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(54) Titre : METHODES DE TRAITEMENT D'ETATS PATHOLOGIQUES AVEC DES ANTICORPS SE LIANT AU RECEPTEUR DU FACTEUR 1 DE STIMULATION DES COLONIES (CSF1R)

(54) Title: METHODS OF TREATING CONDITIONS WITH ANTIBODIES THAT BIND COLONY STIMULATING FACTOR 1 RECEPTOR (CSF1R)

(57) Abrégé/Abstract:
Methods of treating conditions with antibodies that bind colony stimulating factor 1 receptor (CSF1R) are provided. Such methods include, but are not limited to, methods of treating rheumatoid arthritis.

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(54) Title: METHODS OF TREATING CONDITIONS WITH ANTIBODIES THAT BIND COLONY STIMULATING FACTOR 1 RECEPTOR (CSF1R)

(57) Abstract: Methods of treating conditions with antibodies that bind colony stimulating factor 1 receptor (CSF1R) are provided. Such methods include, but are not limited to, methods of treating rheumatoid arthritis.

WO 2015/200089 A1

METHODS OF TREATING CONDITIONS WITH ANTIBODIES THAT BIND COLONY STIMULATING FACTOR 1 RECEPTOR (CSF1R)

[001] This application claims the benefit of US Provisional Application No. 62/015,710, filed June 23, 2014, which is incorporated by reference herein in its entirety for any purpose.

TECHNICAL FIELD

[002] Methods of treating conditions with antibodies that bind colony stimulating factor 1 receptor (CSF1R) are provided. Such methods include, but are not limited to, methods of treating rheumatoid arthritis.

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. Both CSF1 and IL-34 stimulate monocyte survival, proliferation, and differentiation into macrophages, as well as other monocytic cell lineages such as osteoclasts, dendritic cells, and microglia.

[004] Many tumor cells have been found to secrete 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 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).

[005] CSF1 and its receptor have also been found to be involved in various inflammatory and autoimmune diseases. See, e.g., Hamilton, *Nat. Rev.* 8: 533-44 (2008). For example, synovial endothelial cells from joints afflicted with rheumatoid arthritis have been found to produce CSF1, suggesting a role for CSF1 and its receptor in the disease. Blocking CSF1R activity with an antibody results in positive clinical effects in mouse

models of arthritis, including a reduction in the destruction of bone and cartilage and a reduction in macrophage numbers. *See, e.g.*, Kitaura et al., *J. Clin. Invest.* 115: 3418-3427 (2005).

[006] Mature differentiated myeloid lineage cells such as macrophages, microglial cells, and osteoclasts contribute to pathology of various diseases such as rheumatoid arthritis, multiple sclerosis and diseases of bone loss. Differentiated myeloid lineage cells are derived from peripheral blood monocyte intermediates. CSF1R stimulation contributes to development of monocytes from bone marrow precursors, to monocyte proliferation and survival, and to differentiation of peripheral blood monocytes into differentiated myeloid lineage cells such as macrophages, microglial cells, and osteoclasts. CSF1R stimulation thus contributes to proliferation, survival, activation, and maturation of differentiated myeloid lineage cells, and in the pathologic setting, CSF1R stimulation contributes to the ability of differentiated myeloid lineage cells to mediate disease pathology.

SUMMARY

[007] In some embodiments, methods of treating rheumatoid arthritis are provided, comprising administering an effective amount of an antibody that binds colony stimulating factor 1 receptor (CSF1R) to a human subject with rheumatoid arthritis, wherein the antibody blocks binding of colony stimulating factor 1 (CSF1) to CSF1R and blocks binding of IL-34 to CSF1R, wherein the effective amount is sufficient to reduce the number of CD16+ monocytes in the subject by at least 50% for at least 4 weeks after two doses. In some embodiments, the effective dose is between 0.2 mg/kg and 10 mg/kg, or between 1 and 10 mg/kg, or between 1 and 5 mg/kg. In some embodiments, the antibody is administered at a dosing frequency of once per two weeks or longer.

[008] In some embodiments, methods of treating rheumatoid arthritis are provided. In some embodiments, the method comprises administering an antibody that binds colony stimulating factor 1 receptor (CSF1R) to a subject with rheumatoid arthritis, wherein the antibody blocks binding of colony stimulating factor 1 (CSF1) to CSF1R and blocks binding of IL-34 to CSF1R, and wherein the antibody is administered at a dose between 0.2 mg/kg and 10 mg/kg and at a dosing frequency of once per two weeks or longer. In some embodiments, the dosing frequency is less than once per two weeks, once per two weeks, once per three weeks, once per four weeks, once per month, once per five weeks, once per six weeks, once per seven weeks, once per two months, once per three months, or four times per year. In some embodiments, the dose is between 1 mg/kg and 10 mg/kg. In some embodiments, the dose is between 3 mg/kg and 10 mg/kg. In some embodiments, the

method comprises administering one dose of the antibody. In some embodiments, the method comprises administering two doses of the antibody.In some embodiments, the doses are administered at least one week apart, or at least two weeks apart.

[009] In some embodiments, following administration of at least one dose of the antibody, the number of CD16+ monocytes is reduced in the subject by at least 50%. In some embodiments, the number of CD16- monocytes is not reduced or is reduced by less than 20%. In some embodiments, the number of CD16+ monocytes is reduced in the subject by at least 75%. In some embodiments, the number of CD16+ monocytes is reduced by at least 50% for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, or at least eight weeks. In some embodiments, the CD16+ monocytes are CD16+ peripheral blood monocytes.

[010] In some embodiments, the level of at least one marker of bone resorption is reduced following administration of at least one dose of the antibody. In some embodiments, the level of at least one marker of bone resorption is reduced by at least 20%. In some embodiments, the level of at least one marker of bone resorption is reduced by at least 50%. In some embodiments, the at least one marker of bone resorption is selected from CTx and TRAP5b. In some embodiments, the at least one marker of bone resorption is CTx.

[011] In some embodiments, the antibody is detectable in serum from the subject at least two weeks, at least three weeks, at least four weeks, at least one month, at least six weeks, or at least two months after administration of a dose. In some embodiments, the antibody is detectable in serum from the subject at least four weeks, at least one month, at least six weeks, or at least two months after administration of a dose. In some embodiments, the dose is between 3 mg/kg and 10 mg/kg. In some embodiments, the half-life of the antibody in the subject is greater than 2 days. In some embodiments, the half-life of the antibody is greater than 4 days. In some embodiments, the half-life of the antibody is greater than 15 days. In some such embodiments, the dose is between 3 mg/kg and 10 mg/kg.

[012] In any of the embodiments of the methods described herein, the antibody heavy chain and/or the antibody light chain may have the following structure.

[013] In some embodiments, the heavy chain comprises 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 some embodiments, the light chain comprises 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 some embodiments, the heavy chain comprises 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 light chain comprises 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.

[014] In some embodiments, 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. In some embodiments, 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.

[015] In some embodiments, the heavy chain comprises 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 comprises 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.

[016] In some embodiments, the antibody comprises a heavy chain and a light chain, wherein the antibody comprises: (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.

[017] In some embodiments, the antibody comprises a heavy chain and a light chain, wherein the antibody comprises: (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.

[018] In some embodiments, the antibody comprises a heavy chain and a light chain, wherein the antibody comprises: (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, the 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.

[019] In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$. In some embodiments, the antibody is a chimeric antibody. In some embodiments, the

antibody is selected from an IgA, an IgG, and an IgD. In some embodiments, the antibody is an IgG. In some embodiments, the antibody is an IgG4. In some embodiments, the antibody is an IgG4 comprising an S241P mutation in at least one IgG4 heavy chain constant region.

[020] In some embodiments, the antibody binds to human CSF1R and/or binds to cynomolgus CSF1R. In some embodiments, the antibody blocks ligand binding to CSF1R. In some embodiments, an antibody blocks binding of CSF1 and/or IL-34 to CSF1R. In some embodiments, the antibody blocks binding of both CSF1 and IL-34 to CSF1R. In some embodiments, the antibody inhibits ligand-induced CSF1R phosphorylation. In some embodiments, the antibody inhibits CSF1- and/or IL-34-induced CSF1R phosphorylation. In some embodiments, an antibody binds to human CSF1R with an affinity (K_D) of less than 1 nM. In some embodiments, the antibody inhibits monocyte proliferation and/or survival responses in the presence of CSF1 or IL-34.

[021] In some embodiments, a pharmaceutical composition comprising an antibody that binds CSF1R is provided.

[022] In some embodiments, compositions comprising antibodies that bind CSF1R are provided for use in methods of treatment of human or animals. In some embodiments, antibodies that bind CSF1R and compositions comprising antibodies that bind CSF1R are provided for use in a method of treating rheumatoid arthritis in a human or animal.

BRIEF DESCRIPTION OF THE FIGURES

[023] **FIG. 1A-C** shows 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.

[024] **FIG. 2A-C** shows 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.

[025] **FIG. 3A-B** show clearance of serum huAb1 (“FPA008”) in humans following a single administration at the indicated dose, as described in Example 2.

[026] **FIG. 4** shows clearance of serum huAb1 (“FPA008”) in cynomolgus monkeys and humans following a single administration at the indicated dose, as described in Example 2.

[027] **FIG. 5A-B** show serum CTx levels in (A) CSF1 low subjects, who likely received placebo, and (b) CSF1 high subjects, who likely received huAb1, following a single administration of the indicated dose, as described in Example 3.

[028] **FIG. 6A-B** show serum TRAP5b levels in (A) CSF1 low subjects, who likely received placebo, and (b) CSF1 high subjects, who likely received huAb1, following a single administration of the indicated dose, as described in Example 3.

[029] **FIG. 7** shows suppression of nonclassical CD16+ monocytes in subjects in each dosing cohort (including both placebo and huAb1) following a single administration of the indicated dose, as described in Example 4.

[030] **FIG. 8** shows classical CD16- monocytes in subjects in each dosing cohort (including both placebo and huAb1) following a single administration of the indicated dose, as described in Example 4.

[031] **FIG. 9A-B** show (A) serum CSF1 levels and (B) serum IL34 levels in subjects who likely received huAb1.

[032] **FIG. 10** shows serum concentration of huAb1 over time in healthy volunteers (tirangles) and RA patients (open circles) following administration of two doses, two weeks apart.

[033] **FIG. 11** shows reduction of nonclassical CD16+ monocytes in healthy volunteers following two doses of huAb1 (“FPA008”).

[034] **FIG. 12** shows reduction of nonclassical CD16+ monocytes in RA patients following two doses of huAb1.

DETAILED DESCRIPTION

[035] Methods of treating conditions comprising administering antibodies that bind CSF1R and block CSF1 and IL-34 ligand binding are provided. As discussed herein, antibodies that bind CSF1R and block CSF1 and IL-34 ligand binding are effective for treating rheumatoid arthritis. The present inventors found that administering such antibodies to humans reduced the number of CD16+ peripheral blood monocytes in cynomolgus monkeys, but does not affect CD16- peripheral blood monocyte numbers CD16+ peripheral blood monocytes are highly inflammatory monocytes. *See, e.g.*, Ziegler-Heitbrock, *J. Leukocyte Biol.*, 2007, 81: 584-592. While it was previously found that administering such antibodies to cynomolgus monkeys reduced the number of CD16+ monocytes, the effect observed in humans is substantially and unexpectedly prolonged compared to the effect in cynomolgus monkeys. Indeed, at a single dose of just 1 mg/kg, CD16+ monocyte numbers were substantially suppressed for at least a week. At a dose of 3

mg/kg, CD16+ monocyte numbers were substantially suppressed for at least four weeks, while a single dose of 10 mg/kg suppressed CD16+ monocyte numbers for at least eight weeks. Further, administering such antibodies to humans also reduced serum CTx levels and showed a trend toward reduction of serum TRAP5b levels, both of which are markers of bone resorption. Taken together, these results suggest that antibodies that bind CSF1R and block CSF1 and IL-34 ligand binding will be an effective treatment for rheumatoid arthritis with infrequent dosing.

[036] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

Definitions

[037] Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[038] Exemplary techniques used in connection with recombinant DNA, oligonucleotide synthesis, tissue culture and transformation (e.g., electroporation, lipofection), enzymatic reactions, and purification techniques are known in the art. Many such techniques and procedures are described, e.g., in Sambrook et al. *Molecular Cloning: A Laboratory Manual* (2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), among other places. In addition, exemplary techniques for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients are also known in the art.

[039] In this application, the use of "or" means "and/or" unless stated otherwise. In the context of a multiple dependent claim, the use of "or" refers back to more than one preceding independent or dependent claim in the alternative only. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

[040] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[041] 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.

[042] 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.

[043] 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.

[044] The term "**CSF1R extracellular domain**" ("**CSF1R ECD**") as used herein refers to a CSF1R polypeptide that lacks the intracellular and transmembrane domains. CSF1R ECDs include the full-length CSF1R ECD and CSF1R ECD fragments that are capable of binding CSF1R and/or IL-34. The human full-length CSF1R ECD is defined herein as comprising either amino acids 1 to 512 (i.e., including the leader sequence) or amino acids 20 to 512 (i.e., lacking the leader sequence) of SEQ ID NO: 2. In some embodiments, a human CSF1R ECD fragment comprises amino acids 20 to 506 of SEQ ID NO: 2 (see SEQ ID NO:5). In some embodiments, a human CSF1R fragment ends at amino acid 507, 508, 509, 510, or 511. In some embodiments, a cyno CSF1R ECD comprises the sequence of SEQ ID NO: 7 (with leader sequence) or amino acids 20 to 506 of SEQ ID NO: 7 (without leader sequence).

[045] With reference to anti-CSF1R antibodies the terms "**active**" or "**activity**" or "**function**", and grammatical variants thereof, are used to refer to the ability to inhibit (blocking or antagonist antibodies) or mimic (agonist antibodies) at least one of the

foregoing activities. Antibodies and antibody fragments referred to as "functional" are characterized by having such properties.

[046] An "**immunological**" activity refers only to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring CSF1R polypeptide.

[047] 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.

[048] 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.

[049] 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.*

[050] 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.

[051] 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).

[052] 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.

[053] 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.

[054] 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.

[055] 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.

[056] 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.

[057] 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 an Fab, an scFv, a $(Fab')_2$, etc.

[058] 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.

[059] 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.

[060] 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.

[061] 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.

[062] 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.

[063] 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.

[064] 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.

[065] As used herein, "**rheumatoid arthritis**" or "**RA**" refers to a recognized disease state that may be diagnosed according to the 2000 revised American Rheumatoid Association criteria for the classification of RA, or any similar criteria. In some embodiments, the term "rheumatoid arthritis" refers to a chronic autoimmune disease characterized primarily by inflammation of the lining (synovium) of the joints, which can lead to joint damage, resulting in chronic pain, loss of function, and disability. Because RA can affect multiple organs of the body, including skin, lungs, and eyes, it is referred to as a systemic illness.

[066] The term "rheumatoid arthritis" includes not only active and early RA, but also incipient RA, as defined below. Physiological indicators of RA include, symmetric joint swelling which is characteristic though not invariable in RA. Fusiform swelling of the proximal interphalangeal (PIP) joints of the hands as well as metacarpophalangeal (MCP), wrists, elbows, knees, ankles, and metatarsophalangeal (MTP) joints are commonly affected and swelling is easily detected. Pain on passive motion is the most sensitive test for joint inflammation, and inflammation and structural deformity often limits the range of motion for the affected joint. Typical visible changes include ulnar deviation of the fingers at the MCP joints, hyperextension, or hyperflexion of the MCP and PIP joints, flexion contractures of the elbows, and subluxation of the carpal bones and toes. The subject with RA may be resistant to a disease-modifying anti-rheumatic drug (DMARD), and/or a non-steroidal anti-inflammatory drug (NSAID). Nonlimiting exemplary "DMARDs" include hydroxycloroquine, sulfasalazine, methotrexate (MTX), leflunomide, etanercept, infliximab (plus oral and subcutaneous MTX), azathioprine, D-penicillamine, gold salts (oral), gold salts (intramuscular), minocycline, cyclosporine including cyclosporine A and topical cyclosporine, staphylococcal protein A (Goodyear and Silverman, *J. Exp. Med.*,

197(9):1125-1139 (2003)), including salts and derivatives thereof, etc. Further candidates for therapy according to this invention include those who have experienced an inadequate response to previous or current treatment with TNF inhibitors such as etanercept, infliximab and/or adalimumab because of toxicity or inadequate efficacy.

[067] A patient with "**active rheumatoid arthritis**" means a patient with active and not latent symptoms of RA. Subjects with "**early active rheumatoid arthritis**" are those subjects with active RA diagnosed for at least 8 weeks but no longer than four years, according to the revised 1987 ACR criteria for the classification of RA.

[068] Subjects with "**early rheumatoid arthritis**" are those subjects with RA diagnosed for at least eight weeks but no longer than four years, according to the revised 1987 ACR criteria for classification of RA. RA includes, for example, juvenile-onset RA, juvenile idiopathic arthritis (JIA), or juvenile RA (JRA).

[069] Patients with "**incipient rheumatoid arthritis**" have early polyarthritis that does not fully meet ACR criteria for a diagnosis of RA, in association with the presence of RA-specific prognostic biomarkers such as anti-CCP and shared epitope. They include patients with positive anti-CCP antibodies who present with polyarthritis, but do not yet have a diagnosis of RA, and are at high risk for going on to develop bona fide ACR criteria RA (95% probability).

[070] "**Joint damage**" is used in the broadest sense and refers to damage or partial or complete destruction to any part of one or more joints, including the connective tissue and cartilage, where damage includes structural and/or functional damage of any cause, and may or may not cause joint pain/arthalgia. It includes, without limitation, joint damage associated with or resulting from inflammatory joint disease as well as non-inflammatory joint disease. This damage may be caused by any condition, such as an autoimmune disease, especially arthritis, and most especially RA. Exemplary such conditions include acute and chronic arthritis, rheumatoid arthritis (including juvenile-onset RA, juvenile idiopathic arthritis (JIA), and juvenile rheumatoid arthritis (JRA)), and stages such as rheumatoid synovitis, gout or gouty arthritis, acute immunological arthritis, chronic inflammatory arthritis, degenerative arthritis, type II collagen-induced arthritis, infectious arthritis, septic arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis, Still's disease, vertebral arthritis, osteoarthritis, arthritis chronica progrediente, arthritis deformans, polyarthritis chronica primaria, reactive arthritis, menopausal arthritis, estrogen-depletion arthritis, and ankylosing spondylitis/rheumatoid spondylitis), rheumatic autoimmune disease other than RA, and significant systemic involvement secondary to RA (including but not

limited to vasculitis, pulmonary fibrosis or Felty's syndrome). For purposes herein, joints are points of contact between elements of a skeleton (of a vertebrate such as an animal) with the parts that surround and support it and include, but are not limited to, for example, hips, joints between the vertebrae of the spine, joints between the spine and pelvis (sacroiliac joints), joints where the tendons and ligaments attach to bones, joints between the ribs and spine, shoulders, knees, feet, elbows, hands, fingers, ankles and toes, but especially joints in the hands and feet.

[071] The term "**CD16+ disorder**" means a disease in which CD16+ monocytes of a mammal cause, mediate or otherwise contribute to a morbidity in the mammal. Also included are diseases in which reduction of CD16+ monocytes has an ameliorative effect on progression of the disease. Included within this term are CD16+ inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, etc. In certain embodiments, CD16+ inflammatory diseases include inflammatory diseases that are not responsive to methotrexate therapy. In certain embodiments, CD16+ inflammatory diseases include methotrexate-resistant rheumatoid arthritis, methotrexate-resistant multiple sclerosis, methotrexate-resistant lupus, methotrexate-resistant inflammatory bowel disease, methotrexate-resistant Crohn's disease, methotrexate-resistant asthma, and methotrexate-resistant psoriasis. In certain embodiments, patients having methotrexate-resistant diseases, such as methotrexate-resistant rheumatoid arthritis, are referred to as methotrexate incomplete responders or methotrexate inadequate responders.

[072] Examples of CD16+ disorders that can be treated according to the invention include, but are not limited to, systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scieroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjogren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing

cholangitis, inflammatory bowel disease (IBD), including ulcerative colitis: Crohn's disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft-versus-host-disease; fibrosis, including kidney fibrosis and hepatic fibrosis, cardiovascular disease, including atherosclerosis and coronary artery disease, cardiovascular events associated with chronic kidney disease, myocardial infarction, and congestive heart failure, diabetes, including type II diabetes, Bronchiolitis obliterans with organizing pneumonia (BOOP), hemophagocytic syndrome, macrophage activation syndrome, sarcoidosis, and periodontitis. Infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes, etc., bacterial infections, fungal infections, protozoal infections and parasitic infections.

[073] "**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.

[074] "**Chronic**" administration refers to administration of an agent in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "**Intermittent**" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

[075] 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 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 anti-CSF1R antibody to elicit a desired response in the individual. A therapeutically effective amount encompasses an amount in which any toxic or detrimental effects of the anti-CSF1R antibody are outweighed by the therapeutically beneficial effects.

[076] 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.

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

[078] 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

[079] 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

[080] 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.

[081] 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.

[082] 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.

[083] 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

[084] 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.

[085] 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.

[086] 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.

[087] 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

[088] 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.

[089] 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.

[090] In some methods of treatment, effector function may not be desirable. For example, in some embodiments, it may be desirable that antibodies used in the treatment of RA do not have effector function. Thus, in some embodiments, anti-CSF1R antibodies developed for the treatment of cancer may not be suitable for use in treatment of RA. Accordingly, in some embodiments, an anti-CSF1R antibody that lacks significant effector function is used in treatment of RA. In some embodiments, an anti-CSF1R antibody for

treatment of RA comprises a human IgG4 or IgG2 heavy chain constant region. In some embodiments, an IgG4 constant region comprises an S241P mutation.

[091] 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.

[092] 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.

[093] 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.

[094] 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.

[095] 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.

[096] 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

[097] 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).

[098] 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.

[099] 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.

[0100] 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

[0101] 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.

[0102] 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.

[0103] 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

[0104] 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.

[0105] 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

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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

[0111] 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.

[0112] 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.

[0113] In some embodiments, an anti-CSF1R antibody comprises a light chain variable region of an antibody selected from Fabs 0301, 0302, and 311. 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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

[0119] 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.

[0120] 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.

[0121] 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

[0122] 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.

[0123] 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

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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

[0143] 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

[0144] 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.

[0145] 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.

[0146] 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. An antibody is considered to "block 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 in Example 7. 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%, using the assay described in Example 7. In some such embodiments, the antibody is said to block ligand binding by at least 50%, at least 60%, at least 70%, etc.

[0147] 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. 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 in Example 6. 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%, using the assay described in Example 6. 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.

[0148] In some embodiments, an antibody inhibits monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34. 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 in Example 10. 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%, using the assay described in Example 10. 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 Antibody Conjugates

[0149] In some embodiments, an anti-CSF1R 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.

[0150] 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.

[0151] 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

[0152] 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.

[0153] 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 Anti-CSF1R Antibodies

[0154] Nucleic acid molecules comprising polynucleotides that encode one or more chains of anti-CSF1R antibodies are provided. In some embodiments, a nucleic acid molecule comprises a polynucleotide that encodes a heavy chain or a light chain of an anti-CSF1R 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 anti-CSF1R 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.

[0155] 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.

[0156] In some embodiments, a polynucleotide encoding a heavy chain or light chain of an anti-CSF1R 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.

[0157] 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.

Anti-CSF1R Antibody Expression and Production

Vectors

[0158] Vectors comprising polynucleotides that encode anti-CSF1R heavy chains and/or anti-CSF1R light chains are provided. Vectors comprising polynucleotides that encode anti-CSF1R heavy chains and/or anti-CSF1R 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.

[0159] 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.

[0160] 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).

[0161] In some embodiments, a vector is chosen for *in vivo* expression of anti-CSF1R heavy chains and/or anti-CSF1R 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

[0162] In various embodiments, anti-CSF1R heavy chains and/or anti-CSF1R 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, anti-CSF1R heavy chains and/or anti-CSF1R 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 anti-CSF1R heavy chains and/or anti-CSF1R 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.

[0163] 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.

[0164] 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 Anti-CSF1R Antibodies

[0165] Anti-CSF1R 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 CSF1R ECD 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 anti-CSF1R 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 Anti-CSF1R Antibodies

[0166] In some embodiments, an anti-CSF1R 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 Diseases using Anti-CSF1R Antibodies

[0167] Provided herein are methods of treating CD16+ disorders with an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding. Provided herein are methods of treating rheumatoid arthritis with an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding.

[0168] In some embodiments, methods of treating rheumatoid arthritis are provided, wherein the method comprises administering an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding, such as an antibody selected from huAb1 to huAb16, to a subject with rheumatoid arthritis. In some embodiments, methods of treating rheumatoid arthritis are provided, wherein the method comprises administering antibody huAb1 to a subject with rheumatoid arthritis. In some embodiments, the method comprises administering at least one dose of the antibody, wherein the dose is between 0.2 mg/kg and 10 mg/kg, such as between 1 mg/kg and 10 mg/kg or 3 mg/kg and 10 mg/kg. In some embodiments, the antibody is cleared from serum after a single dose at 1 mg/kg in about 2 weeks, after a single dose at 3 mg/kg after about 6 weeks, and after a single dose at 10 mg/kg after about 12 weeks. The clearance from serum in humans administered a single dose of huAb1 was significantly and unexpectedly slower than the clearance from serum in cynomolgus monkeys that received the same dose. The slow clearance rate, in some embodiments, allows for infrequent dosing of the antibody. In some embodiments, the antibody may be administered once per two weeks or less often. For example, in some embodiments, the antibody may be administered once per two weeks, once per three weeks, once per four weeks, once per month, once per five weeks, once per six weeks, once per seven weeks, once per two months, once per three months, or four times per year.

[0169] In some embodiments, the half-life in huAb1 following administration to a human subject is greater than 2 days. In some embodiments, the half-life in huAb1 following administration to a human subject is greater than 4 days. In some embodiments, the half-life in huAb1 following administration to a human subject is greater than 15 days. In some embodiments, the half-life in huAb1 following administration of a dose of about 1.0 mg/kg to a human subject is greater than 2 days. In some embodiments, the half-life in huAb1 following administration of a dose of about 3.0 mg/kg to a human subject is greater than 4 days. In some embodiments, the half-life in huAb1 following administration of a dose of about 10 mg/kg to a human subject is greater than 15 days. In some embodiments, the half-life in huAb1 following administration of a dose of about 10 mg/kg to a human subject is greater than 18 days. In some embodiments, the half-life in huAb1 following administration of a dose of between 1 mg/kg and 10 mg/kg to a human subject is between 2 days and 25 days. In some embodiments, the half-life in huAb1 following administration of a dose of between 3 mg/kg and 10 mg/kg to a human subject is between 4 days and 25 days.

[0170] In some embodiments, methods of reducing the number CD16+ monocytes are provided, wherein the methods comprise administering an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding, such as an antibody selected from huAb1 to huAb16, to a subject with increased CD16+ monocytes. In some embodiments, the subject has rheumatoid arthritis. In some embodiments, administering an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding does not decrease the number of CD16- monocytes. In some embodiments, the number of CD16+ monocytes is reduced to a greater extent than the number of CD16- monocytes when an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding is administered to the subject. In some embodiments, the number of CD16+ monocytes is reduced by at least 20%, at least 30%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% following administration of at least one dose of the antibody, such as huAb1. In some embodiments, the number of CD16- monocytes is reduced by less than 30%, less than 20%, or less than 10%. In some embodiments, the reduction in the number of CD16+ monocytes lasts for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least 6 weeks, at least seven weeks, or at least eight weeks folloing administration of a dose of the antibody. In some embodiments, the CD16+ monocytes are CD16+ peripheral blood monocytes. In some embodiments, the CD16- monocytes are CD16- peripheral blood monocytes.

[0171] In some embodiments, a method of reducing bone resorption associated with rheumatoid arthritis is provided, wherein the method comprises administering an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding, such as an antibody selected from huAb1 to huAb16, to a subject with rheumatoid arthritis. In some embodiments, a method of reducing bone resorption associated with rheumatoid arthritis is provided, wherein the method comprises administering antibody huAb1 to a subject with rheumatoid arthritis. Reducing bone resorption, in some embodiments, comprises reducing the number of osteoclasts in joints affected by rheumatoid arthritis.

[0172] In some embodiments, bone resorption may be measured by determining the level of CTx and/or TRAP5b in plasma from the subject, wherein an elevated level of CTx and/or TRAP5b indicates elevated bone resorption in the subject. Thus, in some embodiments, a reduced level of CTx and/or TRAP5b indicates a reduction in bone resorption. CTx and/or TRAP5b levels may be determined, in certain instances, before and after treatment with an antibody that binds CSF1R, and/or may be determined periodically throughout the course of treatment to monitor the effectiveness of the treatment in reducing bone loss. CTx and/or TRAP5b levels may be determined using any method in the art, including, but not limited to, ELISA (including FAICEA, or fragments absorbed immunocapture enzymatic assay; *see, e.g.*, Quidel® TRAP5b assay, TECOmedical Group, Sissach, Switzerland). In some embodiments, administration of an antibody that binds CSF1R and blocks CSF1 and IL-34 ligand binding, such as huAb1, reduces at least one marker of bone resorption, such as, for example, CTx and/or TRAP5b. In some embodiments, the serum level of a marker of bone resorption is reduced by at elast 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 75%. In some embodiments, the reduction in the serum level of a marker of bone resorption lasts for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least 6 weeks, at least seven weeks, or at least eight weeks folloing administration of a dose of the antibody.

Routes of Administration and Carriers

[0173] In various embodiments, anti-CSF1R 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 anti-CSF1R 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.

[0174] In various embodiments, compositions comprising anti-CSF1R 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.

[0175] In various embodiments, compositions comprising anti-CSF1R 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.

[0176] Pharmaceutical packs and kits comprising one or more containers, each containing one or more doses of an anti-CSF1R antibody are also provided. In some embodiments, a unit dosage is provided wherein the unit dosage contains a predetermined

amount of a composition comprising an anti-CSF1R antibody, 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.

[0177] 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, anti-CSF1R 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, anti-CSF1R 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, anti-CSF1R 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, anti-CSF1R 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, anti-CSF1R 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.

[0178] The anti-CSF1R 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 anti-CSF1R antibody is administered to a subject one or more times. In various embodiments, an effective dose of an anti-CSF1R antibody is administered to the subject once per two weeks, once per three weeks, once per four weeks, once per month, once per five weeks, once per six weeks, once per seven weeks, once per two months, once per three months, four times per year, or less often. An effective dose of an anti-CSF1R antibody is

administered to the subject at least once. In some embodiments, the effective dose of an anti-CSF1R antibody may be administered multiple times, including for periods of at least a month, at least six months, or at least a year.

Combination Therapy

[0179] Anti-CSF1R antibodies 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. For treatment of rheumatoid arthritis, anti-CSF1R antibodies may be administered with other therapeutic agents, for example, methotrexate, anti-TNF agents such as Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), and Enbrel (etanercept); glucocorticoids such as prednisone; leflunomide; azothioprine; JAK inhibitors such as CP 590690; SYK inhibitors such as R788; anti-IL-6 antibodies; anti-IL-6R antibodies such as tocilizumab; anti-CD-20 antibodies such as rituximab; anti-CD19 antibodies; anti-GM-CSF antibodies; anti-GM-CSF-R antibodies; IL-1 receptor antagonists such as anakinra; CTLA-4 antagonists, such as abatacept; immunosuppressants such as cyclosporine.

EXAMPLES

[0180] 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

[0181] Various humanized anti-CSF1R antibodies were developed previously. *See, e.g.*, PCT Publication No. WO 2011/140249.

[0182] 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.

[0183] Table 6, 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

[0184] 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 mouse 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.

[0185] 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: HuAb1 pharmacokinetics in cynomolgus monkeys and humans

[0186] The pharmacokinetics (PK) of huAb1 have been investigated in 3 intravenous (IV) studies in cynomolgus monkeys. The dose range studied was 3–150 mg/kg after a single dose and 3–150 mg/kg after repeat doses. The duration of infusion was 30 minutes. The dosing interval in the repeat-dose studies was once a week with each animal receiving a total of 4 doses.

[0187] The PK profile following a single 30-minute IV infusion of huAb1 in cynomolgus monkeys was characterized by a rapid distribution, followed by a slower terminal phase that ended with an accelerated depletion of huAb1 from the plasma, consistent with target-mediated clearance.

[0188] The rapid decrease may be due in part to anti-huAb1 antibodies in addition to target-mediated clearance. However, a single dose administration of a similar chimeric anti-CSF1R antibody in SCID mice, which lack the ability to mount an ADA response, showed a similar profile. The observed maximum plasma concentration (C_{max}) occurred at the end of

infusion for the lower dose groups and 0.5–1 hour after the end of infusion for the 150 mg/kg dose group. The half-life ($t_{1/2}$) prior to the accelerated terminal decline ranged from 1–12 days. C_{max} and AUC_{∞} increased with increasing dose, and C_{max} increased proportionally to dose at all dose levels tested. AUC_{∞} increases were greater than dose proportional from 3 mg/kg to 10 mg/kg and were dose proportional from 10 mg/kg to 150 mg/kg.

[0189] HuAb1 or placebo was formulated at a concentration of 20 mg/ml in a pH 6.3 buffer containing 20 mM L-histidine, 142 mM L-arginine, and 0.01% polysorbate 20. Adult heathy volunteer subjects were randomized to each dose cohort (8 subjects per cohort; 6 received drug and 2 received placebo). The dose cohorts were a single dose of 0.2 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg huAb1 or placebo. HuAb1 or placebo was administered by IV infusion over 30 minutes, followed by an observation period. Subjects were confined for 72 hours after their study drug administration to undergo assessments and to ensure compliance with the protocol-specific guidance around restriction of alcohol and strenuous exercise.

[0190] The start of infusion was considered time-zero. Blood samples were collected for determination of serum concentrations of huAb1 at the following time points relative to the start of infusion:

t=0 hour (h) (may be collected up to 60 minutes pre-dose),

t=25 (25 minutes after the start of infusion), t=30 minutes (end of infusion),

t=35 minutes (35 minutes from beginning of infusion, which is equivalent to 5 minutes from the end of infusion),

t=45 (45 minutes from beginning of infusion, equivalent to 15 minutes from the end of infusion),

t=60 (60 minutes from beginning of infusion, equivalent to 30 minutes from the end of infusion).

Thereafter, collections occurred relative to beginning of infusion at 2 h, 4 h, 8 h, 24 h, 36 h, 48 h, and 72 h, then on Study Days 8, 15, 22, 29, 57 and 85.

[0191] The mean serum concentration of huAb1 in the subjects was determined by ELISA as follows. Samples were diluted a minimum 1:30 into assay diluent (PBS containing 1% bovine gamma globulin, 0.3M NaCl, and 0.05% Tween20). Human CSF1R-Fc (fusion protein of human CSF1 receptor extracellular domain to a human IgG1 Fc) was coated onto ELISA plates. HuAb1 from a frozen serum sample was captured onto the plates and detected using a horse radish peroxidase-conjugated mouse anti-human IgG4 antibody,

using standard methods. The results of that analysis are shown in Figure 3. Figure 3A shows a log plot of serum huAb1 versus time in weeks. Figure 3B shows a linear plot of the same data. These data suggest that huAb1 will be cleared from subjects in the 10 mg/kg cohort after 13 weeks. The non-linear PK profile is consistent with target-mediated clearance. Table 5 shows the calculated clearance (CL) and half-life of huAb1 at each dose. Values are mean ± standard deviation in 6 subjects.

Table 5: Clearance (CL) and half-life of huAb1 in human subjects

Dose (mg/kg)	**CL (mL/h/kg)**	**t1/2 (h)**	**t1/2 (d)**
0.2	1.62 ± 0.21	12.5 ± 1.3	0.5 ± 0.1
1	0.49 ± 0.10	56.8 ± 11.4	2.4 ± 0.5
3	0.18 ± 0.01	129.8 ± 32.7	5.4 ± 1.4
10	0.11 ± 0.02	490.2 ± 59.4*	20.4 ± 2.5*

* first order elimination half-life prior to accelerated terminal clearance

[0192] The pharmacokinetics observed in humans were substantially and unexpectedly different from the pharmacokinetics observed in cynomolgus monkeys. As shown in Figure 4, clearance of huAb1 in human was much slower than clearance in cynomolgus monkeys.

Example 3: huAb1 suppresses CTx and TRAP5b markers of bone resorption

[0193] Administration of huAb1 has been shown to cause a dramatic increase in the CSF1R ligand, CSF1 and IL-34. That increase was used to categorize the blinded samples into likely huAb1 cohorts and likely placebo cohorts by determining the level of CSF1 and/or IL-34 in serum from the subjects, using commercial ELISAs (R&D Systems, Minneapolis, MN). *See* Figure 9. After the samples were divided into their likely cohorts, serum CTx were measured to determine whether huAb1 was effective to suppress this marker of bone resorption. Serum CTx was also measured using a commercial ELISA (IDS Serum CrossLaps ELISA). Serum samples were previously frozen.

[0194] The results of that experiment are shown in Figure 5. In Figure 5A, which are the CSF1 low subjects, and therefore the likely placebo cohorts, serum CTx levels are substantially unchanged at the three doses indicated (n=2 in that figure means there were 2 subjects per cohort). In Figure 5B, which are the CSF1 high subjects, and therefore the likely huAb1 cohorts, serum CTx levels were suppressed in a dose-dependent manner, indicating that huAb1 may suppress bone resorption (n=6 in that figure means there were 6 subjects per cohort).

[0195] Serum TRAP5b levels were also measured to determine whether huAb1 was effective to suppress TRAP5b levels, also a marker of bone resorption. Serum TRAP5b

was measured using a commercial ELISA (MicroVue Bone Health Trap5b Assay, REF 8033, Quidel). Serum samples were previously frozen. The results of that experiment are shown in Figure 6. In Figure 6A, which are the CSF1 low subjects, and therefore the likely placebo cohorts, serum TRAP5b levels are substantially unchanged at the three doses indicated (n=2 in that figure means there were 2 subjects per cohort). In Figure 6B, which are the CSF1 high subjects, and therefore the likely huAb1 cohorts, serum TRAP5b levels trended lower, suggesting that huAb1 may suppress this marker of bone resorption (n=6 in that figure means there were 6 subjects per cohort).

Example 4: huAb1 suppresses CD16+ monocytes in humans

[0196] HuAb1 was previously demonstrated to suppress CD16+ monocyte levels in cynomolgus monkeys, while leaving CD16- monocyte levels substantially unchanged. CD16+ monocyte levels were determined in each of the eight subjects per dose level (6 subjects receiving huAb1 and 2 subjects receiving placebo) by flow cytometry as follows. Whole blood was collected into Cyto-Chex® blood collection tubes (Streck) and analyzed within 48 hours of collection. 75 µL of blood was stained with anti-CD45, anti-CD14, anti-CD16 (all BD Biosciences) and anti-HLA-DR (R&D Systems) monoclonal antibodies. AccuCheck® Counting Beads (Life Technologies) were added for determination of absolute numbers of cells. Samples were run on a FACSCanto™ II (BD Biosciences) and analyzed using FlowJo software (Tree Star Inc.). Monocytes identified as CD45+HLA-DR+SSC^{int}CD14+ cells were subdivided into 3 monocyte subsets identified as classical (CD14++CD16-), intermediate (CD14++CD16+), and nonclassical (CD14+CD16++) and enumerated per µL of blood.

[0197] The results of that experiment are shown in Figure 7. Substantially reduced nonclassical CD16+ monocyte levels were observed for varying amounts of time in each cohort. At 0.2 mg/kg, nonclassical CD16+ monocyte levels were reduced in the six likely huAb1 subjects for less than one week. At 1 mg/kg, nonclassical CD16+ monocyte levels were reduced in the six likely huAb1 subjects for at least one week. At 3 mg/kg, nonclassical CD16+ monocyte levels were reduced in the six likely huAb1 subjects for at least four weeks. Finally, at 10 mg/kg, nonclassical CD16+ monocyte levels were reduced in the six likely huAb1 subjects for the eight week period of the study. These results suggest that infrequent dosing of huAb1 may exert long-lasting suppression of CD16+ monocytes. Similar reductions in intermediate CD16+ monocytes were also noted (data not shown).

[0198] Classical CD16- monocytes levels were also determined. As shown in Figure 8, changes in CD16- monocyte levels did not differ between the six likely huAb1 subjects and the likely placebo subjects at all dosing levels.

Example 5: HuAb1 pharmacokinetics in healthy vulonteers and RA patients

[0199] HuAb1 was formulated at a concentration of 20 mg/ml in a pH 6.3 buffer containing 20 mM L-histidine, 142 mM L-arginine, and 0.01% polysorbate 20. Two adult heathy volunteers and three RA patients received two doses of 3 mg/kg huAb1, 14 days apart. HuAb1 was administered by intravenous infusion over 30 minutes, followed by an observation period. The start of infusion was considered time zero.

[0200] The serum concentration of huAb1 in the healthy volunteers was determined by ELISA as described under [0190]. The same assay was used to measure serum concentration of huAb1 in RA patients using a different coating agent. The coating agent for samples from RA patients, human CSF1R-Fc protein, was human CSF1 receptor extracellular domain fused to a mouse IgG1 Fc. The results of the analysis from both healthy volunteers and RA patients are shown in Figure 10. Open circle and solid triangle represent data from healthy volunteers and RA patients, respectively. Dashed line and solid line are for group mean for healthy volunteers and RA patients, respectively. Data below lower limit of quantification (LLOQ) was considered as zero for the purpose of calculation of group mean for graphic presentation. HuAb1 serum concentration in the 3mg/kg dual dose cohort was measurable up to approximately 12 weeks for healthy volunteers, and was measurable up to, and possibly longer than, 8 weeks for RA patients (based on the data point measured to date) following first dose administration.

Example 6: huAb1 reduces CD16+ monocytes in RA patients

[0201] CD16+ monocyte levels were determined in each of two healthy volunteers who received two doses of huAb1 at 3 mg/kg, 14 days apart. CD16+ monocyte levels were also determined in each of the three RA patients who received two doses of huAb1 at 3 mg/kg, 14 days apart. Whole blood was collected into Cyto-Chex® blood collection tubes and analyzed as described in Example 4.

[0202] The results of the experiment are shown in Figures 11 and 12. In healthy volunteers, substantially reduced nonclassical CD16+ monocyte levels were observed up to 6 weeks after the first dose of huAb1 ("FPA008"). *See* Figure 11. In RA patients,

substantially reduced nonclassical CD16+ monocyte levels were observed up to 2 weeks after the first dose of huAb1. *See* Figure 12.

TABLE OF SEQUENCES

[0203] Table 6 provides certain sequences discussed herein. All polypeptide and antibody sequences are shown without leader sequences, unless otherwise indicated.

Table 6: 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	NIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDNYMNWY QQKPGQPPKL LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCHLSNEDLS

	region	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	KASQSVDYDG DSHMN

	chain CDR1	
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 FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
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 FR2	WYQQKPGQAP RLLIY
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

CLAIMS

1. A method of treating rheumatoid arthritis comprising administering an effective amount of an antibody that binds colony stimulating factor 1 receptor (CSF1R) to a human subject with rheumatoid arthritis, wherein the antibody blocks binding of colony stimulating factor 1 (CSF1) to CSF1R and blocks binding of IL-34 to CSF1R, wherein the effective amount is sufficient to reduce the number of CD16+ monocytes in the subject by at least 50% for at least 4 weeks after two doses.

2. The method of claim 1, wherein the effective dose is between 0.2 mg/kg and 10 mg/kg, or between 1 and 10 mg/kg, or between 1 and 5 mg/kg.

3. The method of claim 1 or claim 2, wherein the antibody is administered at a dosing frequency of once per two weeks or longer.

4. A method of treating rheumatoid arthritis comprising administering an antibody that binds colony stimulating factor 1 receptor (CSF1R) to a human subject with rheumatoid arthritis, wherein the antibody blocks binding of colony stimulating factor 1 (CSF1) to CSF1R and blocks binding of IL-34 to CSF1R, wherein the antibody is administered at a dose between 0.2 mg/kg and 10 mg/kg and at a dosing frequency of once per two weeks or longer.

5. The method of any one of the preceding claims, wherein the dosing frequency is less than once per two weeks, once per two weeks, once per three weeks, once per four weeks, once per month, once per five weeks, once per six weeks, once per seven weeks, once per two months, once per three months, or four times per year.

6. The method of any one of the preceding claims, wherein the method comprises administering one dose of the antibody.

7. The method of any one of claims 1 to 5, wherein the method comprises administering two doses of the antibody.

8. The method of claim 7, wherein the doses are administered at least one week apart.

9. The method of claim 7, wherein the doses are admininstered at least two weeks apart.

10. The method of any one of the preceding claims, wherein the dose is between 1 mg/kg and 10 mg/kg.

11. The method of any one of the preceding claims, wherein the dose is between 3 mg/kg and 10 mg/kg.

12. The method of any one of the preceding claims, wherein following

administration of at least one dose of the antibody, the number of CD16+ monocytes is reduced in the subject by at least 50%.

13. The method of any one of the preceding claims, wherein the number of CD16- monocytes is not reduced or is reduced by less than 20%.

14. The method of any one of the preceding claims, wherein the number of CD16+ monocytes is reduced in the subject by at least 75%.

15. The method of any one of the preceding claims, wherein the number of CD16+ monocytes is reduced by at least 50% for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, or at least eight weeks.

16. The method of any one of claims 2 to 15, wherein the CD16+ monocytes are CD16+ peripheral blood monocytes.

17. The method of any one of the preceding claims, wherein the level of at least one marker of bone resorption is reduced following administration of at least one dose of the antibody.

18. The method of claim 17, wherein the level of at least one marker of bone resorption is reduced by at least 20%.

19. The method of claim 17, wherein the level of at least one marker of bone resorption is reduced by at least 50%.

20. The method of any one of claims 17 to 19, wherein the at least one marker of bone resorption is selected from CTx and TRAP5b.

21. The method of claim 20, wherein the at least one marker of bone resorption is CTx.

22. The method of any one of the preceding claims, wherein the antibody 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.

23. The method of claim 22, wherein the antibody is a humanized antibody.

24. The method of claim 22 or claim 23, wherein the antibody is selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$.

25. The method of any one of the preceding claims, wherein the antibody is detectable in serum from the subject at least two weeks, at least three weeks, at least four weeks, at least one month, at least six weeks, or at least two months after administration of a dose.

26. The method of claim 25, wherein the antibody is detectable in serum from the subject at least four weeks, at least one month, at least six weeks, or at least two months after administration of a dose.

27. The method of claim 26, wherein the dose is between 3 mg/kg and 10 mg/kg.

28. The method of any one of the preceding claims, wherein the half-life of the antibody in the subject is greater than 2 days.

29. The method of claim 28, wherein the half-life of the antibody is greater than 4 days.

30. The method of claim 28, wherein the half-life of the antibody is greater than 15 days.

31. The method of claim 28, wherein the half-life of the antibody is greater than 28 days.

32. The method of claim 28, wherein the half-life of the antibody is greater than 42 days.

33. The method of any one of claims 28 of claim 32, wherein the dose is between 3 mg/kg and 10 mg/kg.

Ab ID	L/K chains	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	27a	27b	27c, CDR1	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
cAb0101	parental	E	V	Q	L	V	Q	S	G	P	E	L	V	K	P	G	A	S	V	K	M	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	K	Q	S	H	G	K	S	L	E	W	I
human acceptor A		Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S											W	V	R	Q	A	P	G	Q					
Ab1	h0101-L0H0	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	S	L	E	W	I
Ab2	h0101-L0H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	A	L	E	W	I
Ab3	h0101-L0H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	A	L	E	W	I
Ab4	h0101-L1H0	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab5	h0101-L1H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab6	h0101-L1H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	M	I	W	V	R	Q	A	P	G	Q	G	L	E	W	I
cAb0102	parental	E	I	Q	L	Q	Q	S	G	P	E	L	V	K	P	G	A	S	V	K	M	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	K	Q	S	H	G	K	S	L	E	W	I
human acceptor B		Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S											W	V	R	Q	A	P	G	Q					
Ab7	h0102-L0H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	A	L	E	W	I
Ab8	h0102-L1H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab9	h0102-L2H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab10	h0102-L2H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab11	h0102-L3H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab12	h0102-L4H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	S	D	F	Y	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
cAb 0111	parental	E	I	Q	L	Q	Q	S	G	P	D	L	M	K	P	G	A	S	V	K	M	S	C	K	S	S	G	Y	T	F	T	D	Y	S	I	H	W	V	K	Q	S	G	G	S	L	E	W	I
human acceptor C		Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S											W	V	R	Q	A	P	G	Q					
Ab13	h0111-L0H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	S	I	H	W	V	R	Q	A	P	G	Q	A	L	E	W	I
Ab14	h0111-L1H1	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	S	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab15	h0111-L0K0	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	S	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I
Ab16	h0111-L1H2	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	S	I	H	W	V	R	Q	A	P	G	Q	G	L	E	W	I

FIG. 1A

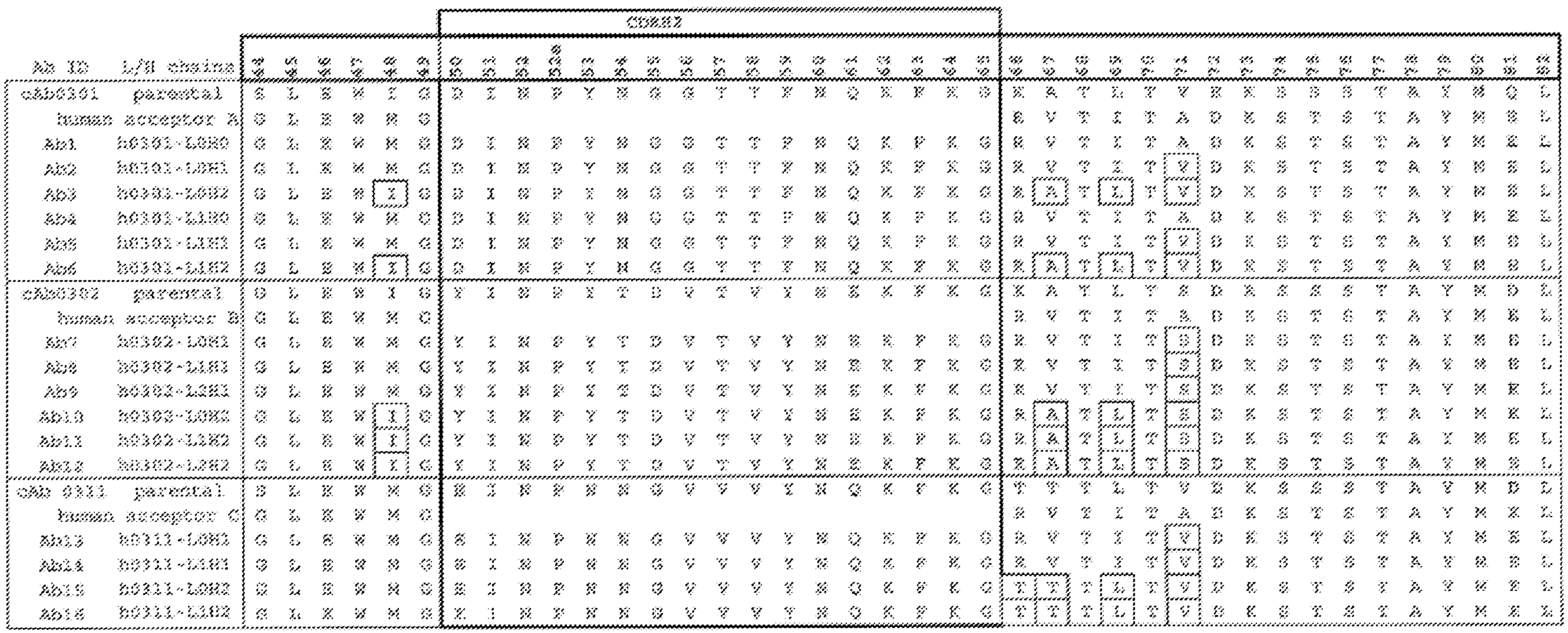

Abs ID
L/H chains
parental
human acceptor A
Ab1
Ab2
Ab3
Ab4
Ab5
Ab6
parental
human acceptor B
Ab7
Ab8
Ab9
Ab10
Ab11
Ab12
parental
human acceptor C
Ab13
Ab14
Ab15
Ab16

FIG. 1B

Ab ID	L/H chains	FR																CDRH3												FR												CDR SEQ ID NO
		H2a	H2b	H2c	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	95	96	97	98	99	100	100a	100b	100c	100d	100e	101	102	H103	H104	H105	H106	H107	H108	H109	H110	H111	H112	H113	
cAb0301	parental	K	S	L	T	S	K	D	S	A	V	Y	Y	C	A	R	E	S	F	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	S	V	T	V	S	S	9
human acceptor A		S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R														W	G	Q	G	T	L	V	T	V	S	S	69-72
Ab1	h0301-L0H0	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	39
Ab2	h0301-L0H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	E	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	40
Ab3	h0301-L0H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	E	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	41
Ab4	h0301-L1H0	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	39
Ab5	h0301-L1H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	40
Ab6	h0301-L1H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	E	E	S	P	Y	F	S	N	L	Y	V	M	D	Y	W	G	Q	G	T	L	V	T	V	S	S	41
cAb0302	parental	S	S	L	T	S	E	D	S	A	V	Y	Y	C	A	S	Y	F	D	G	T	F	D	Y	A	L		D	Y	W	G	Q	G	T	S	I	T	V	S	S	11
human acceptor B		S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	E														W	G	Q	G	T	L	V	T	V	S	S	73-76
Ab7	h0302-L0H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	F	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	42
Ab8	h0302-L1H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	P	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	42
Ab9	h0302-L2H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	P	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	42
Ab10	h0302-L0H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	F	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	43
Ab11	h0302-L1H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	F	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	43
Ab12	h0302-L2H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	Y	F	D	G	T	P	D	Y	A	L		D	Y	W	G	Q	G	T	L	V	T	V	S	S	43
cAb 0311	parental	K	S	L	T	S	E	D	S	A	V	Y	Y	C	T	R	A	L	Y	H	S	N	F	G	W	Y	F	D	S	W	G	K	G	T	T	L	T	V	S	S	13
human acceptor C		S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	E														W	G	Q	G	T	L	V	T	V	S	S	77-80
Ab13	h0311-L0H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	T	S	A	L	Y	H	S	N	F	G	W	Y	F	D	S	W	G	Q	G	T	L	V	T	V	S	S	44
Ab14	h0311-L1H1	S	S	L	R	S	E	D	T	A	V	Y	Y	C	T	R	A	L	Y	H	S	N	F	G	W	Y	F	D	S	W	G	Q	G	T	L	V	T	V	S	S	44
Ab15	h0311-L0H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	T	R	A	L	Y	H	S	N	F	G	W	Y	F	D	S	W	G	Q	G	T	L	V	T	V	S	S	45
Ab16	h0311-L1H2	S	S	L	R	S	E	D	T	A	V	Y	Y	C	T	R	A	L	Y	H	S	N	F	G	W	Y	F	D	S	W	G	Q	G	T	L	V	T	V	S	S	45

FIG. 1C

Ab ID	L/H chains	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	CDRL1											
cAb0101	parental	E	I	V	L	T	Q	S	P	A	S	L	A	V	S	L	G	Q	R	A	T	I	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
human acceptor D		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C													
Ab1	h0101-L0H0	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
Ab2	h0101-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
Ab3	h0101-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
Ab4	h0101-L1H0	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
Ab5	h0101-L1H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
Ab6	h0101-L1H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S
cAb0102	parental	D	V	V	V	T	Q	T	P	A	S	L	A	V	S	L	G	Q	R	A	T	I	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
human acceptor E		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C													
Ab7	h0102-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
Ab8	h0102-L1H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
Ab9	h0102-L2H1	E	I	V	Q	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	D	L	S	F
Ab10	h0102-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
Ab11	h0102-L1H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
Ab12	h0102-L2H2	E	I	V	V	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	E	S	V	D	N	Y	G	L	S	F
cAb 0311	parental	D	I	V	L	T	Q	S	P	A	S	L	A	V	S	L	G	Q	R	A	T	I	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S	H
human acceptor F		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	D	R	A	T	L	S	C													
Ab13	h0311-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S	H
Ab14	h0311-L1H1	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S	K
Ab15	h0311-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S	H
Ab16	h0311-L1H2	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	K	A	S	Q	S	V	D	Y	D	G	D	S	R

FIG. 2A

Ab ID	L/K chains	CDRL3																													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
cAb0301	parental	M	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
human acceptor D		M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y								G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab1	h0301-L0H0	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab2	h0301-L0H1	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab3	h0301-L0H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab4	h0301-L1H0	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab5	h0301-L1H1	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab6	h0301-L1H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
cAb0302	parental	M	F	Q	Q	K	P	G	Q	P	P	R	L	L	I	Y	K	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	R	T	D
human acceptor E		M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y								G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab7	h0302-L0H1	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab8	h0302-L1H1	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	E	T	D
Ab9	h0302-L2H1	M	F	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	K	T	D
Ab10	h0302-L0H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab11	h0302-L1H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	E	T	D
Ab12	h0302-L2H2	M	F	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	K	T	D
cAb 0311	parental	M	Y	Q	Q	K	P	G	Q	P	P	E	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	A	D
human acceptor F		M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y								G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab13	h0311-L0H1	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab14	h0311-L1H1	M	Y	Q	Q	K	P	G	Q	A	P	E	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	K	D
Ab15	h0311-L0H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	T	D
Ab16	h0311-L1H2	M	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S	G	I	P	A	R	F	S	G	S	G	S	G	A	D

FIG. 2B

Ab ID	L/H chains	FR1										CDRL1										FR2										SEQ ID NOs
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	35	36	37	38	39	40	41	42	43	44	
cAb0301	parental	F	T	L	K	I	H	F	V	E	G	S	D	A	A	T	I	Y	C	H	L	S	N	E	D	L	S	T	F	G	G	G	T	K	L	E	I	K	10
	human acceptor D	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C												P	G	G	G	T	K	V	E	I	K	81-84
Ab1	h0301-L0H0	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	E	D	L	S	T	F	G	G	G	T	K	V	E	I	K	46
Ab2	h0301-L0H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	D	D	L	S	T	P	G	G	G	T	K	V	E	I	K	46
Ab3	h0301-L0H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	E	D	L	S	T	F	G	G	G	T	K	V	E	I	K	46
Ab4	h0301-L1H0	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	E	D	L	S	T	F	G	G	G	T	K	V	E	I	K	47
Ab5	h0301-L1H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	D	D	L	S	T	P	G	G	G	T	K	V	E	I	E	47
Ab6	h0301-L1H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	H	L	S	N	K	D	L	S	T	F	G	G	G	T	K	V	E	I	K	47
cAb0302	parental	F	T	L	T	I	D	F	V	E	A	D	D	A	A	T	Y	F	C	Q	Q	S	K	E	L	P	W	T	P	G	G	G	T	R	L	E	I	K	12
	human acceptor E	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C												F	G	Q	G	T	K	V	E	I	E	85-88
Ab7	h0302-L0H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	E	L	P	W	T	F	G	Q	G	T	K	V	E	I	K	48
Ab8	h0302-L1H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	D	L	P	W	T	P	G	Q	G	T	K	V	E	I	E	49
Ab9	h0302-L2H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	K	L	P	W	T	F	G	Q	G	T	K	V	E	I	K	50
Ab10	h0302-L0H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	E	L	P	W	T	P	G	Q	G	T	K	V	E	I	K	48
Ab11	h0302-L1H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	K	L	P	W	T	F	G	Q	G	T	K	V	E	I	K	49
Ab12	h0302-L2H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	S	K	E	L	P	W	T	P	G	Q	G	T	K	V	E	I	E	50
cAb 0311	parental	F	T	L	T	I	H	F	V	E	E	E	D	A	A	T	Y	Y	C	Q	Q	G	N	E	D	P	W	T	F	G	G	G	T	R	L	E	I	K	14
	human acceptor F	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C												F	G	Q	G	T	K	V	E	I	K	89-92
Ab13	h0311-L0H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	G	N	E	D	P	W	T	F	G	Q	G	T	K	V	E	I	K	51
Ab14	h0311-L1H1	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	G	N	E	D	P	W	T	P	G	Q	G	T	K	V	E	I	K	52
Ab15	h0311-L0H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	G	N	E	D	P	W	T	F	G	Q	G	T	K	V	E	I	K	51
Ab16	h0311-L1H2	F	T	L	T	I	S	S	L	E	P	E	D	F	A	V	Y	Y	C	Q	Q	G	N	E	D	P	W	T	F	G	Q	G	T	K	V	E	I	K	52

FIG. 2C

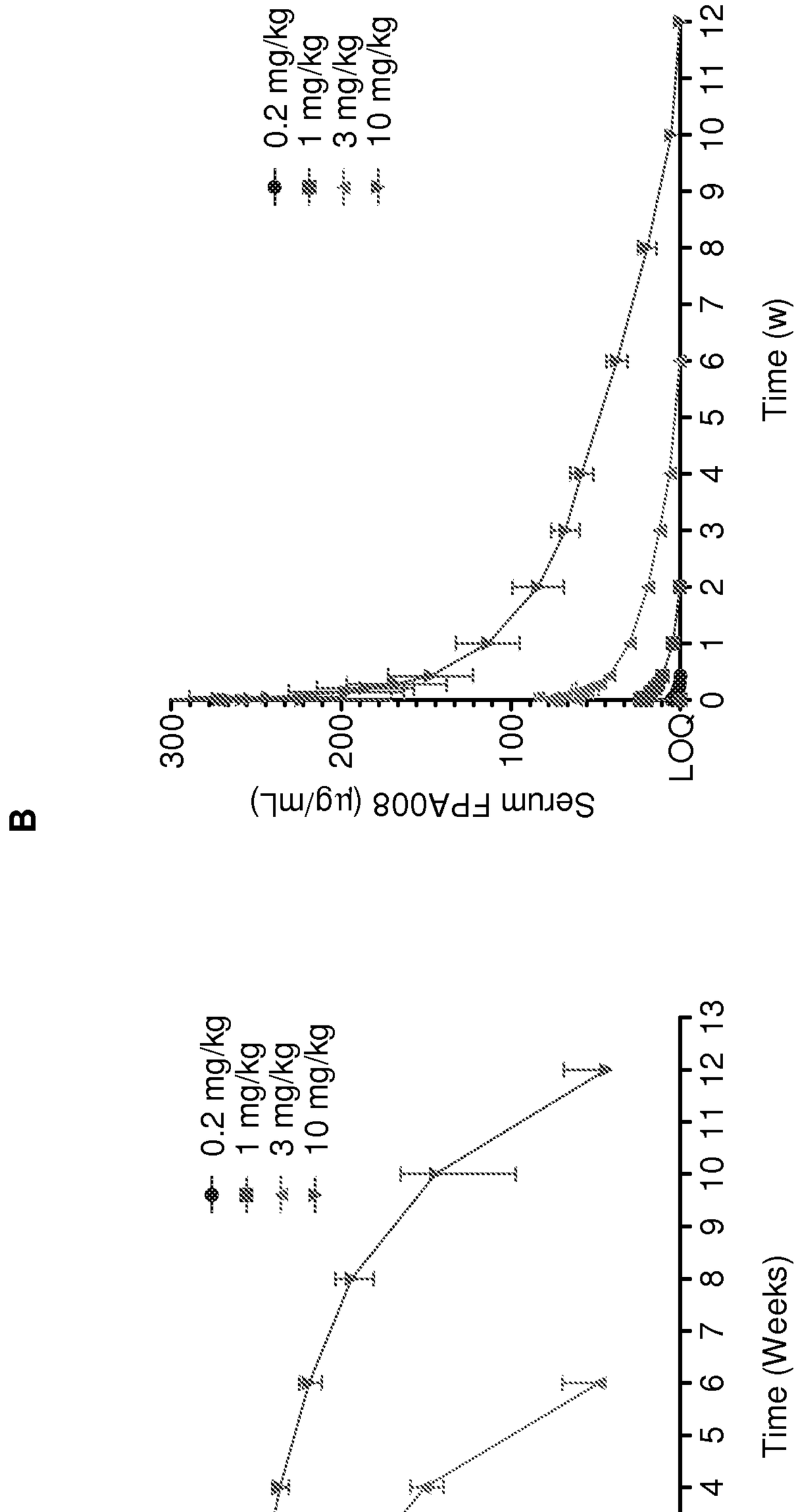

B
0.2 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
Serum FPA008 (µg/mL)
300
200
100
LOQ
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (w)
A
0.2 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
Serum FPA008 (µg/mL)
300
100
10
1
LOQ
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Time (Weeks)

FIG. 3

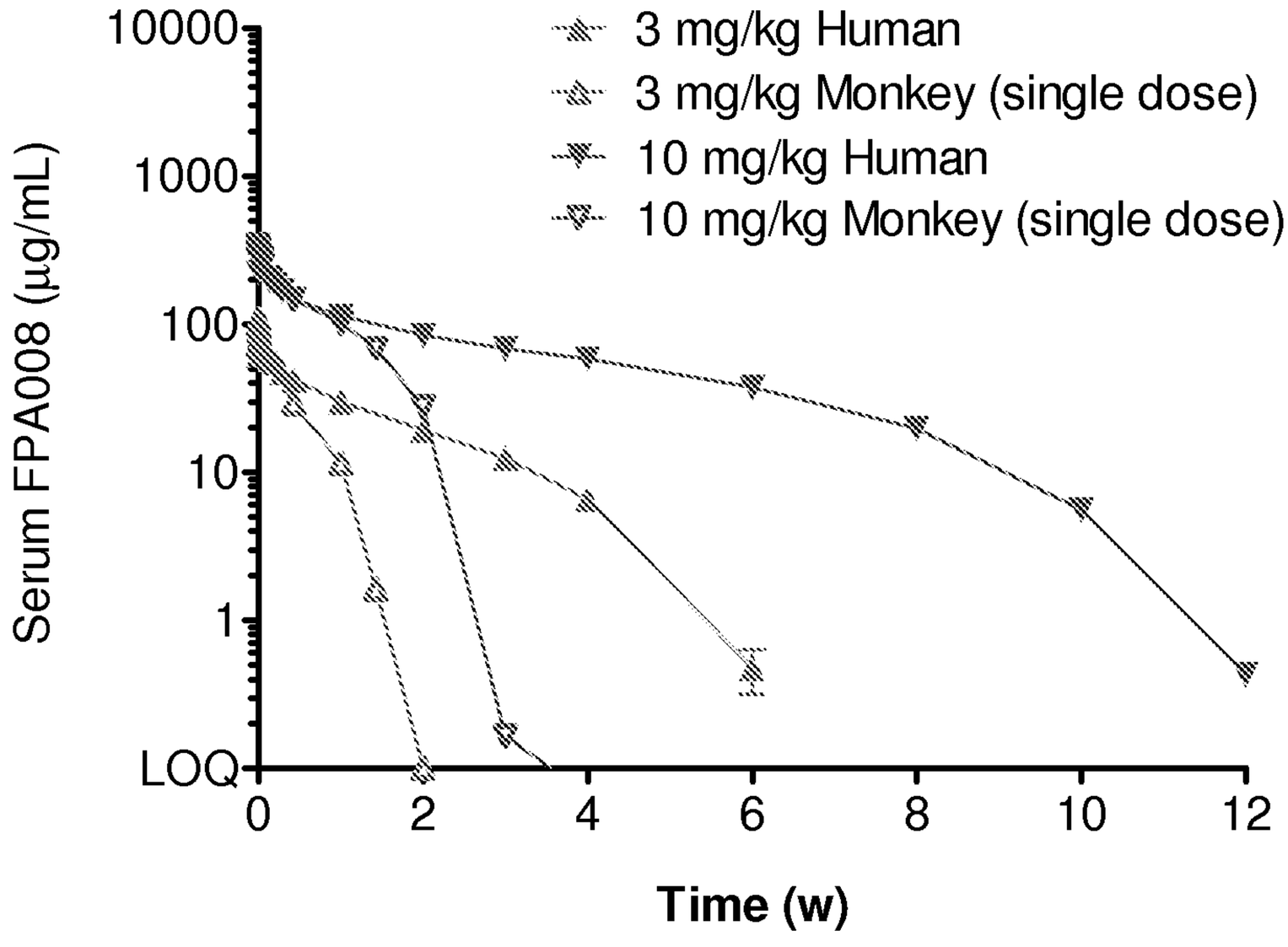

3 mg/kg Human
3 mg/kg Monkey (single dose)
10 mg/kg Human
10 mg/kg Monkey (single dose)
Serum FPA008 (µg/mL)
10000
1000
100
10
1
LOQ
0
2
4
6
8
10
12
Time (w)

FIG. 4

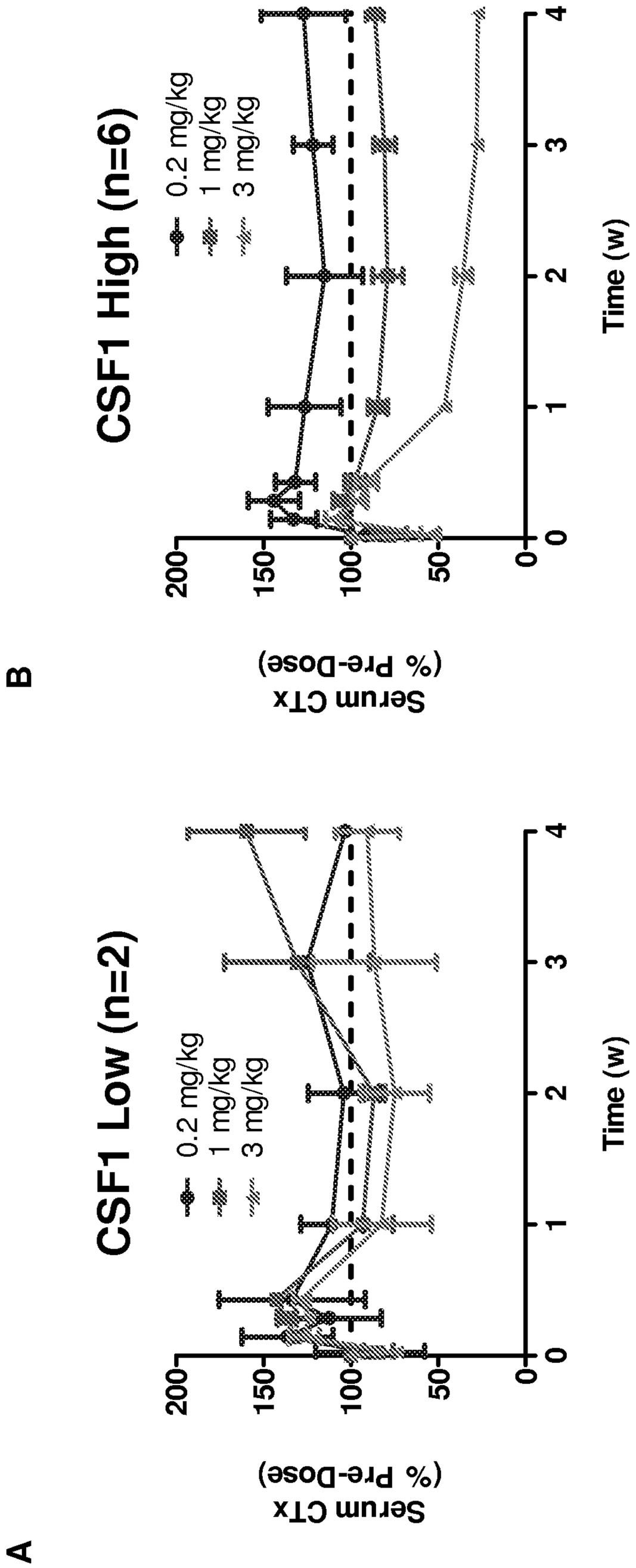

B
CSF1 High (n=6)
0.2 mg/kg
1 mg/kg
3 mg/kg
Serum CTx
(% Pre-Dose)
200
150
100
50
0
0
1
2
3
4
Time (w)
CSF1 Low (n=2)
0.2 mg/kg
1 mg/kg
3 mg/kg
Serum CTx
(% Pre-Dose)
200
150
100
50
0
0
1
2
3
4
Time (w)
A

FIG. 5

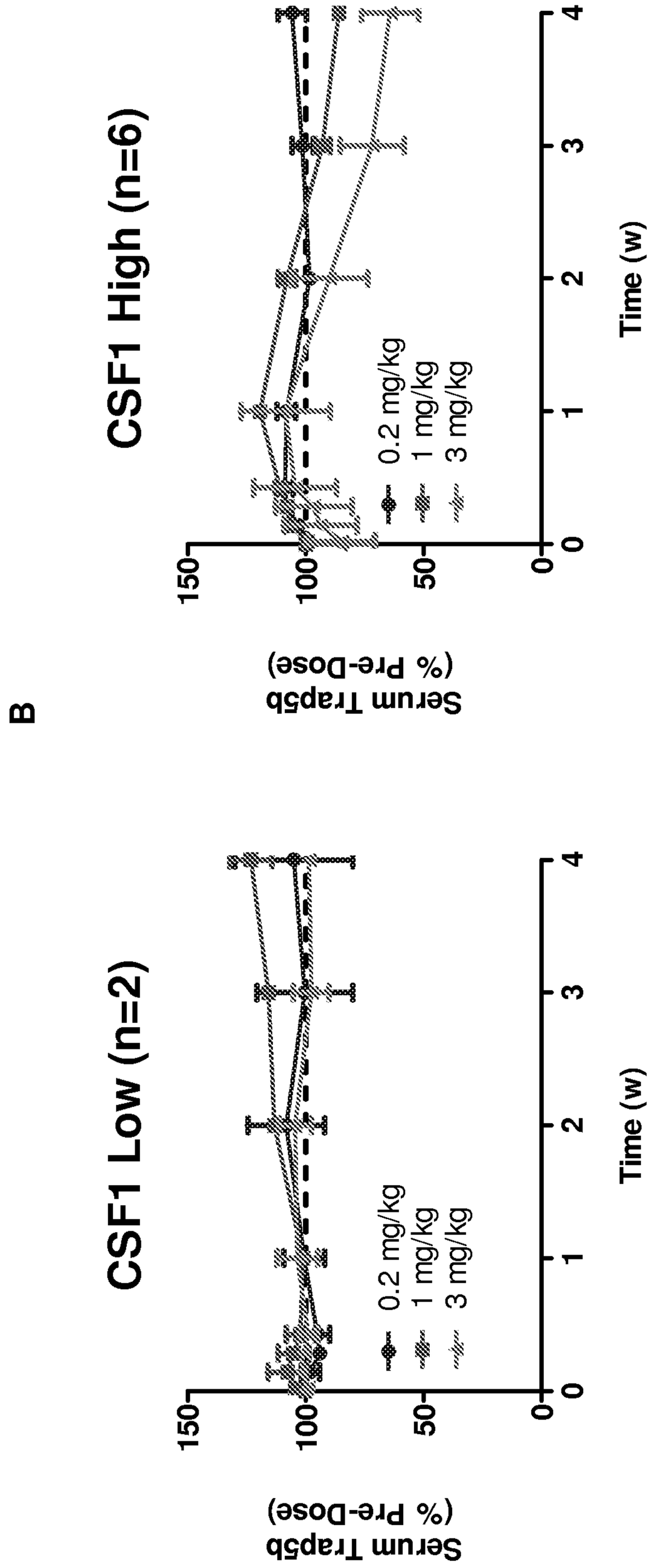
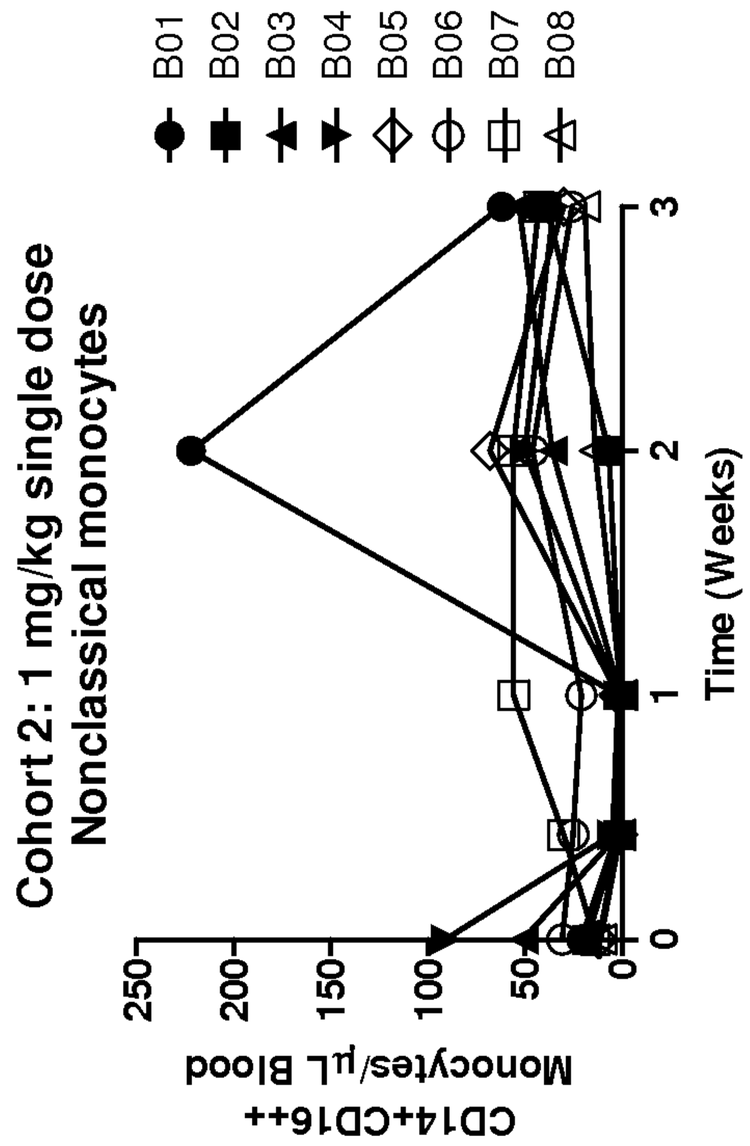
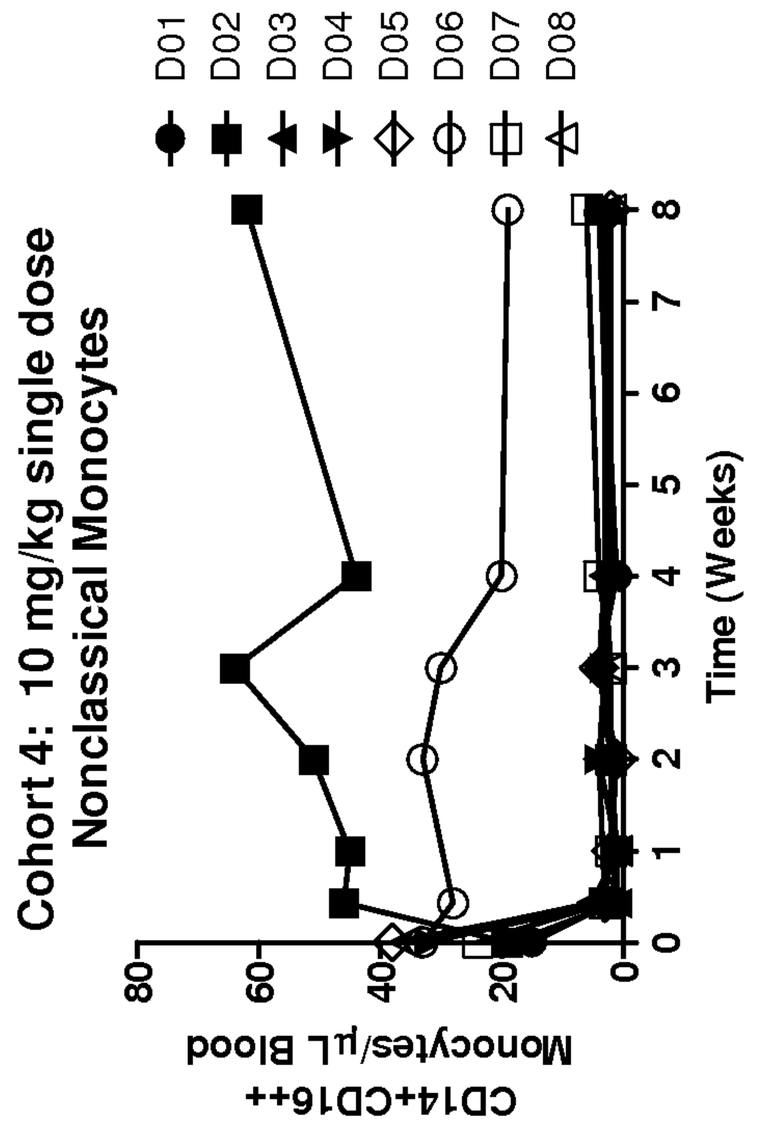
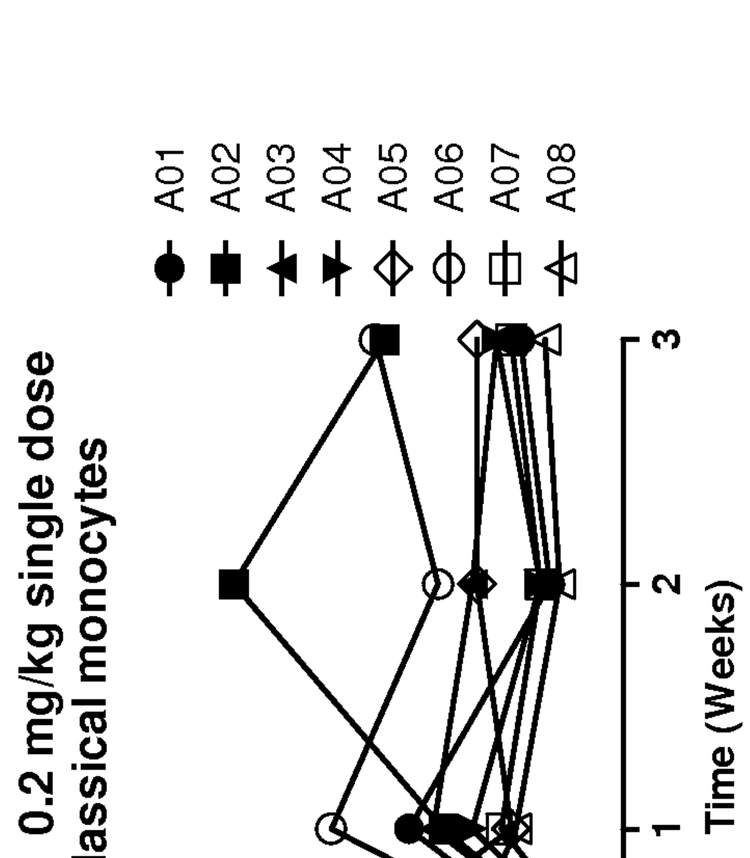

A
CSF1 Low (n=2)
Serum Trap5b (% Pre-Dose)
150
100
50
0
0
1
2
3
4
Time (w)
0.2 mg/kg
1 mg/kg
3 mg/kg
B
CSF1 High (n=6)
Serum Trap5b (% Pre-Dose)
150
100
50
0
0
1
2
3
4
Time (w)
0.2 mg/kg
1 mg/kg
3 mg/kg

FIG. 6


Cohort 2: 1 mg/kg single dose
Nonclassical monocytes
CD14+CD16++
Monocytes/μL Blood
Time (Weeks)
B01
B02
B03
B04
B05
B06
B07
B08


Cohort 4: 10 mg/kg single dose
Nonclassical Monocytes
CD14+CD16++
Monocytes/μL Blood
Time (Weeks)
D01
D02
D03
D04
D05
D06
D07
D08


Cohort 1: 0.2 mg/kg single dose
Nonclassical monocytes
CD14+CD16++
Monocytes/μL Blood
Time (Weeks)
A01
A02
A03
A04
A05
A06
A07
A08

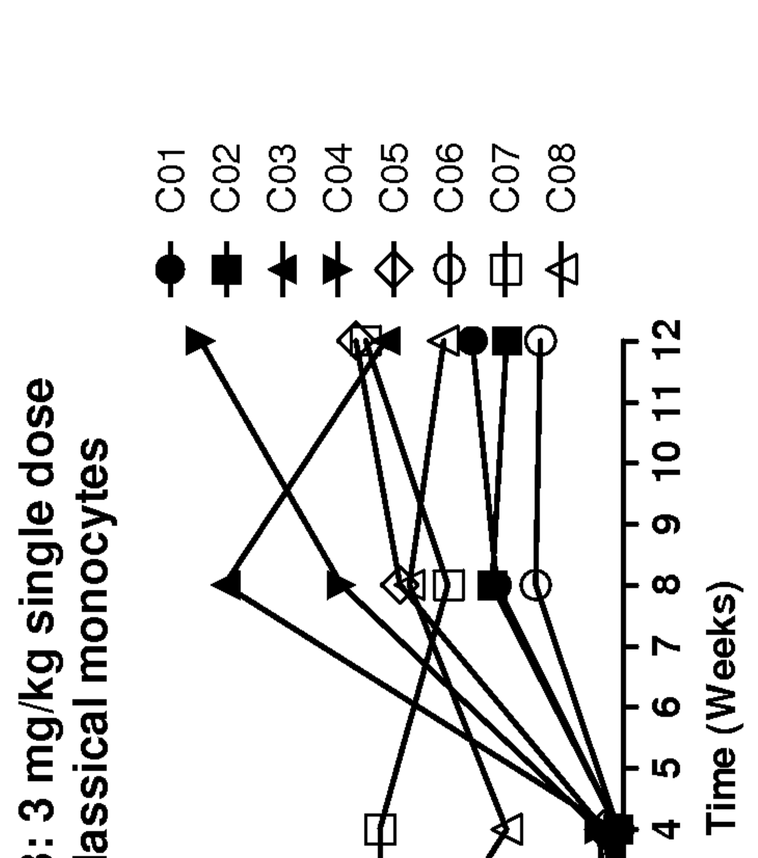

Cohort 3: 3 mg/kg single dose
Nonclassical monocytes
CD14+CD16++
Monocytes/μL Blood
Time (Weeks)
C01
C02
C03
C04
C05
C06
C07
C08

FIG. 7

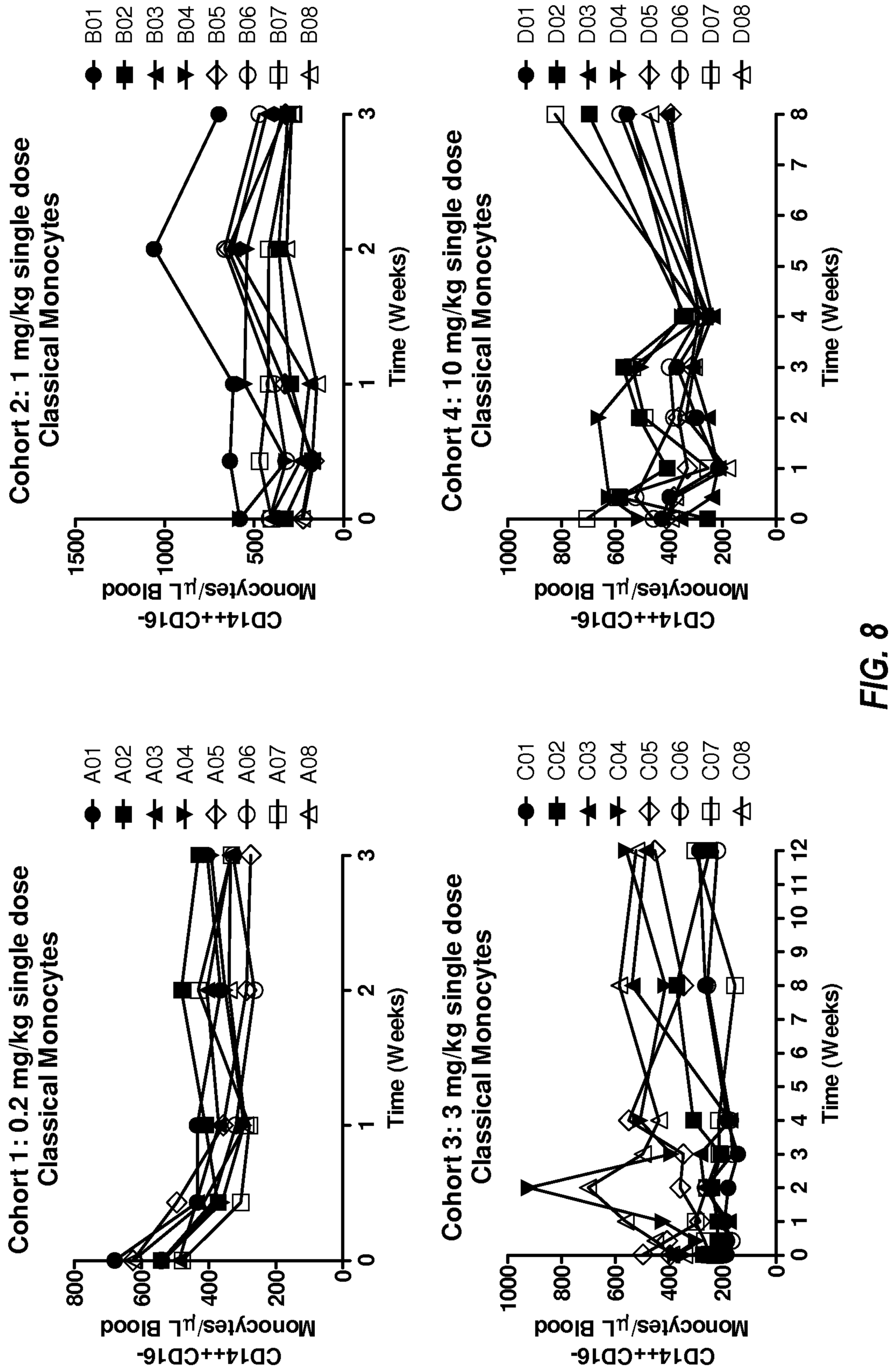

B01 B02 B03 B04 B05 B06 B07 B08
Cohort 2: 1 mg/kg single dose
Classical Monocytes
CD14++CD16- Monocytes/μL Blood
1500
1000
500
0
0
1
2
3
Time (Weeks)
D01 D02 D03 D04 D05 D06 D07 D08
Cohort 4: 10 mg/kg single dose
Classical Monocytes
CD14++CD16- Monocytes/μL Blood
1000
800
600
400
200
0
0 1 2 3 4 5 6 7 8
Time (Weeks)
A01 A02 A03 A04 A05 A06 A07 A08
Cohort 1: 0.2 mg/kg single dose
Classical Monocytes
CD14++CD16- Monocytes/μL Blood
800
600
400
200
0
0
1
2
3
Time (Weeks)
C01 C02 C03 C04 C05 C06 C07 C08
Cohort 3: 3 mg/kg single dose
Classical Monocytes
CD14++CD16- Monocytes/μL Blood
1000
800
600
400
200
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (Weeks)

FIG. 8

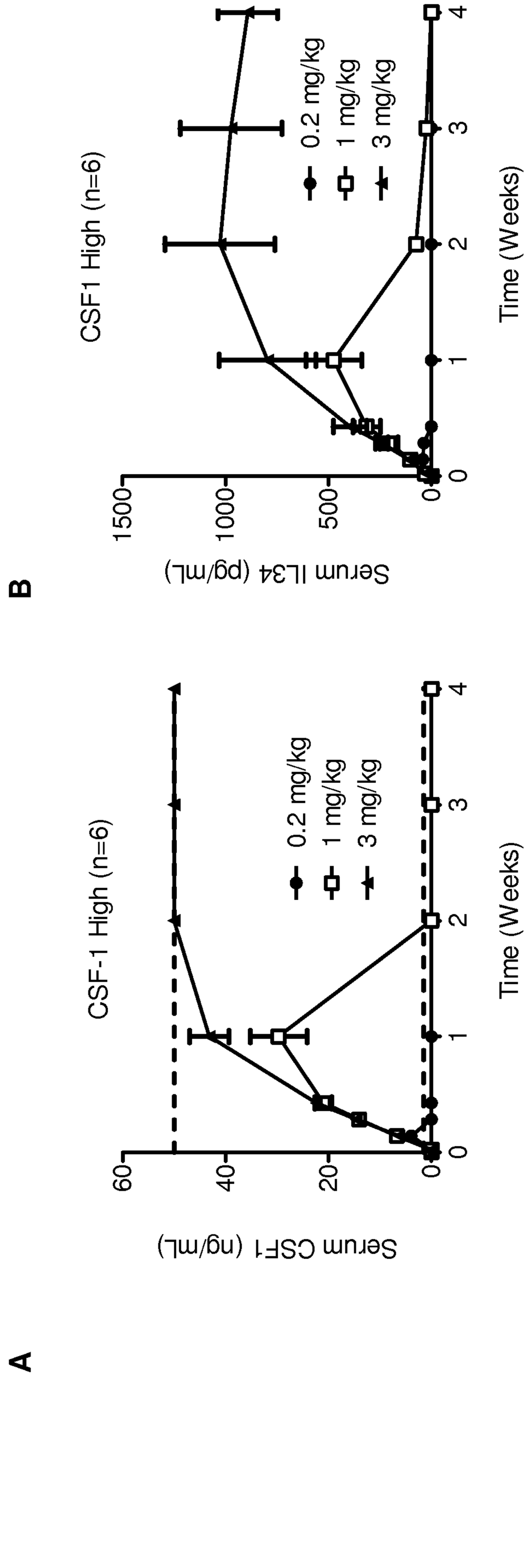

B
Serum IL34 (pg/mL)
1500
1000
500
0
CSF1 High (n=6)
0.2 mg/kg
1 mg/kg
3 mg/kg
0
1
2
3
4
Time (Weeks)
A
Serum CSF1 (ng/mL)
60
40
20
0
CSF-1 High (n=6)
0.2 mg/kg
1 mg/kg
3 mg/kg
0
1
2
3
4
Time (Weeks)

FIG. 9

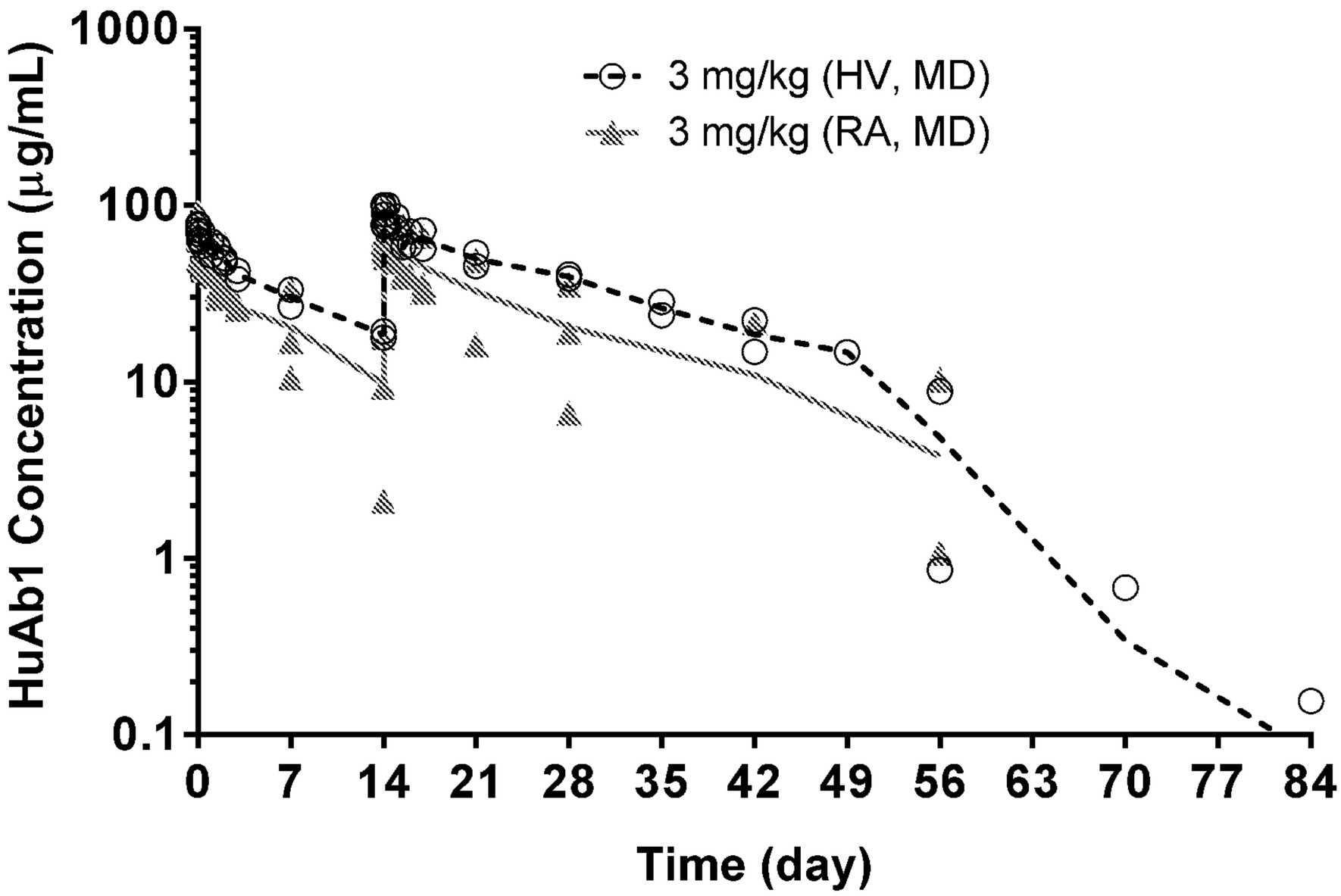

1000
100
10
1
0.1
HuAb1 Concentration (μg/mL)
3 mg/kg (HV, MD)
3 mg/kg (RA, MD)
0
7
14
21
28
35
42
49
56
63
70
77
84
Time (day)

FIG. 10

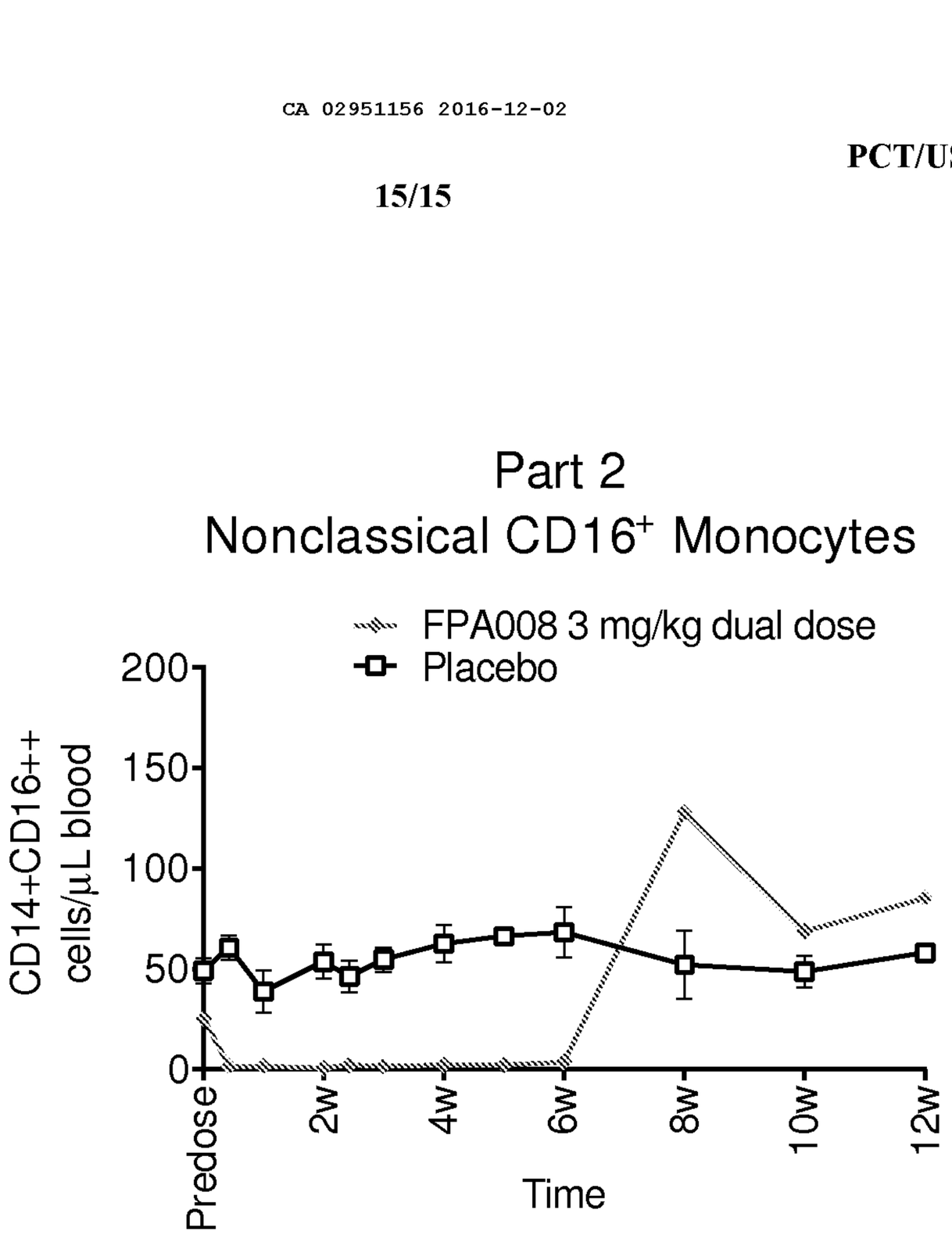

Part 2
Nonclassical CD16+ Monocytes
FPA008 3 mg/kg dual dose
Placebo
CD14+CD16++ cells/µL blood
200
150
100
50
0
Predose
2w
4w
6w
8w
10w
12w
Time

FIG. 11

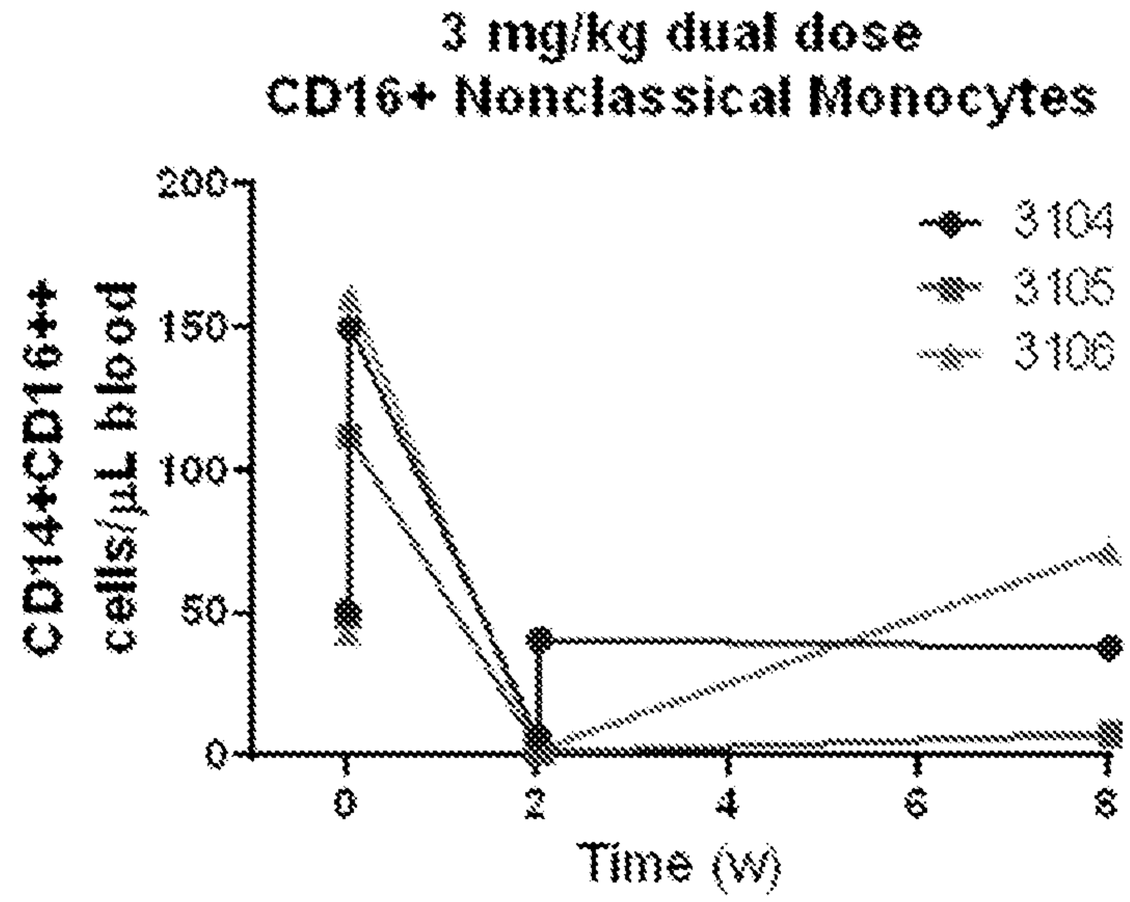

3 mg/kg dual dose
CD16+ Nonclassical Monocytes
CD14+CD16++ cells/µL blood
200
150
100
50
0
3104
3105
3106
0
2
4
6
8
Time (W)

FIG. 12