable region	DVVVTQTPAS LAVSLGQRAT ISCRASESVD NYGLSFMNWF QQKPGQPPKL LIYTASNLES GIPARFSGGG SRTDFTLTID PVEADDAATY FCQQSKELPW TFGGGTRLEI K
13	Fab 0311 heavy chain variable region	EIQLQQSGPD LMKPGASVKM SCKASGYIFT DYNMHWVKQN QGKSLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSSSTAY MDLHSLTSED SAVYYCTRAL YHSNFGWYFD SWGKGTTLTV SS
14	Fab 0311 light chain variable region	DIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDSHMNWY QQKPGQPPKL LIYTASNLES GIPARFSGSG SGADFTLTIH PVEEEDAATY YCQQGNEDPW TFGGGTRLEI K
15	0301 heavy chain CDR1	GYTFTDNYMI
16	0301 heavy chain CDR2	DINPYNGGTT FNQKFKG
17	0301 heavy chain CDR3	ESPYFSNLYV MDY
18	0301 light chain CDR1	KASQSVDYDG DNYMN
19	0301 light chain CDR2	AASNLES
20	0301 light chain CDR3	HLSNEDLST
21	0302 heavy chain CDR1	GYTFSDFNIH
22	0302 heavy chain CDR2	YINPYTDVTV YNEKFKG
23	0302 heavy chain CDR3	YFDGTFDYAL DY
24	0302 light chain CDR1	RASESVDNYG LSFMN
25	0302 light chain CDR2	TASNLES
26	0302 light chain CDR3	QQSKELPWT
27	0311 heavy chain CDR1	GYIFTDYNMH
28	0311 heavy chain CDR2	EINPNNGVVV YNQKFKG
29	0311 heavy chain CDR3	ALYHSNFGWY FDS
30	0311 light chain CDR1	KASQSVDYDG DSHMN
31	0311 light chain CDR2	TASNLES

32	0311 light chain CDR3	QQGNEDPWT
33	cAb 0301 heavy chain	EVQLQQSGPE LVRPGASVKM SCKASGYTFT DNYMIWVKQS HGKSLEWIGD INPYNGGTTF NQKFKGKATL TVEKSSSTAY MQLNSLTSED SAVYYCARES PYFSNLYVMD YWGQGTSVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
34	cAb 0301 light chain	NIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDNYMNWY QQKPGQPPKL LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCHLSNEDLS TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
35	cAb 0302 heavy chain	EIQLQQSGPE LVKPGASVKM SCKASGYTFS DFNIHWVKQK PGQGLEWIGY INPYTDVTVY NEKFKGKATL TSDRSSSTAY MDLSSLTSED SAVYYCASYF DGTFDYALDY WGQGTSITVS 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
36	cAb 0302 light chain	DVVVTQTPAS LAVSLGQRAT ISCRASESVD NYGLSFMNWF QQKPGQPPKL LIYTASNLES GIPARFSGGG SRTDFTLTID PVEADDAATY FCQQSKELPW TFGGGTRLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
37	cAb 0311 heavy chain	EIQLQQSGPD LMKPGASVKM SCKASGYIFT DYNMHWVKQN QGKSLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSSSTAY MDLHSLTSED SAVYYCTRAL YHSNFGWYFD SWGKGTTLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
38	cAb 0311 light chain	DIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDSHMNWY QQKPGQPPKL LIYTASNLES GIPARFSGSG SGADFTLTIH PVEEEDAATY YCQQGNEDPW TFGGGTRLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
39	h0301-H0 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SS
40	h0301-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SS
41	h0301-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWIGD INPYNGGTTF NQKFKGRATL TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SS

42	H0302-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWMGY INPYTDVTVY NEKFKGRVTI TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLVTVS S
43	H0302-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWIGY INPYTDVTVY NEKFKGRATL TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLVTVS S
44	H0311-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLVTV SS
45	H0311-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLVTV SS
46	h0301-L0 light chain variable region	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI K
47	h0301-L1 light chain variable region	NIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI K
48	H0302-L0 light chain variable region	EIVLTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI K
49	H0302-L1 light chain variable region	EIVLTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SRTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI K
50	H0302-L2 light chain variable region	EIVVTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWF QQKPGQAPRL LIYTASNLES GIPARFSGSG SRTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI K
51	H0311-L0 light chain variable region	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDSHMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI K
52	H0311-L1 light chain variable region	DIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDSHMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGADFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI K
53	h0301-H0 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK

54	h0301-H1 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
55	h0301-H2 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWIGD INPYNGGTTF NQKFKGRATL TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
56	H0302-H1 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWMGY INPYTDVTVY NEKFKGRVTI TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLVTVS 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
57	H0302-H2 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWIGY INPYTDVTVY NEKFKGRATL TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLVTVS 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
58	H0311-H1 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
59	H0311-H2 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
60	h0301-L0 light chain	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV

		THQGLSSPVT KSFNRGEC
61	h0301-L1 light chain	NIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
62	H0302-L0 light chain	EIVLTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
63	H0302-L1 light chain	EIVLTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SRTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
64	H0302-L2 light chain	EIVVTQSPAT LSLSPGERAT LSCRASESVD NYGLSFMNWF QQKPGQAPRL LIYTASNLES GIPARFSGSG SRTDFTLTIS SLEPEDFAVY YCQQSKELPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
65	H0311-L0 light chain	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDSHMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
66	H0311-L1 light chain	DIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDSHMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGADFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
67	Human CSF1	EEVSEYCSHM IGSGHLQSLQ RLIDSQMETS CQITFEFVDQ EQLKDPVCYL KKAFLLVQDI MEDTMRFRDN TPNAIAIVQL QELSLRLKSC FTKDYEEHDK ACVRTFYETP LQLLEKVKNV FNETKNLLDK DWNIFSKNCN NSFAECSSQG HERQSEGS
68	Human IL-34	NEPLEMWPLT QNEECTVTGF LRDKLQYRSR LQYMKHYFPI NYKISVPYEG VFRIANVTRL QRAQVSEREL RYLWVLVSLSATESVQDVLL EGHPSWKYLQ EVQTLLLNVQ QGLTDVEVSP KVESVLSLLN APGPNLKLVR PKALLDNCFR VMELLYCSCC KQSSVLNWQD CEVPSPQSCS PEPSLQYAAT QLYPPPPWSP SSPPHSTGSV RPVRAQGEGL LP
69	Human acceptor A FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
70	Human acceptor A FR2	WVRQAPGQGL EWMG
71	Human acceptor A FR3	RVTITADKST STAYMELSSL RSEDTAVYYC AR
72	Human acceptor A FR4	WGQGTLVTVS S
73	Human acceptor B	QVQLVQSGAE VKKPGSSVKV SCKAS

	FR1	
74	Human acceptor B FR2	WVRQAPGQGL EWMG
75	Human acceptor B FR3	RVTITADKST STAYMELSSL RSEDTAVYYC AR
76	Human acceptor B FR4	WGQGTLVTVSS
77	Human acceptor C FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
78	Human acceptor C FR2	WVRQAPGQGL EWMG
79	Human acceptor C FR3	RVTITADKST STAYMELSSL RSEDTAVYYC AR
80	Human acceptor C FR4	WGQGTLVTVS S
81	Human acceptor D FR1	EIVLTQSPAT LSLSPGERAT LSC
82	Human acceptor D FR2	WYQQKPGQAP RLLIY
83	Human acceptor D FR3	GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YC
84	Human acceptor D FR4	FGGGTKVEIK
85	Human acceptor E FR1	EIVLTQSPAT LSLSPGERAT LSC
86	Human acceptor E FR2	WYQQKPGQAP RLLIY
87	Human acceptor E FR3	GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YC
88	Human acceptor E FR4	FGQGTKVEIK
89	Human acceptor F FR1	EIVLTQSPAT LSLSPGERAT LSC
90	Human acceptor F	WYQQKPGQAP RLLIY

	FR2	
91	Human acceptor F FR3	GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YC
92	Human acceptor F FR4	FGQGTKVEIK
93	mCSF1R ECD-Fc	APVIEPSGPE LVVEPGETVT LRCVSNGSVE WDGPISPYWT LDPESPGSTL TTRNATFKNT GTYRCTELED PMAGSTTIHL YVKDPAHSWN LLAQEVTVVE GQEAVLPCLI TDPALKDSVS LMREGGRQVL RKTVYFFSPW RGFIIRKAKV LDSNTYVCKT MVNGRESTST GIWLKVNRVH PEPPQIKLEP SKLVRIRGEA AQIVCSATNA EVGFNVILKR GDTKLEIPLN SDFQDNYYKK VRALSLNAVD FQDAGIYSCV ASNDVGTRTA TMNFQVVESA YLNLTSEQSL LQEVSVGDSL ILTVHADAYP SIQHYNWTYL GPFFEDQRKL EFITQRAIYR YTFKLFLNRV KASEAGQYFL MAQNKAGWNN LTFELTLRYP PEVSVTWMPV NGSDVLFCDV SGYPQPSVTW MECRGHTDRC DEAQALQVWN DTHPEVLSQK PFDKVIIQSQ LPIGTLKHNM TYFCKTHNSV GNSSQYFRAV SLGQSKQEPK SSDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK
94	Human IgG4 S241P	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
95	Human Igκ	RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
96	human CD40 precursor (with signal sequence) UniProtKB/Swiss-Prot: P25942.1, 04-MAR-2015	MVRLPLQCVL WGCLLTAVHP EPPTACREKQ YLINSQCCSL CQPGQKLVSD CTEFTETECL PCGESEFLDT WNRETHCHQH KYCDPNLGLR VQQKGTSETD TICTCEEGWH CTSEACESCV LHRSCSPGFG VKQIATGVSD TICEPCPVGF FSNVSSAFEK CHPWTSCETK DLVVQQAGTN KTDVVCGPQD RLRALVVIPI IFGILFAILL VLVFIKKVAK KPTNKAPHPK QEPQEINFPD DLPGSNTAAP VQETLHGCQP VTQEDGKESR ISVQERQ
97	human CD40 (mature, without signal sequence)	EPPTACREKQ YLINSQCCSL CQPGQKLVSD CTEFTETECL PCGESEFLDT WNRETHCHQH KYCDPNLGLR VQQKGTSETD TICTCEEGWH CTSEACESCV LHRSCSPGFG VKQIATGVSD TICEPCPVGF FSNVSSAFEK CHPWTSCETK DLVVQQAGTN KTDVVCGPQD RLRALVVIPI IFGILFAILL VLVFIKKVAK KPTNKAPHPK QEPQEINFPD DLPGSNTAAP VQETLHGCQP VTQEDGKESR ISVQERQ
98	Dacetuzumab heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGYSFT GYYIHWVRQA PGKGLEWVAR VIPNAGGTSY NQKFKGRFTL SVDNSKNTAY LQMNSLRAED TAVYYCAREG IYWWGQGTLV 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
99	Dcetuzumab	DIQMTQSPSS LSASVGDRVT ITCRSSQSLV HSNGNTFLHW YQQKPGKAPK LLIYTVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YFCSQTTHVP

	light chain	WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC

CLAIMS

The claims defining the invention are as follows:

1. A method of treating cancer in a subject comprising administering to the subject an anti-CSF1R antibody and at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

2. Use of an anti-CSF1R antibody in the manufacture of a medicament for treating cancer in a subject administered at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

3. Use of at least one immune stimulating agent in the manufacture of a medicament for treating cancer in a subject administered an anti-CSF1R antibody, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

4. A composition comprising an anti-CSF1R antibody and at least one immune stimulating agent, wherein the anti-CSF1R antibody binds human CSF1R and is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60;

and wherein the at least one immune stimulating agent comprises an agonist anti-CD40 antibody.

5. The method of claim 1, use of claim 2 or 3, or composition of claim 4, wherein the at least one immune stimulating agent further comprises at least one additional immune stimulating agent chosen from agents falling within one or more of the following categories:

a. an agonist of an immune stimulatory molecule, including a co-stimulatory molecule, such as an immune-stimulatory molecule found on a T cell or NK cell;

b. an antagonist of an immune inhibitory molecule, including a co-inhibitory molecule, such as an immune-stimulatory molecule found on a T cell or NK cell;

c. an antagonist of LAG-3, Galectin 1, Galectin 9, CEACAM-1, BTLA, CD25, CD69, TIGIT, CD113, GPR56, VISTA, B7-H3, B7-H4, 2B4, CD48, GARP, PD1H, LAIR1, TIM1, TIM3, TIM4, ILT4, IL-6, IL-10, TGFβ, VEGF, KIR, LAG-3, adenosine A2A receptor,

PI3Kdelta, or IDO;

d. an agonist of B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD27, CD40, CD40L, DR3, CD28H, IL-2, IL-7, IL-12, IL-15, IL-21, IFNα, STING, or a Toll-like receptor agonist such as a TLR2/4 agonist;

e. an agent that binds to a member of the B7 family of membrane-bound proteins such as B7-1, B7-2, B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6;

f. an agent that binds to a member of the TNF receptor family or a co-stimulatory or co-inhibitory molecule binding to a member of the TNF receptor family such as CD40, CD40L, OX40, OX40L, GITR, GITRL, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, EDA1, EDA2, TACI, APRIL, BCMA, LTβR, LIGHT, DeR3, HVEM, VEGL/TL1A, TRAMP/DR3, TNFR1, TNFβ, TNFR2, TNFα, 1β2, FAS, FASL, RELT, DR6, TROY, or NGFβ;

g. an agent that antagonizes or inhibits a cytokine that inhibits T cell activation such as IL-6, IL-10, TGFβ, VEGF;

h. an agonist of a cytokine that stimulates T cell activation such as IL-2, IL-7, IL-12, IL-15, IL-21, and IFNα; and

i. an antagonist of a chemokine, such as CXCR2, CXCR4, CCR2, or CCR4.

6. The method, use, or composition of any one of claims 1-5, wherein the agonist anti-CD40 antibody comprises the CDRs of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4.

7. The method, use, or composition of claim 6, wherein the agonist anti-CD40 antibody comprises the heavy chain and light chain variable regions of an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4.

8. The method, use, or composition of claim 7, wherein the agonist anti-CD40 antibody is an antibody selected from CP-870,893; dacetuzumab; SEA-CD40; ADC-1013; RO7009789; and Chi Lob 7/4.

9. The method or use of any one of claims 1-3 or 5-8, wherein the anti-CSF1R antibody and the agonist anti-CD40 antibody are administered concurrently or sequentially.

10. The method or use of any one claims 1-3 or 5-9, wherein the anti-CSF1R antibody and the agonist anti-CD40 antibody are administered concurrently.

11. The method or use of claim 9, wherein one or more doses of the agonist anti-CD40 antibody are administered prior to administering an anti-CSF1R antibody.

12. The method or use of claim 9, wherein one or more doses of the anti-CSF1R antibody are

administered prior to administering the agonist anti-CD40 antibody.

13. The method or use of any one of claims 1-3 or 5-12, wherein the cancer is selected from non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, endometrial cancer, Hodgkin's lymphoma, lung cancer, glioma, glioblastoma multiforme, colon cancer, breast cancer, bone cancer, skin cancer, uterine cancer, gastric cancer, stomach cancer, lymphoma, lymphocytic leukemia, multiple myeloma, prostate cancer, mesothelioma, and kidney cancer.

14. The method or use of any one of claims 1-3 or 5-13, wherein the cancer is recurrent or progressive after a therapy selected from surgery, chemotherapy, radiation therapy, or a combination thereof.

15. The method, use or composition of any one of claims 1-14, wherein the anti-CSF1R antibody blocks binding of CSF1 and/or IL-34 to CSF1R.

16. The method, use, or composition of any one of 1-15, wherein the anti-CSF1R antibody inhibits ligand-induced CSF1R phosphorylation *in vitro*.

17. The method, use, or composition of any one of claims 1-16, wherein the antibody is a humanized antibody.

18. The method, use, or composition of any one of claims 1-17, wherein the antibody is selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$.

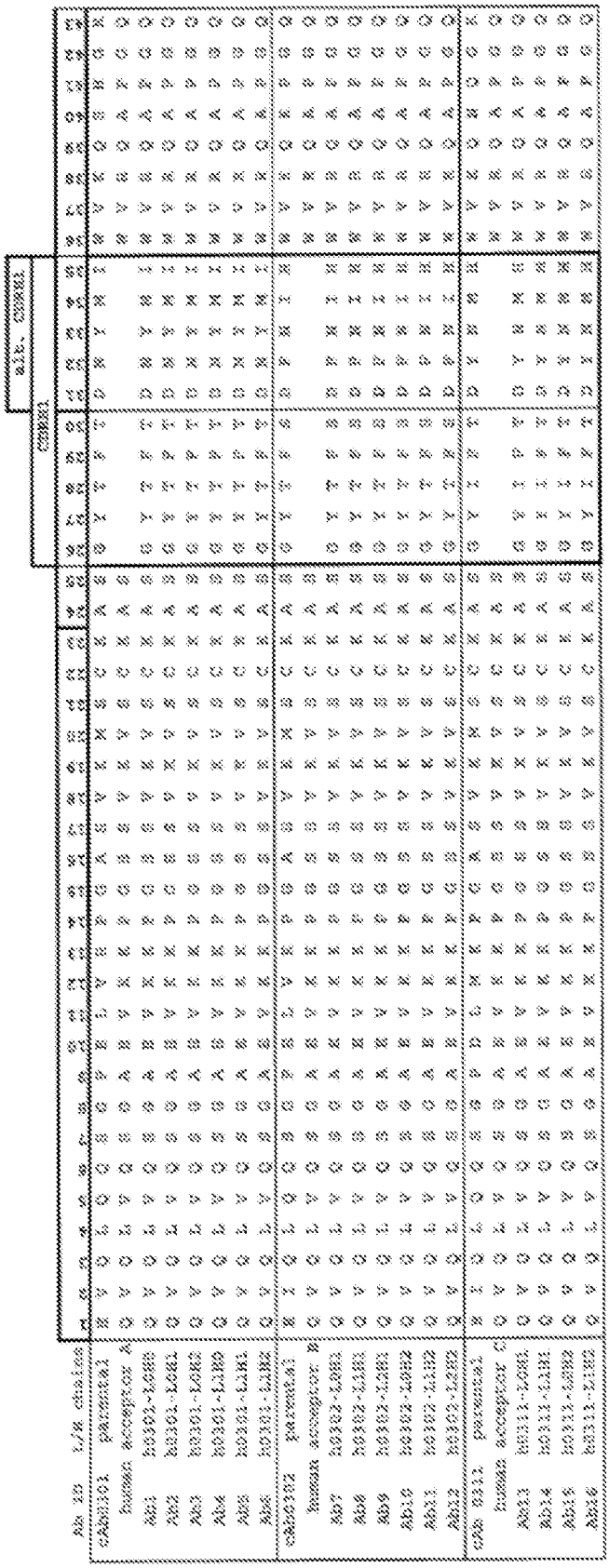

FIG. 1A

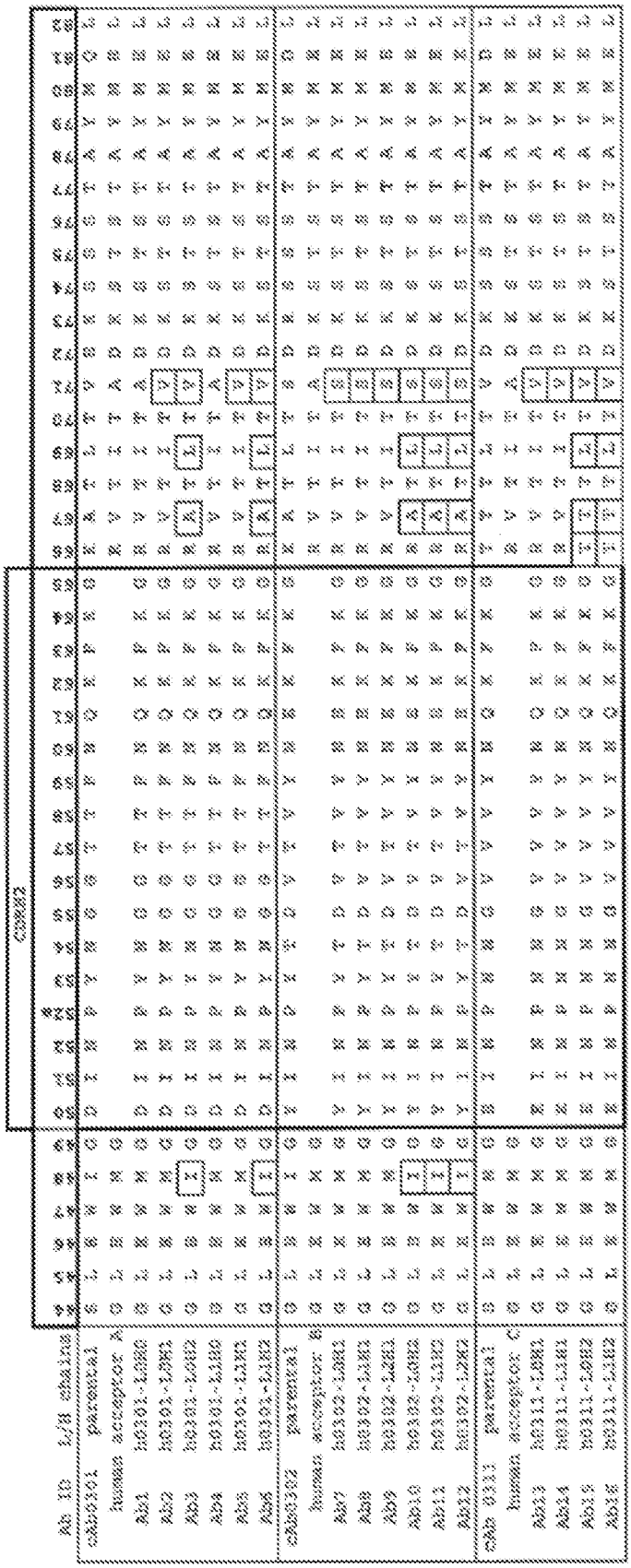

FIG. 1B

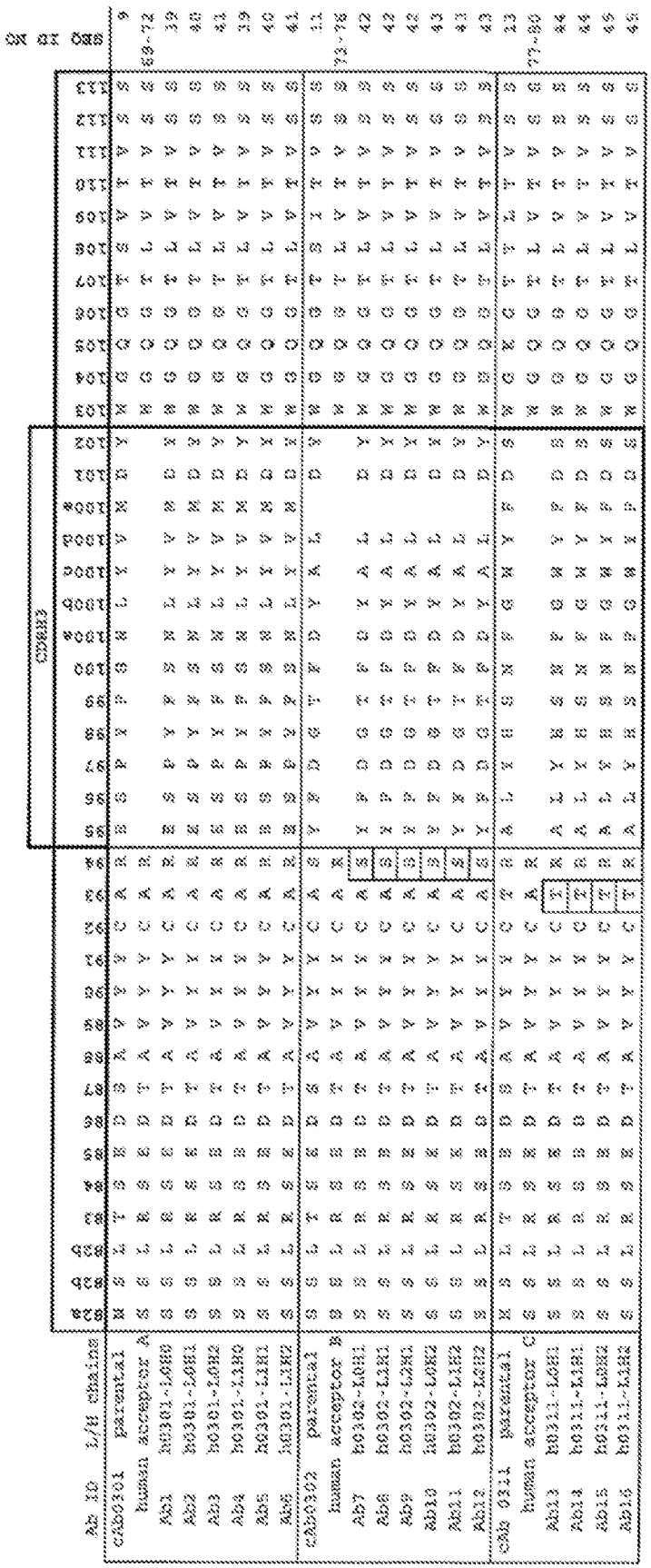

FIG. 1C

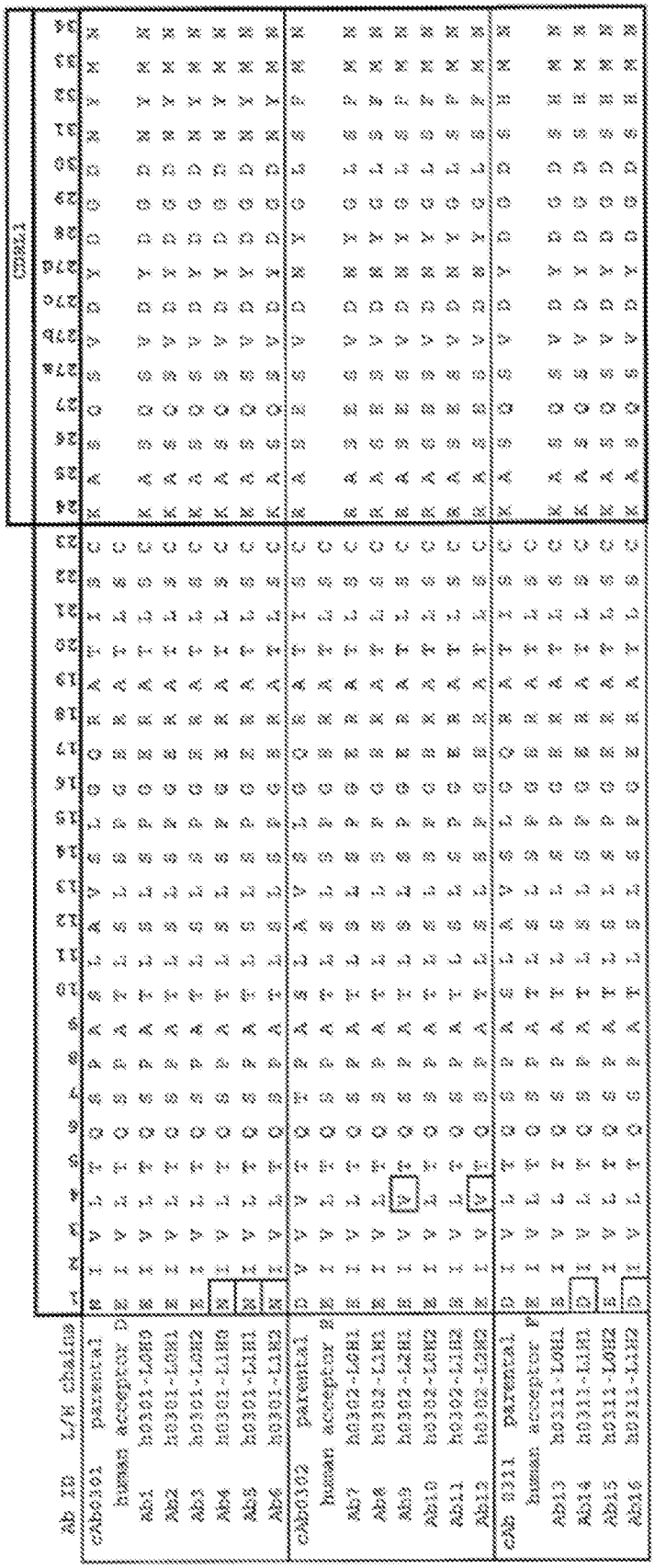

FIG. 2A

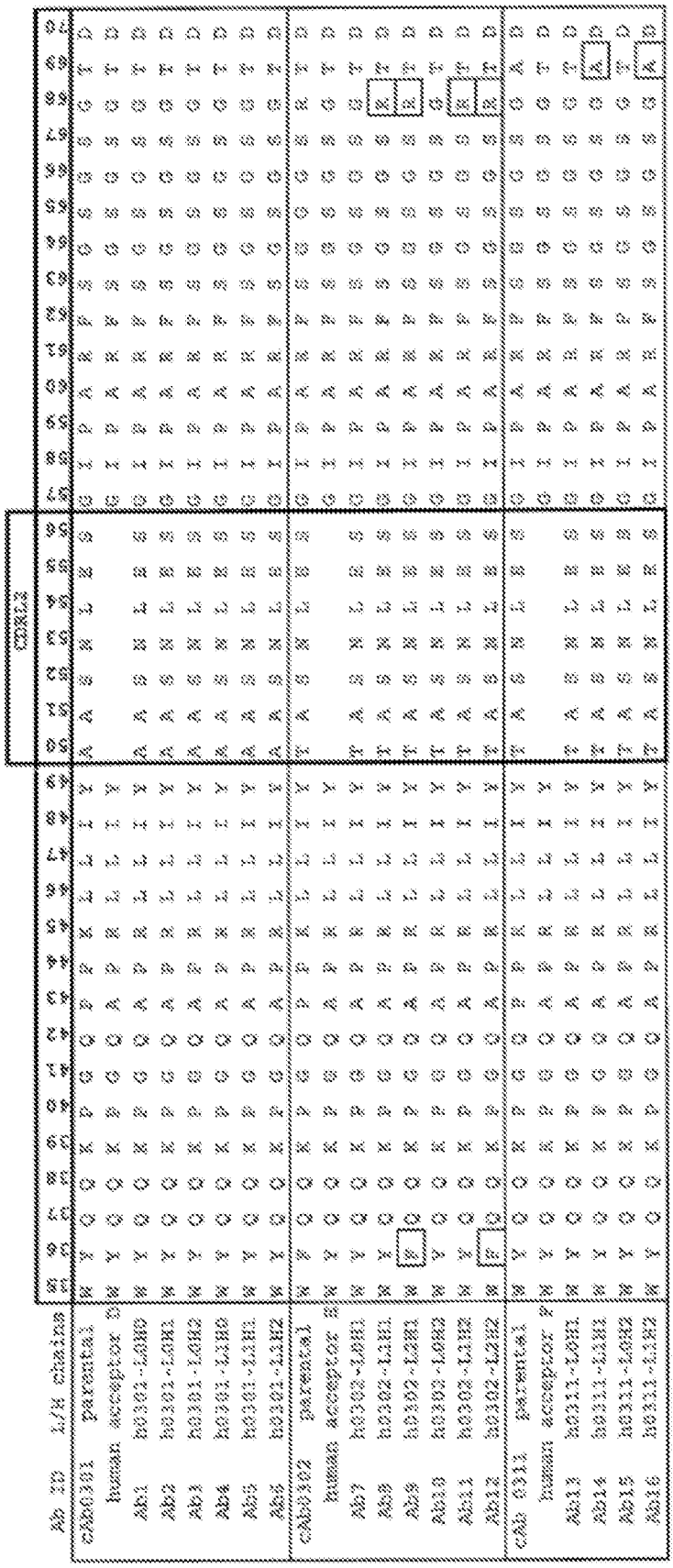

FIG. 2B

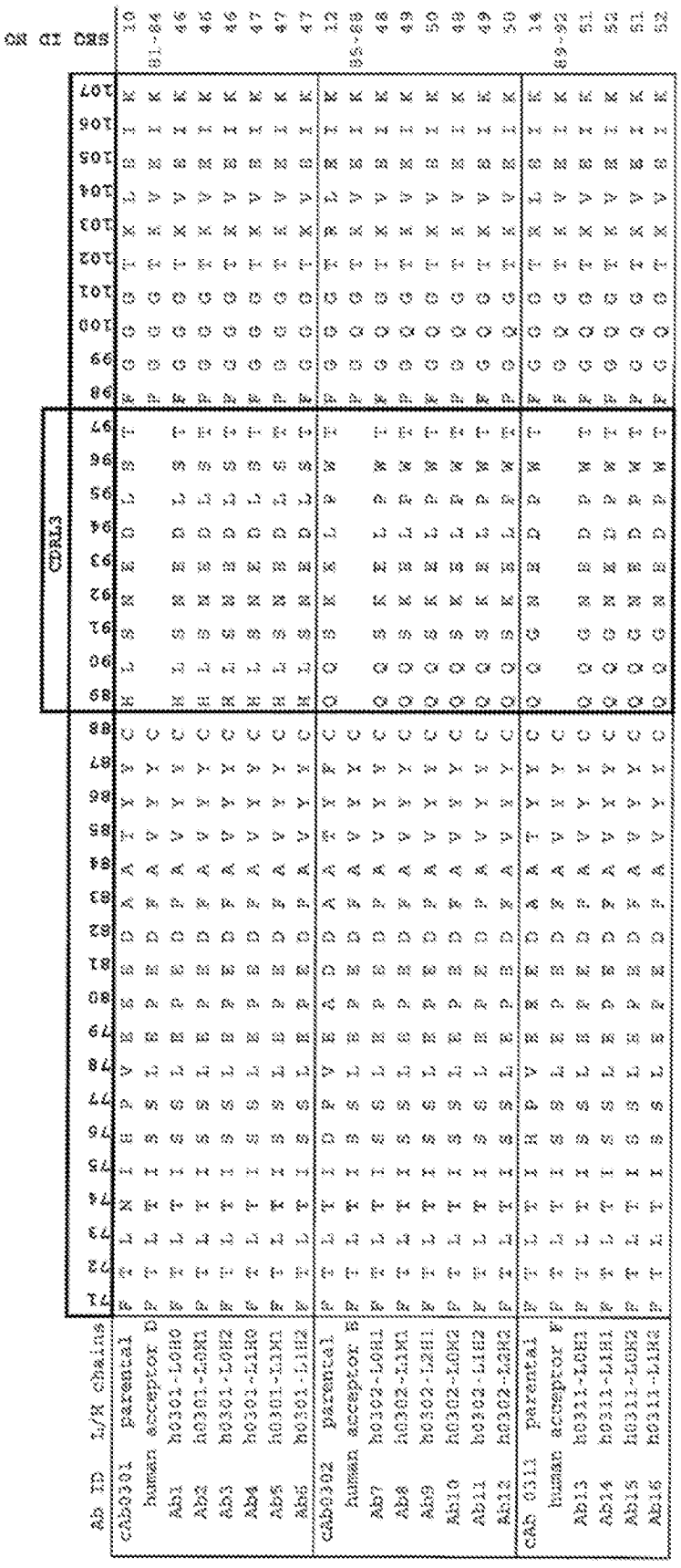

FIG. 2C

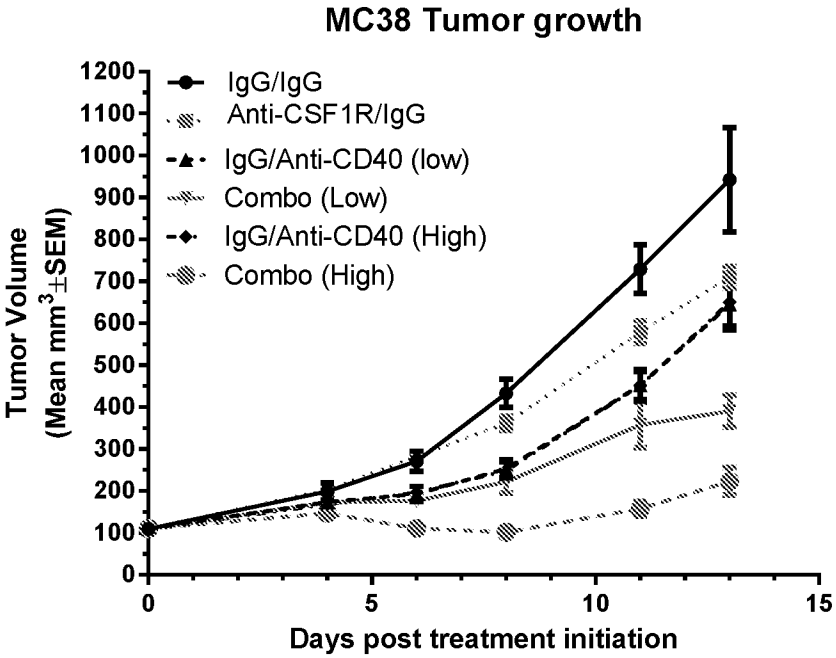
MC38 Tumor growth
IgG/IgG
Anti-CSF1R/IgG
IgG/Anti-CD40 (low)
Combo (Low)
IgG/Anti-CD40 (High)
Combo (High)
Tumor Volume
(Mean mm3±SEM)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
5
10
15
Days post treatment initiation

FIG. 3

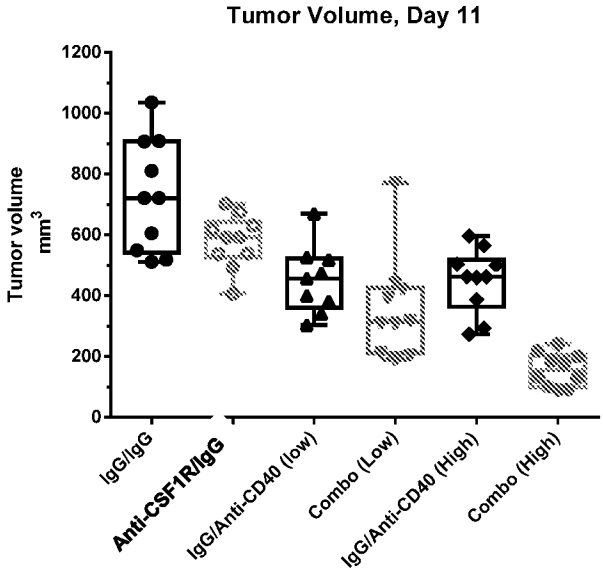
Tumor Volume, Day 11
Tumor volume
mm3
1200
1000
800
600
400
200
0
IgG/IgG
Anti-CSF1R/IgG
IgG/Anti-CD40 (low)
Combo (Low)
IgG/Anti-CD40 (High)
Combo (High)

FIG. 4A

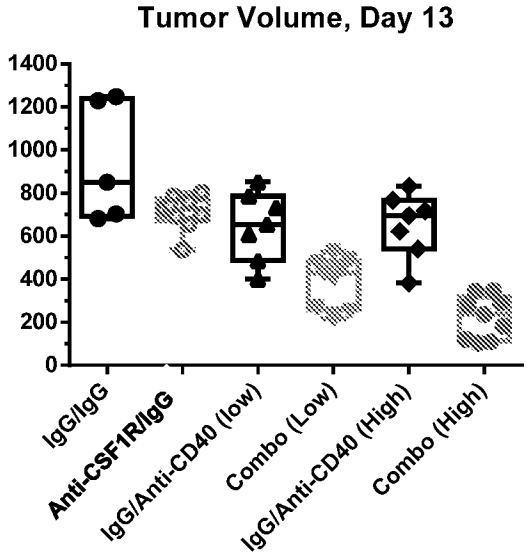
Tumor Volume, Day 13
1400
1200
1000
800
600
400
200
0
IgG/IgG
Anti-CSF1R/IgG
IgG/Anti-CD40 (low)
Combo (Low)
IgG/Anti-CD40 (High)
Combo (High)

FIG. 4B

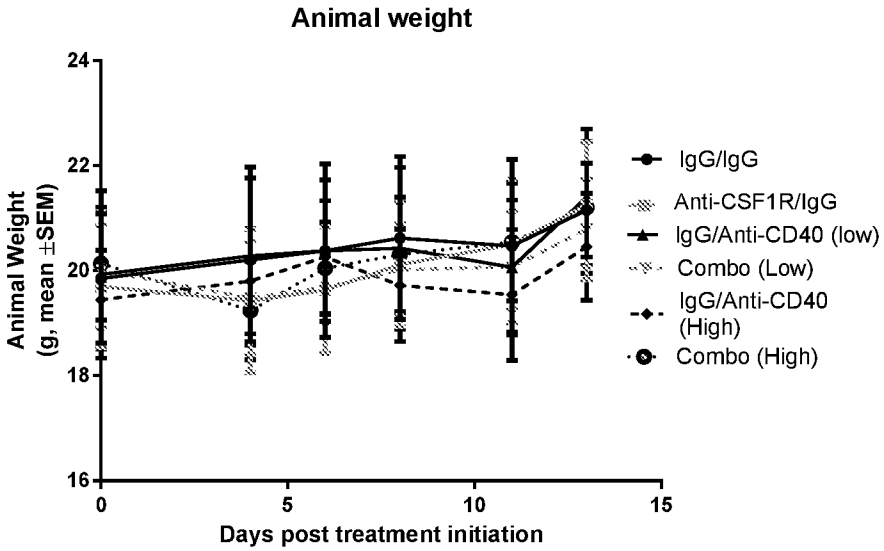
Animal weight
Animal Weight (g, mean ±SEM)
24
22
20
18
16
0
5
10
15
Days post treatment initiation
IgG/IgG
Anti-CSF1R/IgG
IgG/Anti-CD40 (low)
Combo (Low)
IgG/Anti-CD40 (High)
Combo (High)

FIG. 5

SEQUENCE LISTING

<110> FIVE PRIME THERAPEUTICS, INC.
MASTELLER, Emma
BRENNAN, Thomas
BELLOVIN, David
BAKER, Kevin
WONG, Brian

<120> COMBINATION THERAPY FOR CANCER

<130> 01134-0044-00PCT

<150> US 62/146,766
<151> 2015-04-13

<150> US 62/190,945
<151> 2015-07-10

<160> 99

<170> PatentIn version 3.5

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<213> Homo sapiens

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<223> hCSF1R (full-length, no leader sequence)

<400> 1

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Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val Lys Pro Gly
1               5                  10                  15

Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val Glu Trp Asp
            20                  25                  30

Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly Ser Ser Ser
        35                  40                  45

Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly Thr Tyr Arg
    50                  55                  60

Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala Ile His Leu
65                  70                  75                  80

Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala Gln Glu Val
                85                  90                  95

Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu Leu Thr Asp
            100                 105                 110
```

```
Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg Gly Arg Pro
        115                 120                 125

Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His Gly Phe Thr
    130                 135                 140

Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln Cys Ser Ala
145                 150                 155                 160

Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg Leu Lys Val
                165                 170                 175

Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val Pro Ala Glu
            180                 185                 190

Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Ser
        195                 200                 205

Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn Asn Thr Lys
    210                 215                 220

Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg Tyr Gln Lys
225                 230                 235                 240

Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His Ala Gly Asn
                245                 250                 255

Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser Thr Ser Met
            260                 265                 270

Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln
        275                 280                 285

Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn Leu Lys Val
    290                 295                 300

Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp Thr Tyr Leu
305                 310                 315                 320

Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala Asn Ala Thr
                325                 330                 335

Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu Pro Arg Leu
            340                 345                 350

Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg Asn Pro Gly
        355                 360                 365
```

```
Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu
    370                 375                 380

Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr Leu Leu Cys
385                 390                 395                 400

Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu Gln Cys Ser
                405                 410                 415

Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln Val Trp Asp
            420                 425                 430

Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr
        435                 440                 445

Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn Gln Thr Tyr
    450                 455                 460

Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp Ala Phe Ile
465                 470                 475                 480

Pro Ile Ser Ala Gly Ala His Thr His Pro Pro Asp Glu Phe Leu Phe
                485                 490                 495

Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu Leu Leu Leu
            500                 505                 510

Leu Leu Leu Leu Leu Leu Tyr Lys Tyr Lys Gln Lys Pro Lys Tyr Gln
        515                 520                 525

Val Arg Trp Lys Ile Ile Glu Ser Tyr Glu Gly Asn Ser Tyr Thr Phe
    530                 535                 540

Ile Asp Pro Thr Gln Leu Pro Tyr Asn Glu Lys Trp Glu Phe Pro Arg
545                 550                 555                 560

Asn Asn Leu Gln Phe Gly Lys Thr Leu Gly Ala Gly Ala Phe Gly Lys
                565                 570                 575

Val Val Glu Ala Thr Ala Phe Gly Leu Gly Lys Glu Asp Ala Val Leu
            580                 585                 590

Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala His Ala Asp Glu Lys
        595                 600                 605

Glu Ala Leu Met Ser Glu Leu Lys Ile Met Ser His Leu Gly Gln His
```

610 615 620

Glu Asn Ile Val Asn Leu Leu Gly Ala Cys Thr His Gly Gly Pro Val
625 630 635 640

Leu Val Ile Thr Glu Tyr Cys Cys Tyr Gly Asp Leu Leu Asn Phe Leu
645 650 655

Arg Arg Lys Ala Glu Ala Met Leu Gly Pro Ser Leu Ser Pro Gly Gln
660 665 670

Asp Pro Glu Gly Gly Val Asp Tyr Lys Asn Ile His Leu Glu Lys Lys
675 680 685

Tyr Val Arg Arg Asp Ser Gly Phe Ser Ser Gln Gly Val Asp Thr Tyr
690 695 700

Val Glu Met Arg Pro Val Ser Thr Ser Ser Asn Asp Ser Phe Ser Glu
705 710 715 720

Gln Asp Leu Asp Lys Glu Asp Gly Arg Pro Leu Glu Leu Arg Asp Leu
725 730 735

Leu His Phe Ser Ser Gln Val Ala Gln Gly Met Ala Phe Leu Ala Ser
740 745 750

Lys Asn Cys Ile His Arg Asp Val Ala Ala Arg Asn Val Leu Leu Thr
755 760 765

Asn Gly His Val Ala Lys Ile Gly Asp Phe Gly Leu Ala Arg Asp Ile
770 775 780

Met Asn Asp Ser Asn Tyr Ile Val Lys Gly Asn Ala Arg Leu Pro Val
785 790 795 800

Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Cys Val Tyr Thr Val Gln
805 810 815

Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu Ile Phe Ser Leu
820 825 830

Gly Leu Asn Pro Tyr Pro Gly Ile Leu Val Asn Ser Lys Phe Tyr Lys
835 840 845

Leu Val Lys Asp Gly Tyr Gln Met Ala Gln Pro Ala Phe Ala Pro Lys
850 855 860

```
Asn Ile Tyr Ser Ile Met Gln Ala Cys Trp Ala Leu Glu Pro Thr His
865                 870                 875                 880

Arg Pro Thr Phe Gln Gln Ile Cys Ser Phe Leu Gln Glu Gln Ala Gln
                885                 890                 895

Glu Asp Arg Arg Glu Arg Asp Tyr Thr Asn Leu Pro Ser Ser Ser Arg
            900                 905                 910

Ser Gly Gly Ser Gly Ser Ser Ser Ser Glu Leu Glu Glu Glu Ser Ser
        915                 920                 925

Ser Glu His Leu Thr Cys Cys Glu Gln Gly Asp Ile Ala Gln Pro Leu
    930                 935                 940

Leu Gln Pro Asn Asn Tyr Gln Phe Cys
945                 950
```

<210> 2
<211> 972
<212> PRT
<213> Homo sapiens

<220>
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<223> hCSF1R (full-length, + leader sequence)

<400> 2

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Met Gly Pro Gly Val Leu Leu Leu Leu Leu Val Ala Thr Ala Trp His
1               5                   10                  15

Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val
            20                  25                  30

Lys Pro Gly Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
        35                  40                  45

Glu Trp Asp Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
    50                  55                  60

Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly
65                  70                  75                  80

Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
                85                  90                  95

Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
            100                 105                 110
```

```
Gln Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
        115                 120                 125

Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg
    130                 135                 140

Gly Arg Pro Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
145                 150                 155                 160

Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln
                165                 170                 175

Cys Ser Ala Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg
            180                 185                 190

Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
        195                 200                 205

Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
    210                 215                 220

Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn
225                 230                 235                 240

Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg
                245                 250                 255

Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His
            260                 265                 270

Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
        275                 280                 285

Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser
    290                 295                 300

Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
305                 310                 315                 320

Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
                325                 330                 335

Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala
            340                 345                 350

Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu
```

355 360 365

Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg
370 375 380

Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr
385 390 395 400

Pro Pro Glu Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr
405 410 415

Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu
420 425 430

Gln Cys Ser Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln
435 440 445

Val Trp Asp Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His
450 455 460

Lys Val Thr Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn
465 470 475 480

Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp
485 490 495

Ala Phe Ile Pro Ile Ser Ala Gly Ala His Thr His Pro Pro Asp Glu
500 505 510

Phe Leu Phe Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu
515 520 525

Leu Leu Leu Leu Leu Leu Leu Leu Leu Tyr Lys Tyr Lys Gln Lys Pro
530 535 540

Lys Tyr Gln Val Arg Trp Lys Ile Ile Glu Ser Tyr Glu Gly Asn Ser
545 550 555 560

Tyr Thr Phe Ile Asp Pro Thr Gln Leu Pro Tyr Asn Glu Lys Trp Glu
565 570 575

Phe Pro Arg Asn Asn Leu Gln Phe Gly Lys Thr Leu Gly Ala Gly Ala
580 585 590

Phe Gly Lys Val Val Glu Ala Thr Ala Phe Gly Leu Gly Lys Glu Asp
595 600 605

```
Ala Val Leu Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala His Ala
    610                 615                 620

Asp Glu Lys Glu Ala Leu Met Ser Glu Leu Lys Ile Met Ser His Leu
625                 630                 635                 640

Gly Gln His Glu Asn Ile Val Asn Leu Leu Gly Ala Cys Thr His Gly
                645                 650                 655

Gly Pro Val Leu Val Ile Thr Glu Tyr Cys Cys Tyr Gly Asp Leu Leu
            660                 665                 670

Asn Phe Leu Arg Arg Lys Ala Glu Ala Met Leu Gly Pro Ser Leu Ser
        675                 680                 685

Pro Gly Gln Asp Pro Glu Gly Gly Val Asp Tyr Lys Asn Ile His Leu
    690                 695                 700

Glu Lys Lys Tyr Val Arg Arg Asp Ser Gly Phe Ser Ser Gln Gly Val
705                 710                 715                 720

Asp Thr Tyr Val Glu Met Arg Pro Val Ser Thr Ser Ser Asn Asp Ser
                725                 730                 735

Phe Ser Glu Gln Asp Leu Asp Lys Glu Asp Gly Arg Pro Leu Glu Leu
            740                 745                 750

Arg Asp Leu Leu His Phe Ser Ser Gln Val Ala Gln Gly Met Ala Phe
        755                 760                 765

Leu Ala Ser Lys Asn Cys Ile His Arg Asp Val Ala Ala Arg Asn Val
    770                 775                 780

Leu Leu Thr Asn Gly His Val Ala Lys Ile Gly Asp Phe Gly Leu Ala
785                 790                 795                 800

Arg Asp Ile Met Asn Asp Ser Asn Tyr Ile Val Lys Gly Asn Ala Arg
                805                 810                 815

Leu Pro Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Cys Val Tyr
            820                 825                 830

Thr Val Gln Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu Ile
        835                 840                 845

Phe Ser Leu Gly Leu Asn Pro Tyr Pro Gly Ile Leu Val Asn Ser Lys
    850                 855                 860
```

```
Phe Tyr Lys Leu Val Lys Asp Gly Tyr Gln Met Ala Gln Pro Ala Phe
865                 870                 875                 880


Ala Pro Lys Asn Ile Tyr Ser Ile Met Gln Ala Cys Trp Ala Leu Glu
                885                 890                 895


Pro Thr His Arg Pro Thr Phe Gln Gln Ile Cys Ser Phe Leu Gln Glu
            900                 905                 910


Gln Ala Gln Glu Asp Arg Arg Glu Arg Asp Tyr Thr Asn Leu Pro Ser
        915                 920                 925


Ser Ser Arg Ser Gly Gly Ser Gly Ser Ser Ser Ser Glu Leu Glu Glu
    930                 935                 940


Glu Ser Ser Ser Glu His Leu Thr Cys Cys Glu Gln Gly Asp Ile Ala
945                 950                 955                 960


Gln Pro Leu Leu Gln Pro Asn Asn Tyr Gln Phe Cys
                965                 970


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<213>  Artificial Sequence

<220>
<223>  Synthetic:  Light chain leader sequence

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Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15


Gly Ser Thr Gly
            20


<210>  4
<211>  19
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  Heavy chain leader sequence

<400>  4

Met Ala Val Leu Gly Leu Leu Leu Cys Leu Val Thr Phe Pro Ser Cys
1               5                   10                  15


Val Leu Ser
```

<210> 5
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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hCSF1R ECD.506

<400> 5

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Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val Lys Pro Gly
1               5                  10                  15

Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val Glu Trp Asp
            20                  25                  30

Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly Ser Ser Ser
        35                  40                  45

Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly Thr Tyr Arg
    50                  55                  60

Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala Ile His Leu
65                  70                  75                  80

Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala Gln Glu Val
                85                  90                  95

Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu Leu Thr Asp
            100                 105                 110

Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg Gly Arg Pro
        115                 120                 125

Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His Gly Phe Thr
    130                 135                 140

Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln Cys Ser Ala
145                 150                 155                 160

Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg Leu Lys Val
                165                 170                 175

Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val Pro Ala Glu
            180                 185                 190

Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Ser
        195                 200                 205
```

```
Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn Asn Thr Lys
    210                 215                 220

Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg Tyr Gln Lys
225                 230                 235                 240

Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His Ala Gly Asn
                245                 250                 255

Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser Thr Ser Met
            260                 265                 270

Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln
        275                 280                 285

Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn Leu Lys Val
    290                 295                 300

Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp Thr Tyr Leu
305                 310                 315                 320

Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala Asn Ala Thr
                325                 330                 335

Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu Pro Arg Leu
            340                 345                 350

Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg Asn Pro Gly
        355                 360                 365

Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu
    370                 375                 380

Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr Leu Leu Cys
385                 390                 395                 400

Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu Gln Cys Ser
                405                 410                 415

Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln Val Trp Asp
            420                 425                 430

Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr
        435                 440                 445

Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn Gln Thr Tyr
    450                 455                 460
```

```
Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp Ala Phe Ile
465                 470                 475                 480


Pro Ile Ser Ala Gly Ala His
                485
```

<210> 6
<211> 719
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hCSF1R ECD.506-Fc

<400> 6

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1               5                   10                  15


Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val Glu Trp Asp
            20                  25                  30


Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly Ser Ser Ser
        35                  40                  45


Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly Thr Tyr Arg
    50                  55                  60


Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala Ile His Leu
65                  70                  75                  80


Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala Gln Glu Val
                85                  90                  95


Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu Leu Thr Asp
            100                 105                 110


Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg Gly Arg Pro
        115                 120                 125


Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His Gly Phe Thr
    130                 135                 140


Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln Cys Ser Ala
145                 150                 155                 160


Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg Leu Lys Val
                165                 170                 175
```

```
Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val Pro Ala Glu
            180                 185                 190

Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Ser
        195                 200                 205

Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn Asn Thr Lys
    210                 215                 220

Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg Tyr Gln Lys
225                 230                 235                 240

Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His Ala Gly Asn
                245                 250                 255

Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser Thr Ser Met
            260                 265                 270

Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln
        275                 280                 285

Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn Leu Lys Val
    290                 295                 300

Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp Thr Tyr Leu
305                 310                 315                 320

Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala Asn Ala Thr
                325                 330                 335

Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu Pro Arg Leu
            340                 345                 350

Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg Asn Pro Gly
        355                 360                 365

Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu
    370                 375                 380

Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr Leu Leu Cys
385                 390                 395                 400

Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu Gln Cys Ser
                405                 410                 415

Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln Val Trp Asp
            420                 425                 430
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Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr
        435                 440                 445

Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn Gln Thr Tyr
    450                 455                 460

Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp Ala Phe Ile
465                 470                 475                 480

Pro Ile Ser Ala Gly Ala His Glu Pro Lys Ser Ser Asp Lys Thr His
                485                 490                 495

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
            500                 505                 510

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        515                 520                 525

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    530                 535                 540

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
545                 550                 555                 560

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                565                 570                 575

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            580                 585                 590

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
        595                 600                 605

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    610                 615                 620

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
625                 630                 635                 640

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                645                 650                 655

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            660                 665                 670

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
```

675 680 685

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
690 695 700

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
705 710 715

<210> 7
<211> 506
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cynoCSF1R ECD (with leader sequence)

<400> 7

Met Gly Pro Gly Val Leu Leu Leu Leu Leu Val Val Thr Ala Trp His
1 5 10 15

Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Gly Pro Glu Leu Val Val
20 25 30

Lys Pro Gly Glu Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
35 40 45

Glu Trp Asp Gly Pro Ile Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
50 55 60

Pro Ser Ser Val Leu Thr Thr Thr Asn Ala Thr Phe Gln Asn Thr Arg
65 70 75 80

Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
85 90 95

Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
100 105 110

Lys Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
115 120 125

Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Leu Arg
130 135 140

Gly Arg Pro Leu Leu Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
145 150 155 160

Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Gly Gln Asp Tyr Gln
165 170 175

```
Cys Ser Ala Leu Met Gly Ser Arg Lys Val Met Ser Ile Ser Ile Arg
            180                 185                 190

Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
        195                 200                 205

Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
    210                 215                 220

Ser Ala Ser Asn Ile Asp Val Asp Phe Asp Val Phe Leu Gln His Asn
225                 230                 235                 240

Thr Thr Lys Leu Ala Ile Pro Gln Arg Ser Asp Phe His Asp Asn Arg
                245                 250                 255

Tyr Gln Lys Val Leu Thr Leu Ser Leu Gly Gln Val Asp Phe Gln His
            260                 265                 270

Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
        275                 280                 285

Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asp Leu Ser
    290                 295                 300

Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
305                 310                 315                 320

Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
                325                 330                 335

Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala
            340                 345                 350

Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu
        355                 360                 365

Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg
    370                 375                 380

Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr
385                 390                 395                 400

Pro Pro Glu Val Ser Val Ile Trp Thr Ser Ile Asn Gly Ser Gly Thr
                405                 410                 415

Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu
```

420 425 430

Gln Cys Ala Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln
435 440 445

Val Trp Val Asp Pro His Pro Glu Val Leu Ser Gln Glu Pro Phe Gln
450 455 460

Lys Val Thr Val Gln Ser Leu Leu Thr Ala Glu Thr Leu Glu His Asn
465 470 475 480

Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp
485 490 495

Ala Phe Ile Pro Ile Ser Ala Gly Ala Arg
500 505

<210> 8
<211> 740
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cynoCSF1R ECD-Fc (with leader sequence)

<400> 8

Met Gly Pro Gly Val Leu Leu Leu Leu Leu Val Val Thr Ala Trp His
1 5 10 15

Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Gly Pro Glu Leu Val Val
20 25 30

Lys Pro Gly Glu Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
35 40 45

Glu Trp Asp Gly Pro Ile Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
50 55 60

Pro Ser Ser Val Leu Thr Thr Thr Asn Ala Thr Phe Gln Asn Thr Arg
65 70 75 80

Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
85 90 95

Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
100 105 110

Lys Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
115 120 125

```
Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Leu Arg
    130                 135                 140

Gly Arg Pro Leu Leu Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
145                 150                 155                 160

Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Gly Gln Asp Tyr Gln
                165                 170                 175

Cys Ser Ala Leu Met Gly Ser Arg Lys Val Met Ser Ile Ser Ile Arg
            180                 185                 190

Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
        195                 200                 205

Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
    210                 215                 220

Ser Ala Ser Asn Ile Asp Val Asp Phe Asp Val Phe Leu Gln His Asn
225                 230                 235                 240

Thr Thr Lys Leu Ala Ile Pro Gln Arg Ser Asp Phe His Asp Asn Arg
                245                 250                 255

Tyr Gln Lys Val Leu Thr Leu Ser Leu Gly Gln Val Asp Phe Gln His
            260                 265                 270

Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
        275                 280                 285

Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asp Leu Ser
    290                 295                 300

Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
305                 310                 315                 320

Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
                325                 330                 335

Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala
            340                 345                 350

Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu
        355                 360                 365

Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg
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370 375 380

Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr
385 390 395 400

Pro Pro Glu Val Ser Val Ile Trp Thr Ser Ile Asn Gly Ser Gly Thr
405 410 415

Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu
420 425 430

Gln Cys Ala Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln
435 440 445

Val Trp Val Asp Pro His Pro Glu Val Leu Ser Gln Glu Pro Phe Gln
450 455 460

Lys Val Thr Val Gln Ser Leu Leu Thr Ala Glu Thr Leu Glu His Asn
465 470 475 480

Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp
485 490 495

Ala Phe Ile Pro Ile Ser Ala Gly Ala Arg Gly Ser Glu Pro Lys Ser
500 505 510

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
515 520 525

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
530 535 540

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
545 550 555 560

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
565 570 575

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
580 585 590

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
595 600 605

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
610 615 620

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
625 630 635 640

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
645 650 655

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
660 665 670

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
675 680 685

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
690 695 700

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
705 710 715 720

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
725 730 735

Ser Pro Gly Lys
740

<210> 9
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0301 heavy chain variable region

<400> 9

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ile Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Glu Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 10
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0301 light chain variable region

<400> 10

Asn 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn
85 90 95

Glu Asp Leu Ser Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 11
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0302 heavy chain variable region

<400> 11

Glu Ile 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 Ser Asp Phe
20 25 30

Asn Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Arg Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Ile Thr Val Ser Ser
115 120

<210> 12
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0302 light chain variable region

<400> 12

Asp Val Val Val Thr Gln Thr 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 Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Gly Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Ala Asp Asp Ala Ala Thr Tyr Phe Cys Gln Gln Ser Lys
85 90 95

Glu Leu Pro Trp Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys

100 105 110

<210> 13
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0311 heavy chain variable region

<400> 13

Glu Ile Gln Leu Gln Gln Ser Gly Pro Asp Leu Met Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Met
35 40 45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Asp Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp
100 105 110

Gly Lys Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 14
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Fab 0311 light chain variable region

<400> 14

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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Gly Asn
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
100 105 110

<210> 15
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 heavy chain CDR1

<400> 15

Gly Tyr Thr Phe Thr Asp Asn Tyr Met Ile
1 5 10

<210> 16
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 heavy chain CDR2

<400> 16

Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 17
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 heavy chain CDR3

<400> 17

Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr

1 5 10

<210> 18
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 light chain CDR1

<400> 18

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Asn Tyr Met Asn
1 5 10 15

<210> 19
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 light chain CDR2

<400> 19

Ala Ala Ser Asn Leu Glu Ser
1 5

<210> 20
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0301 light chain CDR3

<400> 20

His Leu Ser Asn Glu Asp Leu Ser Thr
1 5

<210> 21
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 heavy chain CDR1

<400> 21

Gly Tyr Thr Phe Ser Asp Phe Asn Ile His
1 5 10

<210> 22
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 heavy chain CDR2

<400> 22

Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> 23
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 heavy chain CDR3

<400> 23

Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr
1 5 10

<210> 24
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 light chain CDR1

<400> 24

Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Leu Ser Phe Met Asn
1 5 10 15

<210> 25
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 light chain CDR2

<400> 25

Thr Ala Ser Asn Leu Glu Ser
1 5

<210> 26
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0302 light chain CDR3

<400> 26

Gln Gln Ser Lys Glu Leu Pro Trp Thr
1 5

<210> 27
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 heavy chain CDR1

<400> 27

Gly Tyr Ile Phe Thr Asp Tyr Asn Met His
1 5 10

<210> 28
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 heavy chain CDR2

<400> 28

Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 29
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 heavy chain CDR3

<400> 29

Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser
1 5 10

<210> 30
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 light chain CDR1

<400> 30

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser His Met Asn
1 5 10 15

<210> 31
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 light chain CDR2

<400> 31

Thr Ala Ser Asn Leu Glu Ser
1 5

<210> 32
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: 0311 light chain CDR3

<400> 32

Gln Gln Gly Asn Glu Asp Pro Trp Thr
1 5

<210> 33
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cAb 0301 heavy chain

<400> 33

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ile Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Glu Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu 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 Leu Gly
435 440 445

Lys

<210> 34
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cAb 0301 light chain

<400> 34

Asn 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn

85 90 95

Glu Asp Leu Ser Thr Phe Gly Gly Gly Thr Lys Leu 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> 35
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cAb 0302 heavy chain

<400> 35

Glu Ile 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 Ser Asp Phe
20 25 30

Asn Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Arg Ser Ser Ser Thr Ala Tyr
65 70 75 80

```
Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Ile 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> 36
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cAb 0302 light chain

<400> 36

Asp Val Val Val Thr Gln Thr 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 Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Gly Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Ala Asp Asp Ala Ala Thr Tyr Phe Cys Gln Gln Ser Lys
85 90 95

```
Glu Leu Pro Trp Thr Phe Gly Gly Gly Thr Arg Leu 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>  37
<211>  449
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  cAb 0311 heavy chain

<400>  37

Glu Ile Gln Leu Gln Gln Ser Gly Pro Asp Leu Met Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20                  25                  30

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Asp Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Lys Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu 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 Leu Gly
435 440 445

Lys

<210> 38
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: cAb 0311 light chain

<400> 38

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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile His
65 70 75 80

```
Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Gly Asn
                85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Arg Leu 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> 39
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H0 heavy chain variable region

<400> 39

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
    50                  55                  60
```

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 40
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H1 heavy chain variable region

<400> 40

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 41
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H2 heavy chain variable region

<400> 41

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 42
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-H1 heavy chain variable region

<400> 42

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Phe
20 25 30

Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 43
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-H2 heavy chain variable region

<400> 43

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Phe
20 25 30

Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 44
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-H1 heavy chain variable region

<400> 44

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 45
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-H2 heavy chain variable region

<400> 45

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 46
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-L0 light chain variable region

<400> 46

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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn
85 90 95

Glu Asp Leu Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 47
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-L1 light chain variable region

<400> 47

```
Asn 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn
                85                  90                  95

Glu Asp Leu Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  48
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  H0302-L0 light chain variable region

<400>  48

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 Glu Ser Val Asp Asn Tyr
            20                  25                  30

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile 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 Gln Ser Lys
                85                  90                  95
```

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 49
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-L1 light chain variable region

<400> 49

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 Glu Ser Val Asp Asn Tyr
20 25 30

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg 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 Gln Ser Lys
85 90 95

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 50
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-L2 light chain variable region

<400> 50

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 Glu Ser Val Asp Asn Tyr
20 25 30

Gly Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg 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 Gln Ser Lys
85 90 95

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 51
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-L0 light chain variable region

<400> 51

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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile 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 Gln Gly Asn
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 52
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-L1 light chain variable region

<400> 52

Asp 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 53
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H0 heavy chain

<400> 53

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu 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 Leu Gly
        435                 440                 445

Lys
```

<210> 54
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H1 heavy chain

<400> 54

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu 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 Leu Gly
        435                 440                 445

Lys
```

<210> 55
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-H2 heavy chain

<400> 55

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu 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 Leu Gly
        435                 440                 445

Lys
```

<210> 56
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-H1 heavy chain

<400> 56

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Phe
            20                  25                  30

Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu 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 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> 57
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-H2 heavy chain

<400> 57

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Phe
            20                  25                  30

Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu 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 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>  58
<211>  449
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  H0311-H1 heavy chain

<400>  58

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20                  25                  30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu 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 Leu Gly
        435                 440                 445

Lys
```

<210> 59
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-H2 heavy chain

<400> 59

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20                  25                  30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser 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 Gln Glu Glu Met 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 Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu 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 Leu Gly
        435                 440                 445

Lys
```

<210> 60
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-L0 light chain

<400> 60

```
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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn
                85                  90                  95

Glu Asp Leu Ser 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> 61
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: h0301-L1 light chain

<400> 61

```
Asn 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Asn Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile 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 His Leu Ser Asn
                85                  90                  95

Glu Asp Leu Ser 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> 62
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-L0 light chain

<400> 62

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 Glu Ser Val Asp Asn Tyr
20 25 30

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile 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 Gln Ser Lys
85 90 95

Glu Leu Pro Trp Thr Phe Gly Gln 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> 63
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0302-L1 light chain

<400> 63

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 Glu Ser Val Asp Asn Tyr
20 25 30

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg 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 Gln Ser Lys
85 90 95

```
Glu Leu Pro Trp Thr Phe Gly Gln 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>  64
<211>  218
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  H0302-L2 light chain

<400>  64

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 Glu Ser Val Asp Asn Tyr
            20                  25                  30

Gly Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg 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 Gln Ser Lys
                85                  90                  95

Glu Leu Pro Trp Thr Phe Gly Gln 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> 65
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-L0 light chain

<400> 65

```
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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile 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 Gln Gly Asn
                85                  90                  95

Glu Asp Pro Trp Thr Phe Gly Gln 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> 66
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: H0311-L1 light chain

<400> 66

```
Asp 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 Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
        35                  40                  45

Arg Leu Leu Ile Tyr Thr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
```

50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln 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> 67
<211> 158
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(158)
<223> Human CSF1

<400> 67

Glu Glu Val Ser Glu Tyr Cys Ser His Met Ile Gly Ser Gly His Leu
1 5 10 15

Gln Ser Leu Gln Arg Leu Ile Asp Ser Gln Met Glu Thr Ser Cys Gln
20 25 30

```
Ile Thr Phe Glu Phe Val Asp Gln Glu Gln Leu Lys Asp Pro Val Cys
        35                  40                  45

Tyr Leu Lys Lys Ala Phe Leu Leu Val Gln Asp Ile Met Glu Asp Thr
    50                  55                  60

Met Arg Phe Arg Asp Asn Thr Pro Asn Ala Ile Ala Ile Val Gln Leu
65                  70                  75                  80

Gln Glu Leu Ser Leu Arg Leu Lys Ser Cys Phe Thr Lys Asp Tyr Glu
                85                  90                  95

Glu His Asp Lys Ala Cys Val Arg Thr Phe Tyr Glu Thr Pro Leu Gln
            100                 105                 110

Leu Leu Glu Lys Val Lys Asn Val Phe Asn Glu Thr Lys Asn Leu Leu
        115                 120                 125

Asp Lys Asp Trp Asn Ile Phe Ser Lys Asn Cys Asn Asn Ser Phe Ala
    130                 135                 140

Glu Cys Ser Ser Gln Gly His Glu Arg Gln Ser Glu Gly Ser
145                 150                 155


<210>  68
<211>  222
<212>  PRT
<213>  Homo sapiens


<220>
<221>  misc_feature
<222>  (1)..(222)
<223>  Human IL-34

<400>  68

Asn Glu Pro Leu Glu Met Trp Pro Leu Thr Gln Asn Glu Glu Cys Thr
1               5                   10                  15

Val Thr Gly Phe Leu Arg Asp Lys Leu Gln Tyr Arg Ser Arg Leu Gln
            20                  25                  30

Tyr Met Lys His Tyr Phe Pro Ile Asn Tyr Lys Ile Ser Val Pro Tyr
        35                  40                  45

Glu Gly Val Phe Arg Ile Ala Asn Val Thr Arg Leu Gln Arg Ala Gln
    50                  55                  60

Val Ser Glu Arg Glu Leu Arg Tyr Leu Trp Val Leu Val Ser Leu Ser
```

65 70 75 80

Ala Thr Glu Ser Val Gln Asp Val Leu Leu Glu Gly His Pro Ser Trp
85 90 95

Lys Tyr Leu Gln Glu Val Gln Thr Leu Leu Leu Asn Val Gln Gln Gly
100 105 110

Leu Thr Asp Val Glu Val Ser Pro Lys Val Glu Ser Val Leu Ser Leu
115 120 125

Leu Asn Ala Pro Gly Pro Asn Leu Lys Leu Val Arg Pro Lys Ala Leu
130 135 140

Leu Asp Asn Cys Phe Arg Val Met Glu Leu Leu Tyr Cys Ser Cys Cys
145 150 155 160

Lys Gln Ser Ser Val Leu Asn Trp Gln Asp Cys Glu Val Pro Ser Pro
165 170 175

Gln Ser Cys Ser Pro Glu Pro Ser Leu Gln Tyr Ala Ala Thr Gln Leu
180 185 190

Tyr Pro Pro Pro Pro Trp Ser Pro Ser Ser Pro Pro His Ser Thr Gly
195 200 205

Ser Val Arg Pro Val Arg Ala Gln Gly Glu Gly Leu Leu Pro
210 215 220

<210> 69
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor A FR1

<400> 69

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser
20 25

<210> 70
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic: Human acceptor A FR2

<400> 70

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> 71
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor A FR3

<400> 71

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 72
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor A FR4

<400> 72

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 73
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor B FR1

<400> 73

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser
20 25

<210> 74
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor B FR2

<400> 74

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> 75
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor B FR3

<400> 75

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 76
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor B FR4

<400> 76

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 77
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor C FR1

<400> 77

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser
20 25

<210> 78
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor C FR2

<400> 78

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> 79
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor C FR3

<400> 79

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 80
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor C FR4

<400> 80

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 81
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor D FR1

<400> 81

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
20

<210> 82
<211> 15
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor D FR2

<400> 82

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 83
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor D FR3

<400> 83

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> 84
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor D FR4

<400> 84

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 85
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor E FR1

<400> 85

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
20

<210> 86
<211> 15

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor E FR2

<400> 86

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 87
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor E FR3

<400> 87

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> 88
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor E FR4

<400> 88

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 89
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor F FR1

<400> 89

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
20

<210> 90

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor F FR2

<400> 90

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 91
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor F FR3

<400> 91

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> 92
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Human acceptor F FR4

<400> 92

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 93
<211> 719
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: mCSF1R ECD-Fc

<400> 93

Ala Pro Val Ile Glu Pro Ser Gly Pro Glu Leu Val Val Glu Pro Gly
1 5 10 15

Glu Thr Val Thr Leu Arg Cys Val Ser Asn Gly Ser Val Glu Trp Asp
20 25 30

```
Gly Pro Ile Ser Pro Tyr Trp Thr Leu Asp Pro Glu Ser Pro Gly Ser
        35                  40                  45

Thr Leu Thr Thr Arg Asn Ala Thr Phe Lys Asn Thr Gly Thr Tyr Arg
    50                  55                  60

Cys Thr Glu Leu Glu Asp Pro Met Ala Gly Ser Thr Thr Ile His Leu
65                  70                  75                  80

Tyr Val Lys Asp Pro Ala His Ser Trp Asn Leu Leu Ala Gln Glu Val
                85                  90                  95

Thr Val Val Glu Gly Gln Glu Ala Val Leu Pro Cys Leu Ile Thr Asp
            100                 105                 110

Pro Ala Leu Lys Asp Ser Val Ser Leu Met Arg Glu Gly Gly Arg Gln
        115                 120                 125

Val Leu Arg Lys Thr Val Tyr Phe Phe Ser Pro Trp Arg Gly Phe Ile
    130                 135                 140

Ile Arg Lys Ala Lys Val Leu Asp Ser Asn Thr Tyr Val Cys Lys Thr
145                 150                 155                 160

Met Val Asn Gly Arg Glu Ser Thr Ser Thr Gly Ile Trp Leu Lys Val
                165                 170                 175

Asn Arg Val His Pro Glu Pro Pro Gln Ile Lys Leu Glu Pro Ser Lys
            180                 185                 190

Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Thr
        195                 200                 205

Asn Ala Glu Val Gly Phe Asn Val Ile Leu Lys Arg Gly Asp Thr Lys
    210                 215                 220

Leu Glu Ile Pro Leu Asn Ser Asp Phe Gln Asp Asn Tyr Tyr Lys Lys
225                 230                 235                 240

Val Arg Ala Leu Ser Leu Asn Ala Val Asp Phe Gln Asp Ala Gly Ile
                245                 250                 255

Tyr Ser Cys Val Ala Ser Asn Asp Val Gly Thr Arg Thr Ala Thr Met
            260                 265                 270

Asn Phe Gln Val Val Glu Ser Ala Tyr Leu Asn Leu Thr Ser Glu Gln
        275                 280                 285
```

```
Ser Leu Leu Gln Glu Val Ser Val Gly Asp Ser Leu Ile Leu Thr Val
    290                 295                 300

His Ala Asp Ala Tyr Pro Ser Ile Gln His Tyr Asn Trp Thr Tyr Leu
305                 310                 315                 320

Gly Pro Phe Phe Glu Asp Gln Arg Lys Leu Glu Phe Ile Thr Gln Arg
                325                 330                 335

Ala Ile Tyr Arg Tyr Thr Phe Lys Leu Phe Leu Asn Arg Val Lys Ala
            340                 345                 350

Ser Glu Ala Gly Gln Tyr Phe Leu Met Ala Gln Asn Lys Ala Gly Trp
        355                 360                 365

Asn Asn Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu Val Ser
    370                 375                 380

Val Thr Trp Met Pro Val Asn Gly Ser Asp Val Leu Phe Cys Asp Val
385                 390                 395                 400

Ser Gly Tyr Pro Gln Pro Ser Val Thr Trp Met Glu Cys Arg Gly His
                405                 410                 415

Thr Asp Arg Cys Asp Glu Ala Gln Ala Leu Gln Val Trp Asn Asp Thr
            420                 425                 430

His Pro Glu Val Leu Ser Gln Lys Pro Phe Asp Lys Val Ile Ile Gln
        435                 440                 445

Ser Gln Leu Pro Ile Gly Thr Leu Lys His Asn Met Thr Tyr Phe Cys
    450                 455                 460

Lys Thr His Asn Ser Val Gly Asn Ser Ser Gln Tyr Phe Arg Ala Val
465                 470                 475                 480

Ser Leu Gly Gln Ser Lys Gln Glu Pro Lys Ser Ser Asp Lys Thr His
                485                 490                 495

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
            500                 505                 510

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        515                 520                 525

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    530                 535                 540
```

```
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
545                 550                 555                 560

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                565                 570                 575

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            580                 585                 590

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
        595                 600                 605

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    610                 615                 620

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
625                 630                 635                 640

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                645                 650                 655

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            660                 665                 670

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        675                 680                 685

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    690                 695                 700

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
705                 710                 715


<210>  94
<211>  327
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic:  Human IgG4 S241P

<400>  94

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
```

```
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 95
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(107)
<223> Human Ig?

<400> 95

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

<210> 96
<211> 277
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature

<222> (1)..(277)
<223> human CD40 precursor (with signal sequence)

<400> 96

```
Met Val Arg Leu Pro Leu Gln Cys Val Leu Trp Gly Cys Leu Leu Thr
1               5                  10                  15

Ala Val His Pro Glu Pro Pro Thr Ala Cys Arg Glu Lys Gln Tyr Leu
            20                  25                  30

Ile Asn Ser Gln Cys Cys Ser Leu Cys Gln Pro Gly Gln Lys Leu Val
        35                  40                  45

Ser Asp Cys Thr Glu Phe Thr Glu Thr Glu Cys Leu Pro Cys Gly Glu
    50                  55                  60

Ser Glu Phe Leu Asp Thr Trp Asn Arg Glu Thr His Cys His Gln His
65                  70                  75                  80

Lys Tyr Cys Asp Pro Asn Leu Gly Leu Arg Val Gln Gln Lys Gly Thr
                85                  90                  95

Ser Glu Thr Asp Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr
            100                 105                 110

Ser Glu Ala Cys Glu Ser Cys Val Leu His Arg Ser Cys Ser Pro Gly
        115                 120                 125

Phe Gly Val Lys Gln Ile Ala Thr Gly Val Ser Asp Thr Ile Cys Glu
    130                 135                 140

Pro Cys Pro Val Gly Phe Phe Ser Asn Val Ser Ser Ala Phe Glu Lys
145                 150                 155                 160

Cys His Pro Trp Thr Ser Cys Glu Thr Lys Asp Leu Val Val Gln Gln
                165                 170                 175

Ala Gly Thr Asn Lys Thr Asp Val Val Cys Gly Pro Gln Asp Arg Leu
            180                 185                 190

Arg Ala Leu Val Val Ile Pro Ile Ile Phe Gly Ile Leu Phe Ala Ile
        195                 200                 205

Leu Leu Val Leu Val Phe Ile Lys Lys Val Ala Lys Lys Pro Thr Asn
    210                 215                 220

Lys Ala Pro His Pro Lys Gln Glu Pro Gln Glu Ile Asn Phe Pro Asp
```

225 230 235 240

Asp Leu Pro Gly Ser Asn Thr Ala Ala Pro Val Gln Glu Thr Leu His
245 250 255

Gly Cys Gln Pro Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser
260 265 270

Val Gln Glu Arg Gln
275

<210> 97
<211> 257
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(257)
<223> human CD40 (mature, without signal sequence)

<400> 97

Glu Pro Pro Thr Ala Cys Arg Glu Lys Gln Tyr Leu Ile Asn Ser Gln
1 5 10 15

Cys Cys Ser Leu Cys Gln Pro Gly Gln Lys Leu Val Ser Asp Cys Thr
20 25 30

Glu Phe Thr Glu Thr Glu Cys Leu Pro Cys Gly Glu Ser Glu Phe Leu
35 40 45

Asp Thr Trp Asn Arg Glu Thr His Cys His Gln His Lys Tyr Cys Asp
50 55 60

Pro Asn Leu Gly Leu Arg Val Gln Gln Lys Gly Thr Ser Glu Thr Asp
65 70 75 80

Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr Ser Glu Ala Cys
85 90 95

Glu Ser Cys Val Leu His Arg Ser Cys Ser Pro Gly Phe Gly Val Lys
100 105 110

Gln Ile Ala Thr Gly Val Ser Asp Thr Ile Cys Glu Pro Cys Pro Val
115 120 125

Gly Phe Phe Ser Asn Val Ser Ser Ala Phe Glu Lys Cys His Pro Trp
130 135 140

```
Thr Ser Cys Glu Thr Lys Asp Leu Val Val Gln Gln Ala Gly Thr Asn
145                 150                 155                 160

Lys Thr Asp Val Val Cys Gly Pro Gln Asp Arg Leu Arg Ala Leu Val
                165                 170                 175

Val Ile Pro Ile Ile Phe Gly Ile Leu Phe Ala Ile Leu Leu Val Leu
            180                 185                 190

Val Phe Ile Lys Lys Val Ala Lys Lys Pro Thr Asn Lys Ala Pro His
        195                 200                 205

Pro Lys Gln Glu Pro Gln Glu Ile Asn Phe Pro Asp Asp Leu Pro Gly
    210                 215                 220

Ser Asn Thr Ala Ala Pro Val Gln Glu Thr Leu His Gly Cys Gln Pro
225                 230                 235                 240

Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser Val Gln Glu Arg
                245                 250                 255

Gln
```

<210> 98
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Dacetuzumab heavy chain

<400> 98

```
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 Tyr Ser Phe Thr Gly Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Arg Val Ile Pro Asn Ala Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Phe Thr Leu Ser Val Asp Asn 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 Glu Gly Ile Tyr Trp Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
        115                 120                 125

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
    130                 135                 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145                 150                 155                 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
                165                 170                 175

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
            180                 185                 190

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
        195                 200                 205

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
    210                 215                 220

Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Lys 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 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                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 Val 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> 99
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Dacetuzumab light chain

<400> 99

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 Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Phe Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45

Pro Lys Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Ser Gln Thr
85 90 95

```
Thr His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```