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(54) **Title:** ANTI-CSF1R ANTIBODIES FOR TREATING PVNS

(57) **Abstract:** Methods of treating pigmented villonodular synovitis (PVNS) with antibodies that bind colony stimulating factor 1 receptor (CSF1R) are provided.



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## ANTI-CSF1R ANTIBODIES FOR TREATING PVNS

### TECHNICAL FIELD

[001] Methods of treating pigmented villonodular synovitis (PVNS) with antibodies that bind colony stimulating factor 1 receptor (CSF1R) are provided.

### BACKGROUND

[002] 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 CD115) is a single-pass transmembrane receptor with an N-terminal extracellular domain (ECD) and a C-terminal intracellular domain with tyrosine kinase activity. Ligand binding of CSF1 or the interleukin 34 ligand (referred to herein as IL-34; Lin et al., *Science* 320: 807-11 (2008)) to CSF1R leads to receptor dimerization, upregulation of CSF1R protein tyrosine kinase activity, phosphorylation of CSF1R tyrosine residues, and downstream signaling events. CSF1R activation by CSF1 or IL-34 leads to the trafficking, survival, proliferation, and differentiation of monocytes and macrophages, as well as other monocytic cell lineages such as osteoclasts, dendritic cells, and microglia.

[003] Pigmented villonodular synovitis (PVNS) is a solid tumor of the synovium with features of both reactive inflammation and clonal neoplastic proliferation in which colony stimulating factor-1 (CSF1) is over expressed. A common translocation of the *CSF1* gene (1p13) to the *COL6A3* promoter (2q35) is present in approximately 60% of PVNS patients. The translocation is accompanied by CSF1 overexpression in the synovium. In addition, approximately 40% of PVNS patients have CSF1 overexpression in the absence of an identified *CSF1* translocation. The consistent presence of CSF1 overexpression in all cases of PVNS and reactive synovitis suggests both an important role for CSF1 in the spectrum of synovial pathologies and the utility of targeting the CSF1/CSF1R interaction therapeutically. *See* West et al., 2006, *Proc. Natl. Acad. Sci USA*, 103: 690-695.

[004] In PVNS, CSF1 overexpression is present in a minority of synovial cells, whereas the majority of the cellular infiltrate expresses CSF1R but not CSF1. This has been characterized as a tumor-landscaping effect with aberrant CSF1 expression in the tumor cells, leading to the abnormal accumulation of non-neoplastic cells that form a mass.

[005] Surgery is the treatment of choice for patients with localized PVNS. Recurrences occur in 8–20% of patients and are often managed by re-excision. Diffuse tenosynovial giant cell tumor (TGCT/PVNS or PVNS/dtTGCT) tends to recur more often (33–50%) and has a much more aggressive clinical course. Patients are often symptomatic and require multiple surgical

procedures during their lifetime. For patients with unresectable disease or multiple recurrences, systemic therapy using CSF1R inhibitors may help delay or avoid surgical procedures and improve functional outcomes. *See* Ravi et al., 2011, *Am. J. Pathol.*, 179: 240-247.

[006] Imatinib, a non-specific inhibitor of CSF1R, has undergone evaluation in PVNS patients. Twenty-nine patients from 12 institutions in Europe, Australia, and the United States were included. The median age was 41 years and the most common site of disease was the knee (n = 17; 59%). Two patients had metastatic disease to the lung and/or bone. Five of 27 evaluable patients had complete (n=1) or partial (n=4) responses per RECIST for an overall response rate of 19%. Twenty of 27 patients (74%) had stable disease. Symptomatic improvement was noted in 16 of 22 patients (73%) who were assessable for symptoms. Despite a high rate of symptomatic improvement and an overall favorable safety profile, 10 patients discontinued treatment for toxicity or other reasons.

[007] Alternative, less toxic treatments for PVNS are needed.

[007a] It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in Australia or any other country.

#### SUMMARY

[007b] A first aspect provides use of an antibody that binds human CSF1R in the manufacture of a medicament for reducing pain in a subject with pigmented villonodular synovitis (PVNS), wherein the antibody that binds human CSF1R is administered at a dose of 1-4 mg/kg, wherein the dose of the antibody is capable of reducing pain in PVNS subjects independently of tumor response, and wherein the antibody is selected from:

- a) an antibody comprising a heavy chain comprising SEQ ID NO: 39 and a light chain comprising SEQ ID NO: 46;
- b) an antibody comprising a heavy chain (HC) comprising an HC CDR1 comprising SEQ ID NO: 15, an HC CDR2 comprising SEQ ID NO: 16, and an HC CDR3 comprising SEQ ID NO: 17, and a light chain (LC) comprising an LC CDR1 comprising SEQ ID NO: 18, an LC CDR2 comprising SEQ ID NO: 19, and an LC CDR3 comprising SEQ ID NO: 20; and
- c) an antibody comprising a heavy chain comprising SEQ ID NO: 53 and a light chain comprising SEQ ID NO: 60.

[007c] A second aspect provides a method of reducing pain in a subject with pigmented villonodular synovitis (PVNS), comprising administering to the subject a dose of 1-4 mg/kg of an

antibody that binds human CSF1R, wherein the dose of the antibody is capable of reducing pain in PVNS subjects independently of tumor response, and wherein the antibody is selected from:

- a) an antibody comprising a heavy chain comprising SEQ ID NO: 39 and a light chain comprising SEQ ID NO: 46;
- b) an antibody comprising a heavy chain (HC) comprising an HC CDR1 comprising SEQ ID NO: 15, an HC CDR2 comprising SEQ ID NO: 16, and an HC CDR3 comprising SEQ ID NO: 17, and a light chain (LC) comprising an LC CDR1 comprising SEQ ID NO: 18, an LC CDR2 comprising SEQ ID NO: 19, and an LC CDR3 comprising SEQ ID NO: 20; and
- c) an antibody comprising a heavy chain comprising SEQ ID NO: 53 and a light chain comprising SEQ ID NO: 60.

[008] In some embodiments, methods of treating a proliferative disorder involving a synovial joint and/or tendon sheath in a subject are disclosed, comprising administering to the subject an effective amount of an antibody that binds CSF1R. In some embodiments, the proliferative disorder is selected from pigmented villonodular synovitis (PVNS), giant cell tumor of the tendon sheath (GCTTS), and tenosynovial giant cell tumor (TGCT) such as diffuse type tenosynovial giant cell tumor (dtTGCT). In some embodiments, the disorder is pigmented villonodular synovitis/diffuse type tenosynovial giant cell tumor (PVNS/dtTGCT). In some embodiments, methods of treating pigmented villonodular synovitis (PVNS) in a subject are disclosed, comprising administering to the subject an effective amount of an antibody that binds CSF1R.

[009] In some embodiments, the antibody is administered once per week, once per two weeks, once per three weeks, or once per month. In some embodiments, the antibody is administered at a dose of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 10, at least 12, at least 15, at least 16, at least 20, at least 30, at least 40, at least 50, or at least 100 mg/kg. In some embodiments, the antibody is administered at a dose of 1, 2, 3, or 4 mg/kg.

[010] In some embodiments, the PVNS tumor volume is reduced by at least 30% or at least 40% or at least 50% or at least 60% or at least 70% after administration of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at

least ten doses of the antibody that binds CSF1R. In some embodiments, the tumor volume is tumor volume in a single joint. In some embodiments, the single joint is selected from a hip joint and a knee joint. In some embodiments, the tumor volume is total tumor volume in all joints affected by PVNS. In some embodiments, the subject experiences one or more than one of the following improvements in symptoms: (a) a reduction in joint pain, (b) an increase range of motion in a joint, and (c) an increase in functional capacity of a joint, following at least one dose of the antibody.

[011] In some embodiments, prior to administering the first dose of the antibody, the subject received a first therapy selected from surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement. In some embodiments, the PVNS recurred or progressed after the first therapy. In some embodiments, the antibody is administered prior to a therapy selected from surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement. In some embodiments, the tumor is unresectable. In some embodiments, the subject has not received prior therapy with imatinib or nilotinib, while in other embodiments the subject has received prior treatment with imatinib or nilotinib. In some embodiments, the subject has not received prior treatment with a CSF1R inhibitor, while in other embodiments the subject has received prior treatment with a CSF1R inhibitor.

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

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

[014] In any of the compositions or methods described herein, the anti-CSF1R antibody HC CDR1, HC CDR2, and HC CDR3 may comprise a set of sequences selected from: (a) SEQ

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

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

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

99%, or 100% identical to SEQ ID NO: 47; (i) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 41 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; and (j) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (k) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (l) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (m) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (n) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (o) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (p) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; (q) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52; (r) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; or (s) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52.

[017] In any of the compositions or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having



the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; (b) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 21, an HC CDR2 having the sequence of SEQ ID NO: 22, and an HC CDR3 having the sequence of SEQ ID NO: 23, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 24, a LC CDR2 having the sequence of SEQ ID NO: 25, and a LC CDR3 having the sequence of SEQ ID NO: 26; or (c) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 27, an HC CDR2 having the sequence of SEQ ID NO: 28, and an HC CDR3 having the sequence of SEQ ID NO: 29, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 30, a LC CDR2 having the sequence of SEQ ID NO: 31, and a LC CDR3 having the sequence of SEQ ID NO: 32.

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

[019] In any of the compositions or methods described herein, the anti-CSF1R antibody may be a humanized antibody. In any of the compositions or methods described herein, the anti-CSF1R antibody may be any of huAb1, huAb2, huAb3, huAb4, huAb5, huAb6, huAb7, huAb8, huAb9, huAb10, huAb11, huAb12, huAb13, huAb14, huAb15, or huAb16. (See Figures 1-2.) In any of the compositions or methods described herein, the anti-CSF1R antibody may be selected from a Fab, an Fv, an scFv, a Fab', and a (Fab')<sub>2</sub>. In any of the compositions or methods described herein, the anti-CSF1R antibody may be a chimeric antibody. In any of the compositions or methods described herein, the anti-CSF1R antibody may be selected from an IgA, an IgG, and an IgD. In any of the compositions or methods described herein, the anti-

CSF1R antibody may be an IgG. In any of the methods described herein, the antibody may be an IgG1 or IgG2.

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

#### BRIEF DESCRIPTION OF THE FIGURES

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

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

[023] **FIG. 3** shows a schematic diagram of the clinical trial summarized in Examples 4 and 5 using antibody huAb1, also known as FPA008.

#### DETAILED DESCRIPTION

[024] The present invention provides methods of treating PVNS in a subject comprising administering an anti-CSF1R antibody to the subject.

[025] 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 herein by reference in their entireties for any purpose.

## Definitions

[026] 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.

[027] 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.

[028] 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.

[028a] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

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

[030] 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.

[031] 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.

[032] 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.

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

[034] 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')<sub>2</sub>. 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.

[035] 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.

[036] 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.*

[037] The term “**heavy chain constant region**” as used herein refers to a region comprising at least three heavy chain constant domains, C<sub>H</sub>1, C<sub>H</sub>2, and C<sub>H</sub>3. Nonlimiting exemplary heavy chain constant regions include  $\gamma$ ,  $\delta$ , and  $\alpha$ . Nonlimiting exemplary heavy chain constant regions also include  $\epsilon$  and  $\mu$ . Each heavy constant region corresponds to an antibody isotype. For example, an antibody comprising a  $\gamma$  constant region is an IgG antibody, an antibody comprising a  $\delta$  constant region is an IgD antibody, and an antibody comprising an  $\alpha$  constant region is an IgA antibody. Further, an antibody comprising a  $\mu$  constant region is an IgM antibody, and an antibody comprising an  $\epsilon$  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  $\gamma_1$  constant region), IgG2 (comprising a  $\gamma_2$  constant region), IgG3 (comprising a  $\gamma_3$  constant region), and IgG4 (comprising a  $\gamma_4$  constant region) antibodies; IgA antibodies include, but are not limited to, IgA1 (comprising an  $\alpha_1$  constant region) and IgA2 (comprising an  $\alpha_2$  constant region) antibodies; and IgM antibodies include, but are not limited to, IgM1 and IgM2.

[038] 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<sub>H</sub>1 and C<sub>H</sub>2), 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).

[039] 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.

[040] 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.

[041] The term “**light chain constant region**” as used herein refers to a region comprising a light chain constant domain, C<sub>L</sub>. Nonlimiting exemplary light chain constant regions include  $\lambda$  and  $\kappa$ .

[042] 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.

[043] 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.

[044] A “**humanized antibody**” as used herein refers to an antibody in which at least one amino acid in a framework region of a non-human variable region has been replaced with the corresponding amino acid from a human variable region. In some embodiments, a humanized

antibody comprises at least one human constant region or fragment thereof. In some embodiments, a humanized antibody is a Fab, an scFv, a (Fab')<sub>2</sub>, etc.

[045] 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.

[046] 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.

[047] 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.

[048] 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.

[049] 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.

[050] 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.

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

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

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

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

[054] 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.

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

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

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

[058] The term “**pigmented villonodular synovitis**” or “**PVNS**” as used herein refers to a condition in which the synovium thickens and overgrows in one or more joints. Localized PVNS typically involves the tendons that support the joint and/or occurs in one area of the joint, while diffuse PVNS is more widespread and may involve the entire joint. Diffuse PVNS typically affects large joints, such as the hip and/or knee joints, while localized (or nodular) PVNS typically occurs in smaller joints such as the hands and feet. The benign growth (sometimes referred to as a benign tumor) may progress, leading to damage to adjacent bone

and/or arthritis. The methods of treating PVNS disclosed in the present application can also be used in treating other proliferative disorders that involve synovial joints and tendon sheaths, such as giant cell tumor of the tendon sheath (GCTTS) and tenosynovial giant cell tumor (TGCT) such as diffuse type tenosynovial giant cell tumor (dtTGCT).

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

[060] “**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.

[061] 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 antibody or antibodies to elicit a desired response in the individual. A therapeutically effective amount encompasses an amount in which any toxic or detrimental effects of the antibody or antibodies are outweighed by the therapeutically beneficial effects. In some embodiments, the expression “effective amount” refers to an amount of the antibody that is effective for treating PVNS.

[062] 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.

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

[064] 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**

[065] 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

[066] 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.

[067] 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.

[068] 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.

[069] 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

	<b>Heavy chain</b>			<b>Light chain</b>		
<b>Ab</b>	<b>CDR1 SEQ ID</b>	<b>CDR2 SEQ ID</b>	<b>CDR3 SEQ ID</b>	<b>CDR1 SEQ ID</b>	<b>CDR2 SEQ ID</b>	<b>CDR3 SEQ ID</b>
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*

[070] 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.

[071] 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.

[072] 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.

[073] 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*

[074] 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  $\kappa$  and  $\lambda$ . 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  $\kappa$  light chain.

[075] 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 tumors, 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.

[076] 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 PVNS do not have effector function. Accordingly, in some embodiments, an anti-CSF1R antibody that lacks significant effector function is used in treatment of PVNS. In some embodiments, an anti-CSF1R antibody for treatment of PVNS comprises a human IgG4 or IgG2 heavy chain constant region. In some embodiments, an IgG4 constant region comprises an S241P mutation.

[077] 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.

[078] 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.

[079] 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.

[080] 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.

[081] 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.

[082] 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

[083] 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).

[084] 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.

[085] 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.

[086] 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*

[087] 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.

[088] 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.

[089] 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*

[090] 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  $\kappa$  and  $\lambda$ . 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  $\kappa$  light chain.

[091] 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

[092] 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.

[093] 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.

[094] 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.

[095] 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  $\kappa$  and  $\lambda$ . 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  $\kappa$  light chain.

[096] 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

[097] 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.

[098] 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.

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

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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*

[0105] 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.

[0106] 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.

[0107] 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*

[0108] 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  $\kappa$  and  $\lambda$ . 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  $\kappa$  light chain.

[0109] 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

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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  $\kappa$  and a human  $\lambda$  light chain constant region.

#### Exemplary Additional CSF1R Binding Molecules

[0129] 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

[0130] 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.

[0131] 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.

[0132] In some embodiments, an anti-CSF1R antibody blocks ligand binding to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of CSF1 to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of IL-34 to CSF1R. In some embodiments, an anti-CSF1R antibody blocks binding of both CSF1 and IL-34 to CSF1R. In some embodiments, an antibody that blocks ligand binding binds to the extracellular domain of CSF1R. In some embodiments, an antibody blocks ligand binding to CSF1R when it reduces the amount of detectable binding of a ligand to CSF1R by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 7, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of detectable binding of a ligand to CSF1R by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the antibody is said to block ligand binding by at least 50%, at least 60%, at least 70%, etc.

[0133] In some embodiments, an anti-CSF1R antibody inhibits ligand-induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits CSF1-induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits IL-34-induced CSF1R phosphorylation. In some embodiments, an anti-CSF1R antibody inhibits both CSF1-induced and IL-34-induced CSF1R phosphorylation. In some embodiments, an antibody is considered to “inhibit ligand-induced CSF1R phosphorylation” when it reduces the amount of detectable ligand-induced CSF1R phosphorylation by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 6, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of detectable ligand-induced CSF1R phosphorylation by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the antibody is said to inhibit ligand-induced CSF1R phosphorylation by at least at least 50%, at least 60%, at least 70%, etc.

[0134] In some embodiments, an antibody inhibits monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34. In some embodiments, an antibody is considered to “inhibit monocyte proliferation and/or survival responses” when it reduces the amount of monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34 by at least 50%, using the assay described, *e.g.*, U.S. Patent No. 8,206,715 B2, Example 10, which is incorporated herein by reference for any purpose. In some embodiments, an antibody reduces the amount of monocyte proliferation and/or survival responses in the presence of CSF1 and/or IL-34 by at least 60%, at least 70%, at least 80%, or at least 90%. In some such embodiments, the

antibody is said to inhibit monocyte proliferation and/or survival responses by at least at least 50%, at least 60%, at least 70%, etc.

#### Exemplary Antibody Conjugates

[0135] In some embodiments, an antibody is conjugated to a label and/or a cytotoxic agent. As used herein, a label is a moiety that facilitates detection of the antibody and/or facilitates detection of a molecule to which the antibody binds. Nonlimiting exemplary labels include, but are not limited to, radioisotopes, fluorescent groups, enzymatic groups, chemiluminescent groups, biotin, epitope tags, metal-binding tags, etc. One skilled in the art can select a suitable label according to the intended application.

[0136] 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.

[0137] 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 Products (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**

[0138] 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.

[0139] Certain exemplary leader sequence sequences are described, e.g., in the online Leader sequence Database maintained by the Department of Biochemistry, National University of Singapore. *See* Choo et al., *BMC Bioinformatics*, 6: 249 (2005); and PCT Publication No. WO 2006/081430.

### **Nucleic Acid Molecules Encoding Antibodies**

[0140] Nucleic acid molecules comprising polynucleotides that encode one or more chains of an antibody are provided. In some embodiments, a nucleic acid molecule comprises a polynucleotide that encodes a heavy chain or a light chain of an antibody. In some embodiments, a nucleic acid molecule comprises both a polynucleotide that encodes a heavy chain and a polynucleotide that encodes a light chain, of an antibody. In some embodiments, a first nucleic acid molecule comprises a first polynucleotide that encodes a heavy chain and a second nucleic acid molecule comprises a second polynucleotide that encodes a light chain.

[0141] 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.

[0142] In some embodiments, a polynucleotide encoding a heavy chain or light chain of an antibody comprises a nucleotide sequence that encodes a leader sequence, which, when translated, is located at the N terminus of the heavy chain or light chain. As discussed above, the leader sequence may be the native heavy or light chain leader sequence, or may be another heterologous leader sequence.

[0143] Nucleic acid molecules may be constructed using recombinant DNA techniques conventional in the art. In some embodiments, a nucleic acid molecule is an expression vector that is suitable for expression in a selected host cell.

### **Antibody Expression and Production**

#### **Vectors**

[0144] Vectors comprising polynucleotides that encode antibody heavy chains and/or light chains are provided. Vectors comprising polynucleotides that encode antibody heavy chains and/or light chains are also provided. Such vectors include, but are not limited to, DNA vectors, phage vectors, viral vectors, retroviral vectors, etc. In some embodiments, a vector comprises a

first polynucleotide sequence encoding a heavy chain and a second polynucleotide sequence encoding a light chain. In some embodiments, the heavy chain and light chain are expressed from the vector as two separate polypeptides. In some embodiments, the heavy chain and light chain are expressed as part of a single polypeptide, such as, for example, when the antibody is an scFv.

[0145] 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.

[0146] 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).

[0147] In some embodiments, a vector is chosen for *in vivo* expression of antibody heavy chains and/or antibody light chains in animals, including humans. In some such embodiments, expression of the polypeptide is under the control of a promoter that functions in a tissue-specific manner. For example, liver-specific promoters are described, e.g., in PCT Publication No. WO 2006/076288.

### **Host Cells**

[0148] In various embodiments, antibody heavy chains and/or light chains may be expressed in prokaryotic cells, such as bacterial cells; or in eukaryotic cells, such as fungal cells (such as yeast), plant cells, insect cells, and mammalian cells. Such expression may be carried out, for example, according to procedures known in the art. Exemplary eukaryotic cells that may be used to express polypeptides include, but are not limited to, COS cells, including COS 7 cells; 293 cells, including 293-6E cells; CHO cells, including CHO-S and DG44 cells; PER.C6® cells (Crucell); and NSO cells. In some embodiments, antibody heavy chains and/or light chains may be expressed in yeast. See, e.g., U.S. Publication No. US 2006/0270045 A1. In some embodiments, a particular eukaryotic host cell is selected based on its ability to make desired post-translational modifications to the antibody heavy chains and/or light chains. For example, in some embodiments, CHO cells produce polypeptides that have a higher level of sialylation than the same polypeptide produced in 293 cells.

[0149] 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*, 3<sup>rd</sup> 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.

[0150] In some embodiments, one or more polypeptides may be produced *in vivo* in an animal that has been engineered or transfected with one or more nucleic acid molecules encoding the polypeptides, according to any suitable method.

#### **Purification of Antibodies**

[0151] Antibodies may be purified by any suitable method. Such methods include, but are not limited to, the use of affinity matrices or hydrophobic interaction chromatography. Suitable affinity ligands include the antigen and ligands that bind antibody constant regions. For example, a Protein A, Protein G, Protein A/G, or an antibody affinity column may be used to bind the constant region and to purify an antibody. Hydrophobic interactive chromatography, for example, a butyl or phenyl column, may also be suitable for purifying some polypeptides. Many methods of purifying polypeptides are known in the art.

#### **Cell-free Production of Antibodies**

[0152] In some embodiments, an antibody is produced in a cell-free system. Nonlimiting exemplary cell-free systems are described, e.g., in Sitaraman et al., *Methods Mol. Biol.* 498: 229-44 (2009); Spirin, *Trends Biotechnol.* 22: 538-45 (2004); Endo et al., *Biotechnol. Adv.* 21: 695-713 (2003).

### **Therapeutic Compositions and Methods**

#### **Methods of Treating Pigmented Villonodular Synovitis (PVNS) and Other Conditions**

[0153] In some embodiments, methods for treating PVNS are provided, comprising administering an effective amount of an anti-CSF1R antibody. In some embodiments, the PVNS is diffuse PVNS. In some such embodiments, the PVNS is in a hip and/or knee joint. In some such embodiments, the PVNS is in a hand or foot joint. In some embodiments, methods of treating other proliferative disorders that involve synovial joints and tendon sheaths, such as giant cell tumor of the tendon sheath (GCTTS) and, tenosynovial giant cell tumor (TGCT) are provided, comprising administering an effective amount of an anti-CSF1R antibody. In some

embodiments, the antibody is administered at a dose described herein, and for example, at a dose of at least 1, at least 2, at least 4, at least 8, at least 10, at least 12, at least 16, at least 20, at least 30, at least 40, at least 50, or at least 100 mg/kg. In some embodiments, the antibody is administered at a dose described herein, and for example, at a dose of 1 mg/kg, 2 mg/kg, or 4 mg/kg. In some embodiments, the antibody is administered with a frequency described herein, and for example, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, or once every ten weeks. 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 ten, at least 11, or at least 12 doses may be administered during a course of antibody treatment.

[0154] In some embodiments, treatment of PVNS with an antibody that binds CSF1R results in a reduction of tumor volume score of at least 30% or at least 40% or at least 50% or at least 60% or at least 70% after at least two or at least three or at least four doses of the antibody. Tumor volume score may be measured, for example, using MRI to assess the tumor volume in an affected joint. In some embodiments, the tumor volume score is measured in one affected joint. In some embodiments, the tumor volume score is measured as the total tumor volume in one or more affected joints.

[0155] The anti-CSF1R antibodies may be administered prior to, concurrently with, and/or following at least one additional therapy. Nonlimiting exemplary additional therapies include surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement.

[0156] In some embodiments, the anti-CSF1R antibody blocks binding of CSF1 and/or IL-34 to CSF1R and/or inhibits CSF1R phosphorylation induced by CSF1 and/or IL-34. In some embodiments, the anti-CSF1R antibody blocks binding of CSF1 and IL-34 to CSF1R and/or inhibits CSF1R phosphorylation induced by CSF1 and/or IL-34. In some embodiments, the anti-CSF1R antibody comprises the CDRs of, or the variable regions of, an antibody selected from huAb1 to huAb16, described herein. In some embodiments, the anti-CSF1R antibody comprises the CDRs of, or the variable regions of, huAb1.

#### **Routes of Administration and Carriers**

[0157] In various embodiments, antibodies may be administered *in vivo* by various routes, including, but not limited to, oral, intra-arterial, parenteral, intranasal, intramuscular, intracardiac, intraventricular, intratracheal, buccal, rectal, intraperitoneal, intradermal, topical, transdermal, and intrathecal, or otherwise by implantation or inhalation. The subject

compositions may be formulated into preparations in solid, semi-solid, liquid, or gaseous forms; including, but not limited to, tablets, capsules, powders, granules, ointments, solutions, suppositories, enemas, injections, inhalants, and aerosols. A nucleic acid molecule encoding an antibody may be coated onto gold microparticles and delivered intradermally by a particle bombardment device, or “gene gun,” as described in the literature (see, e.g., Tang et al., *Nature* 356:152-154 (1992)). The appropriate formulation and route of administration may be selected according to the intended application.

[0158] In various embodiments, compositions comprising antibodies are provided in formulations with a wide variety of pharmaceutically acceptable carriers (see, e.g., Gennaro, *Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus*, 20<sup>th</sup> ed. (2003); Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7<sup>th</sup> ed., Lippencott Williams and Wilkins (2004); Kibbe et al., *Handbook of Pharmaceutical Excipients*, 3<sup>rd</sup> 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.

[0159] In various embodiments, compositions comprising antibodies may be formulated for injection, including subcutaneous administration, by dissolving, suspending, or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids, or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. In various embodiments, the compositions may be formulated for inhalation, for example, using pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen, and the like. The compositions may also be formulated, in various embodiments, into sustained release microcapsules, such as with biodegradable or non-biodegradable polymers. A non-limiting exemplary biodegradable formulation includes poly lactic acid-glycolic acid polymer. A non-limiting exemplary non-biodegradable formulation includes a polyglycerin fatty acid ester. Certain methods of making such formulations are described, for example, in EP 1 125 584 A1.

[0160] Pharmaceutical packs and kits comprising one or more containers, each containing one or more doses of an antibody or combination of antibodies are also provided. In some



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

[0161] Pharmaceutical compositions are administered in an amount effective for treatment or prophylaxis of the specific indication. The therapeutically effective amount is typically dependent on the weight of the subject being treated, his or her physical or health condition, the extensiveness of the condition to be treated, or the age of the subject being treated. In general, antibodies may be administered in an amount in the range of about 10 µg/kg body weight to about 100 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 50 µg/kg body weight to about 5 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 100 µg/kg body weight to about 10 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 100 µg/kg body weight to about 20 mg/kg body weight per dose. In some embodiments, antibodies may be administered in an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose. In some embodiments, antibodies may be administered at a dose of at least 1, at least 2, at least 4, at least 8, at least 10, at least 12, at least 16, at least 20, at least 30, at least 40, at least 50, or at least 100 mg/kg. In some embodiments, antibodies may be administered at a dose of 1 mg/kg, 2 mg/kg, or 4 mg/kg.

[0162] The antibody compositions may be administered as needed to subjects. Determination of the frequency of administration may be made by persons skilled in the art, such as an attending physician based on considerations of the condition being treated, age of the subject being treated, severity of the condition being treated, general state of health of the subject being treated and the like. In some embodiments, an effective dose of an antibody is administered to a subject one or more times. In various embodiments, an effective dose of an antibody is

administered to the subject once a month, less than once a month, such as, for example, every two months or every three months. In other embodiments, an effective dose of an antibody is administered more than once a month, such as, for example, every three weeks, every two weeks or every week. In some embodiments, an effective dose of an antibody is administered once per 1, 2, 3, 4, or 5 weeks. In some embodiments, an effective dose of an antibody is administered twice or three times per week. An effective dose of an antibody is administered to the subject at least once. In some embodiments, the effective dose of an antibody may be administered multiple times, including for periods of at least a month, at least six months, or at least a year.

### **Combination Therapy**

[0163] 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, radiation therapy, joint replacement, and/or another therapeutic agent. In some embodiments, the PVNS has recurred or progressed following a therapy selected from surgery, radiation therapy, joint replacement, administration of another therapeutic agent, or a combination thereof.

[0164] In some embodiments, the anti-CSF1R antibody is administered before, concurrently, or after at least one treatment selected from surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement.

### **EXAMPLES**

[0165] 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**

[0166] Various humanized anti-CSF1R antibodies were developed previously. *See, e.g.*, PCT Publication No. WO 2011/140249.

[0167] 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.

[0168] Table 8, below, shows the full sequences for the humanized heavy chains and humanized light chains of antibodies huAb1 to huAb16. The name and SEQ ID Nos of the humanized heavy chain and humanized light chain of each of those antibodies is shown in Table 3.

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

Humanized antibody	Humanized HC	SEQ ID NO	Humanized LC	SEQ ID NO
huAb1	h0301-H0	53	h0301-L0	60
huAb2	h0301-H1	54	h0301-L0	60
huAb3	h0301-H2	55	h0301-L0	60
huAb4	h0301-H0	53	h0301-L1	61
huAb5	h0301-H1	54	h0301-L1	61
huAb6	h0301-H2	55	h0301-L1	61
huAb7	h0302-H1	56	h0302-L0	62
huAb8	h0302-H1	56	h0302-L1	63
huAb9	h0302-H1	56	h0302-L2	64
huAb10	h0302-H2	57	h0302-L0	62
huAb11	h0302-H2	57	h0302-L1	63
huAb12	h0302-H2	57	h0302-L2	64
huAb13	h0311-H1	58	h0311-L0	65
huAb14	h0311-H1	58	h0311-L1	66
huAb15	h0311-H2	59	h0311-L0	65
huAb16	h0311-H2	59	h0311-L1	66

[0169] The 16 humanized antibodies were tested for binding to human, cynomolgus monkey, and mouse CSF1R ECD, as described previously. *See, e.g.*, PCT Publication No. WO 2011/140249. The antibodies were found to bind to both human and cynomolgus monkey CSF1R ECD, but not to mouse CSF1R ECD. The humanized antibodies were also found to block binding of CSF1 and IL-34 to both human and cynomolgus CSF1R and to inhibit CSF1-induced

and IL-34-induced phosphorylation of human CSF1R expressed in CHO cells. *See, e.g.*, PCT Publication No. WO 2011/140249.

[0170] 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	$3.22 \times 10^6$	$1.11 \times 10^{-03}$	0.35
huAb 0301-L0H1	$3.56 \times 10^6$	$1.22 \times 10^{-03}$	0.34
huAb 0301-L0H2	$2.32 \times 10^6$	$6.60 \times 10^{-04}$	0.28
huAb 0301-L1H0	$3.29 \times 10^6$	$1.15 \times 10^{-03}$	0.35
huAb 0301-L1H1	$2.87 \times 10^6$	$9.21 \times 10^{-04}$	0.32
huAb 0301-L1H2	$2.95 \times 10^6$	$7.42 \times 10^{-04}$	0.25
huAb 0302-L0H1	$3.54 \times 10^6$	$3.69 \times 10^{-03}$	1.04
huAb 0302-L1H1	$3.47 \times 10^6$	$4.04 \times 10^{-03}$	1.17
huAb 0302-L2H1	$1.60 \times 10^6$	$9.14 \times 10^{-04}$	0.57
huAb 0302-L0H2	$3.40 \times 10^6$	$1.79 \times 10^{-03}$	0.53
huAb 0302-L1H2	$2.71 \times 10^6$	$1.53 \times 10^{-03}$	0.56
huAb 0302-L2H2	$1.84 \times 10^6$	$8.40 \times 10^{-04}$	0.46
huAb 0311-L0H1	$1.22 \times 10^6$	$5.40 \times 10^{-04}$	0.44
huAb 0311-L1H1	$1.32 \times 10^6$	$6.64 \times 10^{-04}$	0.50
huAb 0311-L0H2	$1.34 \times 10^6$	$4.73 \times 10^{-04}$	0.35
huAb 0311-L1H2	$1.51 \times 10^6$	$6.09 \times 10^{-04}$	0.40

**Example 2: Pharmacokinetics and pharmacodynamics of anti-CSF1R antibody**

[0171] The pharmacokinetics (PK) and toxicokinetics (TK) 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.

[0172] The single and repeat-dose PK of a chimeric surrogate antibody was studied in SCID mice to help elucidate the mechanism of huAb1 clearance and better understand the mechanism of the prolonged exposure observed in the monkeys in the recovery group of the GLP toxicology study relative to the monkeys in the single-dose PK study.

[0173] 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.

[0174] The rapid decrease may be due in part to huAb1 antibodies in addition to target-mediated clearance. However, a single dose administration of a chimeric surrogate antibody in SCID mice, which lack the ability to mount an ADA response, showed a similar profile and supported the contribution of target-mediated clearance to total clearance of huAb1, especially at low doses.

[0175] The observed maximum plasma concentration ( $C_{max}$ ) increased proportionally to dose at all dose levels tested, while area under plasma concentration-time curve from time zero extrapolated to infinity ( $AUC_{\infty}$ ) 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. The half-life ( $t_{1/2}$ ) prior to the accelerated terminal decline ranged from 1–12 days and the total clearance ranged from 0.14–1.25 mL/h/kg. In summary, huAb1 has saturable nonlinear clearance in cynomolgus monkeys.

[0176] The effects of huAb1 on various pharmacodynamics (PD) markers known to be modulated *in vivo* by CSF1R inhibition were examined in 3 cynomolgus monkey studies. These markers include CSF1, CD16<sup>+</sup> monocytes, and bone resorption markers.

[0177] CSF1 levels: Plasma or serum levels of CSF1 are a measure of huAb1 target engagement. CSF1 is cleared from circulation under normal physiological conditions by macrophages (primarily splenic macrophages and liver Kupffer cells) via CSF1R-mediated endocytosis and intracellular degradation. Steady state levels of CSF1 in normal individuals are < 1 µg/mL. huAb1 binds to and prevents CSF1 being cleared by CSF1R, resulting in a large, rapid increase in circulating CSF1 concentration, after which CSF1 levels reach a new steady state of approximately 10 µg/mL. In the pilot toxicology study, plasma CSF1 and plasma huAb1 samples were obtained at trough (7 days post-dose) following once-a-week dosing for 4 weeks in cynomolgus monkeys. The data show that a minimum biological effect occurred at 5 µg/mL huAb1, and a half-maximal response ( $EC_{50}$ ) was 8 µg/mL huAb1.

[0178] CD16<sup>+</sup> monocytes: In the GLP toxicology study, CD16<sup>+</sup> monocytes were reduced in monkeys receiving 4 weekly IV infusions of 50 mg/kg or 150 mg/kg huAb1, consistent with CSF1R pathways supporting the growth and maintenance of this monocyte subpopulation *in vivo*. CD16<sup>+</sup> monocyte reduction occurred within 1 week of dosing and was sustained throughout the dosing and exposure periods. The CD16<sup>+</sup> monocytes were restored to normal baseline levels after huAb1 cleared. The CD16<sup>-</sup> monocyte subpopulation remained unaffected by administration of huAb1.

[0179] Bone resorption markers: Plasma and urine markers of bone resorption were evaluated in monkeys following repeat dosing with huAb1. Urine NTx, plasma CTx, and TRAP5b were all decreased. The effects were reversible upon clearance of huAb1.

**Example 3: Treatment of PVNS with an anti-CSF1R antibody**

[0180] huAb1 antibody (an antibody comprising heavy chain and light chain variable regions of SEQ ID NOs: 53 and 60, respectively) is administered to patients with PVNS at increasing dosages ranging from 1mg/kg to 4 mg/kg. huAb1 is administered every 2 weeks. Patients are treated in 28-day cycles, with each cycle consisting of 2 doses on day 1 and day 15. After completing a cycle a patient may be administered an increased dose in the next cycle.

[0181] Patients are monitored for symptomatic improvement and tumor volume score (TVS). Baseline and post-treatment tumor tissue resections and synovial fluid may be obtained from patients before and after beginning huAb1 treatment. Patients are additionally monitored for overall response, immune-related response, and overall survival.

[0182] MRI tumor assessments are performed within 28 days prior to first dose of huAb1, and then at certain time intervals following the first dose (e.g., 4, 8, 16, and 24 weeks, and every 12-16 thereafter). Clinical assessment of health outcomes (e.g., function and symptoms) are also done every 4 weeks after the first dose. Response to huAb1 is evaluated using RECIST for measurable disease.

[0183] Patients may be classified according to their best overall tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]). Frequencies, proportions, and exact 95% CI of patients, when appropriate, stratified by their best overall tumor response are calculated. Patients with a best overall tumor response of CR or PR with duration of at least 4 weeks (28 days) are further classified as having an objective tumor response.

[0184] Patients will be classified for response by RECIST and the Tumor Volume Score. The Tumor Volume Score classifies response according to the following definitions: Complete Response [(CR) lesion completely gone after treatment cycle], Partial Response [(PR)  $\geq 50\%$  decrease in volume score relative to Baseline], Progressive Disease [(PD)  $\geq 30\%$  increase in volume relative to lowest score during the treatment whether at baseline or some other visit] or Stable Disease [(SD) does not meet any of the prior criteria based on score].

[0185] Duration of response is calculated as the number of days from the first documentation of overall response (CR or PR) to the first documentation of disease progression.

**Example 4: Summary of a Phase I/II Clinical Trial in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tensosynovial Giant Cell Tumor (dt-TGCT)**

[0186] A phase I/II clinical trial is conducted in patients with one or both of pigmented villonodular synovitis (PVNS) and diffuse type tensynovial giant cell tumor (dt-TGCT) using huAb1 (also known as FPA008). The objective of phase I will be to determine a recommended dose of huAb1 in the patients, while phase II will be conducted to estimate the objective response rate (ORR) of huAb1 in the patients.  $ORR = \text{complete response (CR)} + \text{partial response (PR)}$ . The study will also characterize the safety and tolerability of huAb1 in the patients as well as determine the duration of response in responding patients and assess the pharmacokinetics of huAb1 in the patients. In addition, the study will assess the pharmacodynamics of huAb1 as measured by changes in serum levels of CSF1, IL34, TRAP5b, CTx, and whole blood CD14+/CD16+ monocyte subsets; evaluate synovial biopsies by immunohistochemistry (IHC) for CSF1, CSF1R and CD68; evaluate synovial fluid for huAb1 concentration and changes in cellularity; and assess functional outcomes as measured by the Ogilvie-Harris score developed specifically for PVNS (Ogilvie-Harris, 1992; Rhee, 2010) and by the EQ-5D-5L score (Rabin, 2001; Herdmann, 2011).

[0187] The phase I/II study is open label and patients will be enrolled into either phase but not both. Patients are treated with huAb1 every 2 weeks in 28 day cycles. Treatments may be continued after one 28-day cycle. For example, the first dose cycle may be used for a safety and pharmacokinetic assessment, but patients may participate in an extended treatment period of, for example, 1, 2, or 3, additional 28-day cycles or until disease progression (if before 24 weeks), unacceptable toxicity, patient or physician decision to discontinue, or termination of the study.

[0188] In phase I, 3 patients are enrolled in each of 3 cohorts, the cohorts administered 1 mg/Kg huAb1, 2 mg/Kg huAb1, or 4 mg/Kg huAb1, respectively. Additional cohorts may be added and an intermediate 3 mg/Kg huAb1 cohort may be added. If dose escalation continues higher than 4 mg/kg, the recommended dose (RD) for phase II may or may not be a maximum tolerated dose (MTD), assuming that an MTD is identified in phase I, but would not be higher than the MTD. The phase II study is based on the dose selected from the phase I results, or a dose anticipated to be less than or equal to 4 mg/Kg. The phase II dose will be identified based on overall safety, tolerability, objective response, PK, PD and estimates of efficacious exposures extrapolated from nonclinical data.



[0189] The phase II study duration is 24 weeks and involves 30 patients.

[0190] Treated patients are 18 or more years of age and have a histologically confirmed diagnosis of inoperable PVNS/dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss or morbidity as determined by a qualified surgeon or multi-disciplinary tumor board. Patients may have measurable PVNS/dt-TGCT by RECIST 1.1 on MRI.

[0191] Treated patients have not received prior therapy with an anti-CSF1R antibody or with PLX3397 unless discontinued for intolerance. Patients may have received prior therapy with imatinib or nilotinib, however. Patients have not had any surgical procedure of the involved joint within 12 weeks prior to first study dose administration.

[0192] Pharmacokinetic parameters will be assessed in the patients. The following PK parameters will be derived from concentration-time data for FPA008, when appropriate and applicable (other parameters, such as accumulation ratio and half-life, may also be calculated): Area under serum concentration-time curve (AUC); Maximum serum concentration ( $C_{\max}$ ); Minimum serum concentration ( $C_{\min}$ ); Clearance (CL); Volume of distribution at steady state ( $V_{ss}$ ).

[0193] Pharmacodynamic (PD) parameters are also assessed: Serum - CSF1 and IL34 ligand concentration, CTx, and TRAP5b bone resorption marker concentrations; Whole blood – CD14<sup>+</sup>/CD16<sup>+</sup> monocyte subsets; Synovium (optional) - evaluate synovial biopsy for *CSF1* gene translocation (if not previously done), baseline and on treatment synovial biopsy, IHC for: CSF1 and CSF1R and/or for CD68; Synovial fluid (optional) – huAb1 concentration; cellular component for above markers by IHC.

[0194] Immunogenicity is assessed, for example, by collecting blood samples and assaying samples for anti-drug antibodies to huAb1.

[0195] Responsiveness is assessed, for example, by the following: MRI of affected joints will be performed at Screening, 4, 8, and 16 weeks (or until treatment discontinuation) following the start of treatment. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review. In addition, if there is a good tumor response rate, changes in surrounding bone and other joint tissues may be evaluated based on the whole organ MRI score (WORMS) and rheumatoid arthritis MRI score (RAMRIS). Clinical assessment of health outcomes (function, symptoms) will be done at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks or until treatment is discontinued. Patients who have not progressed at Treatment Completion/Early Termination and

agree to continue participation in the study are to be followed (MRI and assessment of health outcomes) every 14 ( $\pm$  2) weeks until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

[0196] Safety is assessed by monitoring adverse events and changes in physical examinations, vital signs, 12-lead ECGs, and clinical laboratory measurements.

[0197] All analyses will be descriptive and will be presented by dose group and overall as appropriate. Patient data from the Phase 2 will be summarized as a separate group. All patients dosed at the RD will also be summarized. Because of the low number of patients that may be enrolled at lower dose levels, some dose levels may be combined for summarization. Missing values in the efficacy data will be treated as missing; no efficacy data will be imputed.

[0198] Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. 95% confidence intervals will be presented where appropriate. Response rates and the corresponding confidence interval (CI) will be used to assess efficacy. It is anticipated that there will be a total of approximately 33 to 36 patients treated at the RD overall. Table 6 displays the corresponding 95% confidence interval and the precision for various sample sizes and observed response rates. PK parameters will be calculated using non-compartmental analysis methods, though compartmental analysis methods may be employed if appropriate.

### **Example 5: Phase I/II Clinical Trial in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)**

#### **1. Introduction**

##### **1.1. PVNS Background**

[0199] Pigmented villonodular synovitis (PVNS) is a benign neoplasm of the synovium with features of both reactive inflammation and clonal neoplastic proliferation in which colony stimulating factor-1 (CSF1) is over expressed. A common translocation of the CSF1 gene (1p13) to the COL6A3 promoter (2q35) is present in approximately 60% of PVNS patients. The translocation is accompanied by CSF1 overexpression in the synovium. In addition, approximately 40% of PVNS patients have CSF1 overexpression in the absence of an identified CSF1 translocation. The consistent presence of CSF1 overexpression in all cases of PVNS and

reactive synovitis suggests both an important role for CSF1 in the spectrum of synovial pathologies and the utility of targeting the CSF1/CSF1R interaction therapeutically (West, 2006).

[0200] In PVNS, CSF1 overexpression is present in a minority of synovial cells, whereas the majority of the cellular infiltrate expresses CSF1R but not CSF1. This has been characterized as a tumor-landscaping effect with aberrant CSF1 expression in the neoplastic cells, leading to the abnormal accumulation of non-neoplastic cells that form a mass.

[0201] Surgery is the treatment of choice for patients with localized PVNS. Recurrences occur in 8-20% of patients and are easily managed by re-excision. PVNS/dt-TGCT tends to recur more often (33–50%) and has a much more aggressive clinical course. Patients are often symptomatic and require multiple surgical procedures during their lifetime. For patients with unresectable disease or multiple recurrences, systemic therapy using CSF1R inhibitors may help delay or avoid surgical procedures and improve functional outcomes (Ravi, 2011).

[0202] Imatinib, a non-specific inhibitor of CSF1R, has undergone evaluation in 29 PVNS patients. The median age was 41 years and the most common site of disease was the knee (n = 17; 59%). Five of 27 evaluable patients had complete (n=1) or partial (n=4) responses per RECIST for an overall response rate of 19%. Twenty of 27 patients (74%) had stable disease. Symptomatic improvement was noted in 16 of 22 patients (73%) who were assessable for symptoms. Despite a high rate of symptomatic improvement and an overall favorable safety profile, 10 patients discontinued treatment for either toxicity or other reasons (Cassier, 2012).

[0203] Recently two studies of potent inhibitors of CSF1 signaling have shown preliminary but compelling clinical activity in patients with PVNS. PLX3397, a CSF1R kinase inhibitor, and RG7155, a monoclonal antibody targeting CSF1R have been evaluated in patients with PVNS (Cassier, 2014; Tap, 2014). In both studies, a majority of patients with PVNS responded to treatment based on RECIST, FDG-PET, and/or total volume score, which is a measure of disease volume by MRI.

[0204] In PVNS, overexpression of CSF1 by a minority of cells leads to recruitment of CSF1R-expressing cells that make up the bulk of the tumor mass. FPA008 antagonizes CSF1R activation and should result in the reduction of CSF1R-expressing cells in the tumor thereby providing clinical benefit.

## **1.2. FPA008: Description of the Molecule**

[0205] HuAB1, also called FPA008, is a humanized IgG4 monoclonal antibody with a single amino acid substitution in the hinge region to prevent hemi-dimer exchange. FPA008 has

high affinity binding to human colony stimulating factor 1 receptor (CSF1R), a receptor tyrosine kinase.

### **1.2.1. Nonclinical Studies with FPA008**

#### **1.2.1.1. FPA008 Inhibition of CSF1R Signaling**

[0206] FPA008 inhibited both CSF1 and IL34-induced CSF1R phosphorylation in a cell line engineered to overexpress CSF1R (CHO-CSF1R), demonstrating FPA008 blocks the activation of ligand-induced CSF1R signaling pathways. FPA008 also inhibits CSF1 and IL34-induced proliferation/survival of peripheral blood monocytes *in vitro*, demonstrating FPA008 inhibits not only the initiation of CSF1 and IL34 signaling pathways, but also the subsequent physiologic responses of primary human monocytes to these ligands (for further details, see the FPA008 Investigator's Brochure [IB]).

### **1.2.2. Nonclinical Pharmacokinetics and Pharmacodynamics**

#### **1.2.2.1. Pharmacokinetics**

[0207] The pharmacokinetics (PK) and toxicokinetics (TK) of FPA008 have been investigated in 4 intravenous (IV) studies in cynomolgus monkeys. The dose range studied was 3–150 mg/kg after a single intravenous bolus dose and 3–150 mg/kg after repeat intravenous infusion 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 in two studies and 13 doses in one study.

[0208] The PK profile following a single IV bolus administration of FPA008 in cynomolgus monkeys was characterized by a rapid distribution, followed by a slower terminal phase that ended with an accelerated depletion of FPA008 from the plasma, consistent with target-mediated clearance.

[0209] The rapid decrease may be due in part to anti-FPA008 antibodies in addition to target-mediated clearance. However, a single dose administration of cmFPA008 in SCID mice, which lack the ability to mount an ADA response, showed a similar profile and supported the contribution of target-mediated clearance to total clearance of FPA008, especially at low doses.

[0210] The observed maximum plasma concentration ( $C_{\max}$ ) increased proportionally to dose at all dose levels tested, while area under plasma concentration-time curve from time zero extrapolated to infinity ( $AUC_{\infty}$ ) 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. The half-life ( $t_{1/2}$ ) prior to the

accelerated terminal decline ranged from 1–12 days and the total clearance ranged from 0.14–1.25 mL/h/kg. In summary, FPA008 has saturable target-mediated clearance in cynomolgus monkeys.

#### 1.2.2.2. Pharmacodynamics

[0211] The effects of FPA008 on various pharmacodynamics (PD) markers known to be modulated *in vivo* by CSF1R inhibition were examined in 3 cynomolgus monkey studies (details are provided in Section 5.1.1.7 of the IB). These markers include CSF1, CD16<sup>+</sup> monocytes, and bone resorption markers. IL34 was not measured in monkeys due to lack of an appropriate assay.

[0212] **CSF1 levels:** Plasma or serum levels of CSF1 are a measure of FPA008 target engagement. CSF1 is cleared from circulation under normal physiological conditions by macrophages (primarily splenic macrophages and liver Kupffer cells) via CSF1R-mediated endocytosis and intracellular degradation (Bartocci, 1987). Steady state levels of CSF1 in normal individuals are <1 ng/ml. FPA008 binds to and prevents CSF1 being cleared by CSF1R, resulting in a large, rapid increase in circulating CSF1 concentration, after which CSF1 levels reach a new steady state of approximately 10 µg/ml. In the pilot toxicology study, plasma CSF1 and plasma FPA008 samples were obtained at trough (7 days post-dose) following once-a-week dosing for 4 weeks in cynomolgus monkeys. The data show that a minimum biological effect occurred at 5 µg/mL FPA008, and a half-maximal response (EC<sub>50</sub>) was 8 µg/mL FPA008. While FPA008 elevates CSF1, FivePrime believes that these elevations will have no consequence because:

- CSF1R is the only identified receptor through which CSF1 signals and this is antagonized by FPA008.
- The levels of CSF1 fall concomitantly with the clearance of FPA008.
- In the presence of FPA008, when CSF1 is elevated, the potential for extremely high concentrations of CSF1 to displace FPA008 from the CSF1R receptor was evaluated in the FPA008 cell potency assay. The data showed that concentrations as high as 10 µg/mL CSF1 had no impact on FPA008 potency or maximal inhibition of CSF1R signaling.
- No rebound increase in CD16<sup>+</sup> monocytes was observed once FPA008 is cleared in preclinical *in vivo* studies.

[0213] **CD16<sup>+</sup> monocytes:** In the GLP toxicology study, CD16<sup>+</sup> monocytes were reduced in monkeys receiving 4 weekly IV infusions of 50 mg/kg or 150 mg/kg FPA008, consistent with CSF1R pathways being necessary to support the growth and maintenance of this monocyte

subpopulation *in vivo*. CD16<sup>+</sup> monocyte reduction occurred within 1 week of dosing and was sustained throughout the dosing and exposure periods. The CD16<sup>+</sup> monocytes were restored to normal baseline levels after FPA008 cleared. The CD16<sup>-</sup> monocyte subpopulation remained unaffected by administration of FPA008.

[0214] **Bone resorption markers:** Plasma and urine markers of bone resorption were evaluated in monkeys following repeat dosing with FPA008. Urine NTX, plasma CTx, and TRAP5b were all decreased. The effects were reversible upon clearance of FPA008.

### 1.2.3. Nonclinical Toxicology Studies and Findings

[0215] Full details of the nonclinical toxicology studies are provided in Section 5.3 of the IB. All toxicity studies were performed in cynomolgus monkey since FPA008 is not cross-reactive to rodents but shows similar *in vitro* binding affinity to cynomolgus monkey and human CSF1R and similar tissue binding profile in a tissue cross reactivity study comparing a panel of human and cynomolgus monkey tissues. Four nonclinical *in vivo* toxicology studies were performed using FPA008: A single-dose pharmacokinetic (PK)/tolerability study with doses of 3, 10, 30, and 150 mg/kg, a dose range finding repeat-dose toxicity study with 4 weekly IV doses of 3, 10, and 150 mg/kg, a repeat-dose GLP toxicity study with 4 weekly IV doses of 50 mg/kg and 150 mg/kg and a 30 week recovery phase, and a subchronic repeat-dose GLP toxicity study with 13 weekly IV doses of 20, 50, and 100 mg/kg and a 29-week recovery phase.

[0216] In the *in vivo* toxicology studies in cynomolgus monkeys, FPA008 was generally well tolerated. Test article-related findings included clinical observations, hematology and clinical chemistry changes, and histologic changes. The majority of these observations were considered non-adverse.

#### 1.2.3.1. Periorbital Edema

[0217] The most prominent physical finding was reversible periorbital edema, seen after prolonged exposure to FPA008. The onset of the edema did not show a clear relationship to exposure levels, however edema resolved after systemic clearance of the drug. Periorbital edema is a known side effect with drugs affecting the CSF1 pathway (Ries, 2014).

#### 1.2.3.2. Monocyte Depletion

[0218] The main hematologic change was a decrease in circulating CD16<sup>+</sup> monocytes, which was considered a pharmacodynamic (PD) effect. The decreased cell numbers normalized with clearance of FPA008 from circulation.

#### 1.2.3.3. Enzyme Elevations

[0219] FPA008-related clinical chemistry effects included reversible increased alanine transaminase (ALT), aspartate transaminase (AST), and creatine kinase (CK) serum levels. These laboratory abnormalities were not associated with any histopathological evidence of liver, cardiac, or muscle tissue injury at terminal or recovery necropsy. Cardiac troponin, skeletal troponin, myoglobin, and aldolase were also measured during the in-life portion of the study, and no changes were detected in any of these parameters further confirming the lack of any liver or muscle injury. The increased serum levels are attributed to diminished clearance of the ALT, AST, and CK molecules from serum due to a reduced number of liver Kupffer cells (Radi, 2011). Accordingly, the ALT, AST, and CK elevations are considered non-toxic and an indirect PD effect of FPA008 exposure.

#### 1.2.3.4. Accumulation of Extracellular Matrix

[0220] The most noteworthy histopathological finding in both pivotal studies at terminal necropsy was the observation of reversible expansion of the submucosal collagen fibers by clear space and varying amounts of a blue, granular extracellular matrix (ECM). This finding was present in a large variety of tissues and was generally minimal to mild in severity. It was most prominently seen in the esophagus. This change was not associated with inflammatory cells or with any sign of degeneration or other alteration of the collagen fibers, fibroblasts, or the smooth muscle cells within the area of expansion. A similar observation was also noted in *op/op* mice that lack functional CSF1 (Radi, 2009). In this publication, the authors postulated that the reduction of tissue macrophages likely causes the observed accumulation of ECM due to a decreased clearance of glycosaminoglycans by macrophages. Glycosaminoglycans, especially hyaluronic acid, are prominent in connective tissue and are normally catabolized by macrophages (Radi, 2009). This change is considered to be an indirect PD effect of FPA008. There was no evidence that the accumulation of the blue granular ECM was adverse; there were no associated clinical observations or organ weight changes that correlated to the histopathologic observations. In addition, these changes in the ECM were reversible during a drug-free recovery period, and therefore, were considered non-adverse.

#### 1.2.3.5. Other Findings

[0221] Unique to the 4-week GLP study was a finding in a single female dosed with 150 mg/kg. At terminal sacrifice microscopic evidence of mild inflammation of the epicardium and vacuolation of cardiac myocytes was seen. The significance of this finding is unknown, but

association with FPA008 cannot be excluded. Chronic, mild epicardial inflammation can be a background lesion in nonhuman primates. However, vacuolation of a cell can be an early sign of a non-specific, cellular response to injurious stimuli. Vacuolation of myocytes was not found in any of the other dosed animals. It is important to note that this vacuolation did not lead to degeneration or necrosis, and did not cause changes in recorded ECGs. No cardiac changes were detected in any animals at recovery or in the 13-week toxicity study. This event was considered an adverse finding in the 4-week toxicity study.

[0222] Also unique to the 4-week study was increased spleen organ weights with corresponding histopathological findings of minimal to mild follicular hyperplasia in female animals. The finding was considered of low toxicological significance and non-adverse, and no spleen hyperplasia was seen in the 13-week toxicity study.

[0223] As macrophages engulf pathogens to destroy them (Dale, 2008), treatment with FPA008 may be associated with an increased risk of susceptibility to intracellular pathogens such as *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Leishmania*, and others. While no spontaneous infections have been noted in FPA008 animal studies to date, clinical study protocols will contain exclusion criteria for those patients at greatest risk. Patients will be monitored regularly for adverse events and infections while on study.

#### 1.2.3.6. Summary

[0224] The no-observable-adverse-effect level (NOAEL) for FPA008 was determined to be 100 mg/kg when administered for 13 weekly doses to cynomolgus monkeys.

### 1.3. **Clinical Experience with FPA008**

[0225] FPA008 is currently being evaluated in a double-blind, randomized, placebo-controlled first-in-human trial designed in 3 parts to study safety, pharmacokinetics (PK), and PD biomarkers. In Part 1, 8 healthy volunteers were randomized (3:1) to receive a single intravenous infusion of FPA008 or placebo, per dose cohort of 0.2, 1, 3, or 10 mg/kg. In Part 2, 8 healthy volunteers were randomized (3:1) to receive 2 doses of FPA008 or placebo administered 14 days apart, at 1 mg/kg or 3 mg/kg. Dose escalation decisions were based on the incidence of dose limiting toxicities (DLTs) plus attributed adverse events beyond the DLT period. Part 3 consists of an open-label evaluation of 3 dose levels in RA patients whose disease is not responding to disease modifying anti-rheumatic drugs (DMARDs) and on a stable dose of methotrexate. Three subjects per dose level will receive 2 doses of FPA008 administered intravenously 14 days apart in the open-label part. Thereafter, 30 new subjects will be randomized (2:2:1) to one of two dose



levels of FPA008 or placebo, respectively, and receive 3 doses administered intravenously every 14 days. No clinical safety data are yet available for Part 3 patients.

[0226] Forty-eight healthy volunteers completed Parts 1 and 2 of the study; 36 of these subjects received FPA008 and 12 received placebo. FPA008 was well tolerated in healthy volunteers up to 3 mg/kg dual doses. The most common FPA008 treatment-related toxicities were pruritus, eyelid edema along with facial swelling, fatigue, and headache. The events were Grade 1 or 2, and self-limited. At 10 mg/kg, all 6 active subjects experienced moderate (Grade 2) eyelid edema or facial swelling, some accompanied with swelling in hands and feet, blurry vision, and weight gain. The events lasted up to 3 months and coincided with prolonged PK exposure at this dose level. No adverse events met protocol definitions for dose-limiting toxicities.

[0227] Dose-dependent elevations of CK up to 6.8 times the upper limit of normal and lactate dehydrogenase (LDH) up to 2.2 times the upper limit of normal were noted at 1 mg/kg and above; AST elevation up to 2.1 times the upper limit of normal occurred at 3 mg/kg and above and occurred in a greater percentage of volunteers with increasing dose; and mild ALT elevation up to 1.2 times the upper limit of normal occurred at 10 mg/kg in 1 subject. Peak values occurred 2-8 weeks following drug administration, typically with normalization by 12 weeks. These elevations were not associated with clinical signs/symptoms or abnormalities in total bilirubin, CK isoenzymes, or troponin. They were reversible and were expected due to FPA008-mediated inhibition of Kupffer cells responsible for their clearance (Radi, 2011) and are considered to be a pharmacologic effect of inhibiting CSF1R rather than representing tissue injury.

[0228] The adverse event profile observed in this study is relatively similar to what has been reported in other compounds targeting the CSF1R pathway (Cassier, 2014; Tap, 2014).

[0229] FPA008 exhibited saturable target-mediated clearance in the dose range tested. The PK characteristics observed in healthy volunteers support dosing of FPA008 once every 2 weeks or less frequently to maintain desired drug exposure. Reduction of CD16<sup>+</sup> monocytes, decreased bone turnover biomarkers (CTx, TRAP5b), and dose-dependent increase in serum CSF1 and IL34 concentrations were observed.

#### **1.4. Risk-Benefit Assessment**

[0230] The safety, PK, and PD of FPA008 in healthy volunteers were generally predicted based on the nonclinical toxicology studies of FPA008. More details on the toxicology studies

are provided in the IB.

[0231] In the nonclinical toxicology studies, FPA008 was well tolerated in animals at high doses up to 100 mg/kg for up to 13 weekly doses. PD effects (CSF1 and CD16<sup>+</sup> monocytes) occurred at drug exposure levels well below those associated with adverse events or abnormal laboratory findings.

[0232] Evidence from mouse models to evaluate potential risk of pharmacologically mediated toxicity associated with interruption of CSF1 and IL34 signaling has shown that the deletion of CSF1, IL34, or CSF1R is non-lethal. Mice deficient in CSF1 show a loss of bone osteoclasts and display deficiency in some myeloid cells at birth (Yoshida, 1990); mice deficient in IL34 lack Langerhans cells in the epidermis and microglia in some areas of the brain (Wang, 2012; Greter, 2012); and mice deficient in CSF1R display both osteoporosis and deficiency of Langerhans cells and microglia (Hamilton, 2013).

[0233] Binding of FPA008 to CSF1R does not produce an agonist effect as demonstrated by experiments conducted at FivePrime (details provided in the IB). Additionally, FPA008 is an IgG4 antibody, and *in vitro* testing has confirmed that it has no specific antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity.

[0234] Although PVNS is managed by local intervention in most patients, some patients present with or have chronic or recurrent disease that is not well managed by surgery or other available therapies. Imatinib is effective in a minority of patients but has some on-target and off-target toxicities that limit its usefulness. Preliminary reports of specific CSF1R inhibitors suggest that FPA008 may be a beneficial treatment for non-surgical PVNS, which can be a debilitating disease.

## **2. Study Objectives and Endpoints**

### **2.1. Primary Objective**

[0235] Phase 1: To determine the recommended dose (RD) of FPA008 in patients with PVNS/dt-TGCT

[0236] Phase 2: To estimate the objective response rate (ORR = CR+PR) of FPA008 in patients with PVNS/dt-TGCT

### **2.2. Secondary Objectives**

[0237] To characterize the safety and tolerability of FPA008 in patients with PVNS/dt-TGCT

[0238] To determine the duration of response in responding patients

[0239] To assess the pharmacokinetics of FPA008 in patients with PVNS/dt-TGCT

### **2.3. Exploratory Objective**

[0240] To assess the pharmacodynamics of FPA008 as measured by changes in serum levels of CSF1, IL34, TRAP5b, CTx, and whole blood CD14<sup>+</sup>/CD16<sup>+</sup> monocyte subsets

[0241] To evaluate synovial biopsies by immunohistochemistry (IHC) for CSF1, CSF1R and CD68 markers in selected patients

[0242] To evaluate synovial fluid for FPA008 concentration and changes in cellularity in selected patients

[0243] To assess functional outcomes as measured by the Ogilvie-Harris score developed specifically for PVNS and by the EQ-5D-5L score

### **2.4. Primary Study Endpoints**

[0244] Phase 1: The incidence of Grade 3 and Grade 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)

[0245] Phase 2: The incidence of confirmed objective responses per RECIST 1.1

### **2.5. Secondary Endpoints**

[0246] PK parameters

[0247] The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities

[0248] Duration of response per RECIST 1.1

### **2.6. Exploratory Endpoints**

[0249] PD parameters

[0250] Symptom and Functional Outcomes as measured by the Ogilvie-Harris score developed specifically for PVNS and by the EQ-5D-5L score

## **3. Overall Design and Plan of the Study**

### **3.1. Overview**

[0251] This is a Phase 1/2 study. Phase 1 is a dose escalation, open-label, safety, tolerability, PK, and PD study of FPA008. Patients will be enrolled into either Phase 1 or Phase 2 of the study, but not both.

[0252] Enrolled patients will be treated in 28-day cycles. Each cycle will consist of 2

doses: on Day 1 and Day 15.

### **3.1.1. Screening Period**

[0253] All Screening evaluations must be completed and reviewed by the Investigator and Medical Monitor to confirm that patients meet all eligibility criteria before the first infusion of FPA008 (Appendix 1). Written informed consent for participation in the study must be obtained before performing any study specific Screening tests or procedures. Screening assessments will be performed within 28 days prior to the first dose of FPA008 unless otherwise specified.

[0254] Study-procedure-related AEs that occur after signing of the informed consent form and before administration of the first FPA008 dose will be collected during this period.

### **3.1.2. Phase 1 (Dose Escalation)**

[0255] Dose escalation will continue until either the MTD or maximum feasible dose is reached, with a minimum of 3 patients enrolled in each cohort. The anticipated dose levels and schedules are: Dose level 1: 1 mg/kg q2w; Dose level 2: 2 mg/kg q2w; Dose level 3: 4 mg/kg q2w.

[0256] All dose escalation decisions will be based on assessment of DLTs, overall safety, and tolerability and will be made after the last patient enrolled in each cohort has completed the first treatment cycle. Dose escalation decisions will be agreed upon between the Investigators and the Sponsor. Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein Investigators and the Sponsor review patient data, including, but not limited to, demographics, FPA008 dosing, concomitant medications, hematology and serum chemistry, and AEs; and confer and document agreement that dose escalation or expanding an existing dose level is considered appropriate. If the Sponsor and Investigators collectively agree that following review of safety and pharmacokinetic data, that a different dose escalation scheme should be used than the one outlined, this will be permitted. Review of safety, PK and PD parameters may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g., less frequent dosing or with a loading dose) in order to reach an optimal target exposure.

[0257] The following algorithm will be used for dose escalation decisions:

**Table 1: Dose-Escalation Considerations**

<b>Number of Patients with DLT at a Given Dose Level</b>	<b>Dose Escalation Decision Rule</b>
0/3	Escalation will occur to the next higher dose cohort
1/3	Enroll three more patients in same cohort
$\geq 2/3$	Stop enrollment. Enter three more patients at dose level below, if only three were previously entered
1/6	Open next cohort
$\geq 2/6$	Stop enrollment. Enter 3 more patients at a dose level below or at an intermediate dose level if the current dose level is $\geq 50\%$ higher than the previous dose level in the same manner as described above.

[0258] The MTD is defined as the highest dose associated with DLTs in less than 33% of patients receiving FPA008 administered on Days 1 and 15 of a 28-day cycle. This will normally be the dose recommended for further study (RD); however, based on review of safety and PK data, the RD could be lower than the MTD. If the MTD is not reached, and the highest evaluated FPA008 dose is well tolerated, the data will be reviewed to assess whether further dose escalations are warranted. The protocol may be amended if additional dose escalation is considered appropriate.

[0259] If the MTD is not reached during Phase 1, or subsequent cycles of treatment in Phase 1 provide additional insight on the safety profile, an RD may be selected based on overall tolerability, safety, and PK.

[0260] If a patient does not receive 2 doses and does not complete the safety and PK assessment in Cycle 1 for reasons other than toxicity (e.g., disease progression or withdrawal of consent), then an additional patient will be enrolled into the cohort so that the cohort has at least three patients evaluable for tolerability through Cycle 1. All such discussions and decisions will be documented as part of the dose escalation decision-making process.

[0261] Intra-patient dose escalation above the starting dose for each patient is not permitted.

[0262] If a patient's dose is decreased for an adverse event, dose escalation to the

originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without the opportunity for re-escalation.

[0263] On completion of Cycle 1 (Safety and PK Assessment Period), Phase 1 patients may participate in an Extended Treatment Period, which begins on Day 1 of Cycle 2. FPA008 will be administered every 2 weeks in 4-week cycles for up to 24 weeks or until disease progression (if before 24 weeks), unacceptable toxicity, patient or physician decision to discontinue, death, or Sponsor termination of the study, assuming no limitations with availability of drug supply, or other issues that may preclude the Sponsor from providing FPA008.

### **3.1.3. Phase 2**

[0264] Enrollment in Phase 2 will begin when the RD has been identified by the CRC, based on overall safety, tolerability, objective response, PK, PD and estimates of efficacious exposures extrapolated from nonclinical data. The RD is anticipated to be  $\leq 4$  mg/kg. However, it is possible that PVNS/dt-TGCT patients may have different drug exposure relative to healthy volunteers. If dose escalation continues higher than 4 mg/kg, the RD may or may not be an MTD, if an MTD is identified in Phase 1. For example, if an MTD is not reached, or if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

[0265] Treatment is planned to continue every 2 weeks for up to 24 weeks (no more than 12 doses) or until disease progression.

[0266] If a patient appears to have stable or improving symptoms with stable measurable disease or better by MRI, but is having intolerable or Grade 3 or greater adverse events, dose reduction by 25–50% may be allowed with Sponsor agreement.

### **3.2. Procedures**

[0267] Patients will undergo safety evaluations (DLTs and other AEs, vital signs, ECGs, clinical laboratory tests), determination of ECOG performance status (PS), and physical examinations (Appendix 1). Additionally, blood samples will be collected for PK and PD analyses for all patients (Appendix 2).

[0268] MRI of affected joints will be performed at Screening, 4, 8, and 16 weeks following the start of treatment. An MRI should also be performed at the 30 days ( $\pm 7$  days) and 90 days ( $\pm 7$  days) End of Treatment Follow-up Visits unless already performed within the

previous 6 weeks or if tumor progression was previously determined. Patients who have not progressed and enter Long-Term Follow-up should have MRI every 14 ( $\pm$  2) weeks until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review.

[0269] Clinical assessment of health outcomes (function, symptoms) will be done every 4 weeks after the first administration of study drug.

[0270] Safety will be assessed by monitoring AEs and changes in physical examinations, weight, vital signs, 12-lead ECGs, and laboratory measurements. Assessment of AEs will follow the guidelines provided in the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Blood samples will also be drawn at scheduled time points (Appendix 2) during the study for determination of drug serum concentration, and anti-drug antibodies (ADAs) (i.e., antibody response to FPA008).

[0271] In patients who have archival tumor tissue available and who have signed the Optional Research Sample Informed Consent Form, the tissue will be evaluated for *CSF1* gene translocation if not previously done (Appendix 1). In addition, CSF1 and CSF1R and CD68 markers and will be determined.

[0272] For patients who sign the applicable Optional Research Sample Informed Consent Form, baseline tumor tissue resections ( $\geq 0.5$  cm to  $\leq 2$  cm) and synovial fluid (if applicable) will be obtained from patients prior to starting FPA008 treatment and after eligibility criteria have been fulfilled. The baseline tissue sample will be reviewed by a pathologist to determine whether the tissue is evaluable. If the Screening tissue sample is evaluable, a subsequent biopsy will be performed before the Cycle 2, Day 1 administration of FPA008 (Appendix 1).

[0273] Patients enrolled in Phase 1 or Phase 2 of the study may continue treatment with FPA008 in 28-day cycles for up to 24 weeks or until disease progression, intolerable toxicity, patient or physician decision to discontinue, or Sponsor termination of the study. Responding patients who discontinue treatment while still in response (CR, PR or SD) should get follow-up scans at 14 ( $\pm 2$ )-week intervals during the Long-Term Follow-up Period to determine the duration of response, unless other therapy is started for the treatment of PVNS/dt-TGCT or consent is withdrawn.

[0274] All patients should return to the clinic for three End of Treatment Follow-Up visits irrespective of whether a patient is withdrawn or withdraws at a planned visit or mid-cycle.

[0275] AEs will be assessed from the time the first dose of FPA008 is administered

through 90 days ( $\pm 7$  days) after the last dose of FPA008 (see Section 6.2.1.1). All serious adverse events (SAEs) will be collected after signing of the informed consent form through 90 days ( $\pm 7$  days) after the last dose (see Section 6.2.1.1).

### **3.3. Rationale for the Study Design**

[0276] The Phase 1 component of this study is a dose escalation, open-label study to assess the safety, PK, PD, and preliminary efficacy of FPA008 in patients with PVNS/dt-TGCT. The 3+3 dose escalation design is standard for early stage trials of novel anticancer treatments.

[0277] The Phase 2 component is a single-stage trial designed to estimate the objective response rate with a precision of approximately 20%, assuming the response rate is similar to that reported for PLX3397 and RG.7155, other potent inhibitors of the CSF1R signaling pathway. The Phase 2 component will also allow a more thorough investigation of the safety, PK, and biological effects of FPA008 in the target population for future trials.

## **4. Study Eligibility and Withdrawal Criteria**

### **4.1. Planned Number of Patients and Study Centers**

[0278] Phase 1: Approximately 12-15 patients with PVNS/dt-TGCT will be enrolled. Enrollment in Phase 1 will continue until the MTD has been reached or until the RD for Phase 2 has been defined.

[0279] Phase 2: Approximately 30 patients with PVNS/dt-TGCT will be enrolled. The study will be conducted at approximately 12 investigational centers in North America, Europe, and Asia.

### **4.2. Inclusion Criteria for Study Participation**

[0280] Patients enrolling into Phase 1 or 2 must meet *all* of the following inclusion criteria:

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Age  $\geq 18$  years
3. Histologically confirmed diagnosis of inoperable PVNS/ dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss or morbidity as determined by a qualified surgeon or multi-disciplinary tumor board (must be documented in the CRF during screening)
4. Measurable PVNS/dt-TGCT by RECIST 1.1 on MRI



5. ECOG performance status  $\leq 1$
6. Willing and able to comply with all study procedures
7. In sexually-active patients (i.e., females of childbearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA008. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Females <55 years of age should have FSH >40. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living.

[0281] No waivers of these inclusion criteria will be permitted.

#### **4.3. Exclusion Criteria for Study Participation**

[0282] Patients enrolling into Phase 1 or 2 will be excluded if any of the following criteria apply:

1. Prior therapy with an anti-CSF1R antibody
2. Prior therapy with PLX3397 unless discontinued for intolerance (i.e., non-progression on prior kinase inhibitor); prior therapy with imatinib or nilotinib is allowed
3. CK and liver function tests (including ALT, AST, and total bilirubin), outside of the range of local laboratory normal at Screening
4. Inadequate organ or bone marrow function defined as: hemoglobin < 10 g/dL, absolute neutrophil count <  $1.5 \times 10^9/L$ , platelet count <  $100 \times 10^9/L$ , serum creatinine >  $1.5 \times ULN$  or calculated creatinine clearance < 30 mL/min
5. Any surgical procedure of the involved joint within 12 weeks prior to first study dose administration (except baseline synovium biopsy, if performed)
6. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels

7. History of congestive heart failure or myocardial infarction <1 year prior to first study dose administration
8. Decreased cardiac function with NYHA > Class 2
9. Uncontrolled or significant heart disorder such as unstable angina
10. Significant abnormalities on ECG at Screening. QTcF >450 msec for males or >470 msec for females at Screening
11. Contraindications to MRI and use of intravenous gadolinium-based contrast agents
12. History of severe allergic, anaphylactic, or other infusion related reaction to a previous biologic agent
13. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs  $\leq$  28 days prior to first dose of FPA008
14. Known history of ADAs to previous biologic agents
15. Known history of sensitivity to Tween 20 (polysorbate 20)
16. Consumption of non-pasteurized milk on a regular basis, or known significant risk of exposure to opportunistic intracellular infections such as *listeria*, or other such pathogens.
17. Receipt of any vaccine within 28 days prior to first day of treatment. The effect of FPA008 on mounting an immunologic vaccine response is not known. Flu or other vaccinations may be administered while on study but the impact of FPA008 on the safety and efficacy of the vaccination is unknown.
18. Current unresolved infection or history of chronic active clinically significant infection (viral [e.g., HBV, HCV], bacterial, fungal, or other), which in the opinion of the Investigator would place the patient at risk from exposure to a CSF1R inhibitor
19. Known positive test for human immunodeficiency virus (HIV)
20. Active TB
21. Positive test for latent TB at Screening (Quantiferon test)
22. History of prior malignancy, except:
  - Curatively treated non-melanoma skin malignancy
  - Cervical cancer *in situ*

- Solid tumor treated curatively more than 2 years previously without evidence of recurrence
23. Lack of peripheral venous access or any condition that would interfere with drug administration or collection of study samples
  24. Any uncontrolled medical condition or psychiatric disorder which in the opinion of the Investigator would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results
  25. Inability to perform and/or comply with study and follow-up procedures.

[0283] No waivers of these exclusion criteria will be permitted.

#### **4.4. Patient Withdrawal and Replacement**

[0284] The patient has the right to stop treatment or to withdraw from the study at any time. Patients may continue to repeat cycles (up to 6 cycles) of FPA008 treatment until at least one of the following criteria applies:

- Consent withdrawal at the patient's request or at the request of their legally authorized representative
- Progression of patient's underlying disease
- Any event that would pose an unacceptable safety risk to the patient
- An intercurrent illness that would affect assessments of the clinical status to a significant degree and require discontinuation of therapy
- A positive pregnancy test at any time during the study
- At the specific request of the Sponsor or its authorized representative (for example, if the study is terminated for reasons of patient safety).

[0285] The date and reason for cessation of FPA008 will be documented, and the Investigator must make every effort to perform the End of Treatment Follow-Up visits. Patients will be followed for 90 days ( $\pm 7$  days) after the last dose of FPA008 for safety; those with ongoing SAEs will be followed until either resolution or stabilization.

[0286] Data from patients who discontinue prematurely will remain part of the study database.

#### **4.5. Patient Identification and Enrollment**

[0287] Patients must be able to provide written informed consent and meet all inclusion criteria and none of the exclusion criteria. No waivers of inclusion or exclusion criteria will be granted by the Investigator and Sponsor or its designee for any patient enrolled in the study. Before enrolling a patient, all eligibility criteria must be satisfied. Patients who qualify for Phase 1 of the study will be enrolled into the first available cohort. In Phase 2, a cohort of approximately 30 patients will be enrolled. A total of approximately 42-45 patients will be enrolled in the study.

[0288] The Investigator may repeat qualifying lab tests and vitals/ECGs prior to enrollment if a non-qualifying finding is considered an error or an acute finding is likely to meet eligibility criteria on repeat testing.

### **5. Study Drug**

#### **5.1. FPA008 Drug Product**

[0289] The investigational drug product in this study is FPA008. The investigational supply of FPA008 will be provided to the study centers by the Sponsor (or designee) and will be administered to patients in the clinical study by a trained healthcare professional.

[0290] A brief description of the FPA008 drug product is provided below:

- Formulation: FPA008 drug substance is comprised of 20 mg/mL FPA008 in a pH 6.3 buffer containing 20 mM L-histidine, 142 mM L-arginine, and 0.01% polysorbate 20.
- How Supplied: FPA008 drug product is supplied for IV administration as a sterile, aqueous, colorless, pyrogen-free solution in 5 mL ISO6R Type 1 glass vials fitted with butyl rubber stoppers and flip-up aluminum seals. Each vial contains a minimum of 5 mL of a 20 mg/mL solution of FPA008 (approximately 100 mg per vial).
- Storage Conditions: 2–8°C (36–46°F).
- FPA008 vials and cartons will be labeled according to local regulations.

#### **5.2. Administration**

[0291] The dose of FPA008 will be administered based on weight to patients in this study.

[0292] A research pharmacist (or other responsible personnel) will prepare the solution for administration. After calculating the number of vials, based on the patient's weight, the study drug product will be diluted in approximately 100 mL of 0.9% sodium chloride solution.

Prepared FPA008 should be administered  $\leq 6$  hours after preparation (ambient temperature). The IV administration set for FPA008 infusion must contain a 0.22  $\mu\text{m}$  in-line filter or a 0.22  $\mu\text{m}$  syringe filter. FPA008 will be administered under medical supervision over approximately 30-minute IV infusion via a peripheral vein or central venous catheter.

[0293] If a patient experiences an infusion reaction prior to completion of the infusion, the infusion must be stopped, and the patient should be promptly managed according to signs and symptoms, and local clinical protocol. The infusion may be restarted at a slower rate if all signs and symptoms have resolved. If the signs and symptoms do not resolve, the infusion should not be restarted. Patient should be kept under close observation for at least 1 hour after the end of study drug infusion.

[0294] All vials are for single use only. Instructions on study drug preparation and administration will be provided in a Pharmacy Manual.

### **5.3. Starting Dose and Dose Modifications**

[0295] The starting dose level of FPA008 and subsequent dose escalations between cohorts in Phase 1 are described in Section 3.1.2. The dose of FPA008 in Phase 2 will be determined by evaluation of the data from Phase 1 of the study.

#### **5.3.1. Dose Escalation of FPA008 between Cohorts**

[0296] Dose escalation to the next cohort will only start after the preceding dose cohort has completed the DLT period. Twenty-eight days (DLT period) of safety data must be available for at least 3 safety-evaluable patients prior to a potential dose-escalation decision by the CRC per the CRC Charter. In the event that a patient in a cohort is lacking adequate safety data (e.g., due to early withdrawal from study or poor compliance with the protocol), an additional patient will be enrolled to the cohort.

[0297] Dose escalation in each successive dose cohort will proceed in a stepwise fashion. All relevant safety information for the first cohort or the preceding dose cohort will be reviewed by the CRC.

[0298] Dose escalation is planned to continue until dose-limiting toxicities occur in 2 or more patients in a cohort. The decision to discontinue dose escalation will be made jointly by the Sponsor and Investigator(s) based on reaching the MTD or a dose level that shows an adequate pharmacodynamic effect.

[0299] In Cohort 1, 3 patients will be enrolled initially at a starting dose of 1 mg/kg FPA008, given by infusion. The occurrence of DLTs (Section 5.3.3) will determine whether the

dose will be escalated in subsequent cohorts.

[0300] The dose escalation decision rules are summarized in Table 2.

**Table 2: Decision Criteria for Escalation**

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more in same cohort
$\geq 2/3$	Stop enrollment. Enter 3 more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
$\geq 2/6$	Stop enrollment. Enter 3 more patients at a dose level below or at an intermediate dose level if the current dose level is $\geq 50\%$ higher than the previous dose level.

#### 5.3.1.1. Maximum Tolerated Dose

[0301] The selection of the RD will be based on clinical response data as well as PK and PD profiles. The Sponsor and Investigators may decide to discontinue dose escalation before reaching the highest planned dose of 4 mg/kg or, potentially, evaluate a higher ( $>4$  mg/kg) or intermediate (3 mg/kg) dose if the safety, PK, and PD data support evaluation of different dose levels.

[0302] Escalation to an MTD is not intended, however, may occur. If so, the MTD is defined as the highest dose associated with DLTs in Cycle 1 in less than 33% of patients receiving FPA008 administered on Day 1 and Day 15 of a planned 28-day cycle.

[0303] If the MTD is not reached during Phase 1 or subsequent cycles of treatment in Phase 1 provide additional insight regarding the safety profile, the RD may be selected depending on overall tolerability, PK, and estimates of efficacious exposures extrapolated from ongoing clinical evaluations.

#### 5.3.1.2. Toxicity at Lowest Dose Level

[0304] If the first dose level of 1 mg/kg is, unexpectedly, found to exceed an MTD, then

decisions on how to proceed will be based on safety, tolerability, and PK data; and will be agreed on between the Investigators and the Sponsor.

[0305] A lower dose level may be chosen as the next cohort.

### **5.3.2. Dose Escalation within a Cohort**

[0306] Intra-patient dose escalation above the starting dose is not permitted. If a patient's dose is decreased for an AE, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without re-escalation.

### **5.3.3. Dose-Limiting Toxicity**

[0307] DLTs are defined as any of the following events that occur during Cycle 1 of treatment and are assessed by the Investigator with concurrence by the CRC as related to FPA008. As applicable, events will be classified according to the NCI CTCAE (Version 4.03).

- Any Grade  $\geq 3$  related event except the following:
  - For elevations in ALT, AST, or CK without associated clinical or laboratory abnormality, the following DLT definitions apply:
    - CK associated DLT: CK  $>10\times$  the upper limit of normal (ULN)
    - ALT or AST associated DLT:
      - ♦ ALT or AST  $>8\times$  ULN
      - ♦ ALT or AST  $>3\times$  ULN and associated total bilirubin  $>2\times$  ULN

[0308] Phase 1 patients who experience a DLT during the DLT assessment period (Cycle 1) will be removed from study treatment. Patients experiencing toxicity in cycles after Cycle 1 that would be considered dose limiting during the DLT assessment period are not required to discontinue study participation in the study.

### **5.3.4. Dose Modification Criteria**

[0309] Dose reductions may be permitted for patients on prolonged treatment beyond the DLT period in Phase 1 or any patient in Phase 2 per the following guidelines. If dose reductions or interruptions that do not fall within these guidelines are being considered by the Investigator, these will require discussion with and approval by the Sponsor.

[0310] Patients may miss up to 2 consecutive doses (up to 6 weeks between doses) for

adverse or other events and may resume the study drug if the event returns to baseline or  $\leq$  Grade 1 within 6 weeks of treatment interruption. Omission of additional dosing longer than 6 weeks for adverse events will necessitate the patient's discontinuation from the study unless allowed by the Sponsor. Patients may miss doses in the course of participation in the study, including missed doses for scheduled vacations or other personal reasons as needed, but not more than 2 doses sequentially.

[0311] The Cycle 2, Day 1 infusion of FPA008 can only be administered after completion of the 28-day DLT window. All subsequent infusions can be administered with a  $\pm 3$  day window. Patients should not have 2 doses of FPA008 within 7 days. The first dose of each cycle is considered Day 1 of each cycle, cycles will repeat every 28 days unless there is a treatment delay. Patients can have treatment delay of Day 1 of the subsequent cycle as long as the Day 1 treatment is within 6 weeks of the last treatment.

[0312] If a patient has an elevation of CK  $>5x$  ULN but  $<10x$  ULN, the next scheduled study treatment may be delayed up to a maximum of 28 days from the last administered treatment dose, based on Investigator assessment of accompanying signs, symptoms, and additional laboratory findings (Table 3).

[0313] In the event of ALT or AST elevations:

- At any time, if the elevation in ALT or AST is  $>3x$  ULN and accompanied by an elevation in total bilirubin of  $>2x$  ULN, FPA008 should be held, and the patient should be withdrawn into safety follow-up.
- If ALT or AST is elevated  $>3x$  ULN but  $<5x$  ULN without bilirubin  $>2x$  ULN, the test should be repeated at the next scheduled visit and if ALT or AST are persistently high but still  $<5x$  ULN, the dose can be delayed up to a maximum of 28 days. The minimum interval between 2 consecutive doses cannot be less than 7 days.
- If a patient has an elevation of ALT or AST  $>5x$  ULN but  $<8x$  ULN, the next scheduled study treatment may be delayed up to a maximum of 28 days from the last administered treatment dose, based on Investigator assessment of accompanying signs, symptoms, and additional laboratory findings.



- If a patient experiences a Grade 3 or higher ALT or AST adverse event attributed to study treatment, or ALT or AST elevation  $>8\times$  ULN regardless of attribution, the study drug should be discontinued and the patient should be withdrawn from study treatment. Withdrawal from treatment should also occur for patients with ALT or AST elevations  $>3\times$  ULN accompanied by an elevation in total bilirubin of  $>2\times$  ULN.

[0314] In the event of CK elevations:

- Treatment should be discontinued for a CK elevation  $> 10\times$  ULN

**Table 3: Dose Delay and Modification Guidelines for Study Drug-Related Events other than ALT, AST and CK**

Toxicity Grade	FPA008 Dose	Dose Schedule
1	Continue 100% of dose	No delay or missed dose required
2	Continue 100% of dose	No delay or missed dose required
3	<p><b>Phase 1:</b> May continue at next lower dose level evaluated (e.g., if a Grade 3 AE occurs at 2 mg/kg, patient may continue at 1 mg/kg) following recovery to baseline or Grade 1; If at lowest dose level evaluated (i.e., 1 mg/kg), use Phase 2 dose modification guideline</p> <p><b>Phase 2:</b> Continue 75% of starting dose following recovery to baseline or Grade 1</p>	Up to 2 missed doses allowed without Sponsor approval to continue
4	<p><b>Phase 1:</b> May continue at next lower dose level evaluated (e.g., if a Grade 3 AE occurs at 2 mg/kg, patient may continue at 1 mg/kg) following recovery to baseline or Grade 1; If at lowest dose level evaluated use Phase 2</p> <p><b>Phase 2:</b> Continue 50–75% of starting dose following recovery to baseline or Grade 1</p>	Up to 2 missed doses allowed without Sponsor approval to continue

**Note:** Table 3 applies to adverse events other than the ALT, AST, and CK rules above.

[0315] If a patient's dose is decreased for an adverse event, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without re-escalation.

### 5.3.5. Dose Interruptions during Study Drug Infusion

[0316] Infusion of FPA008 must be stopped if any AE  $\geq$  Grade 3 occurs during the infusion. If bronchospasm or dyspnea occurs in a patient during infusion, the infusion should be stopped.

[0317] In addition, at the Investigator's discretion, the infusion rate may be reduced or stopped if a less severe AE (Grade 1 or 2) occurs during the infusion. If a Grade 3 or less severe AE resolves within 6 hours, the infusion may be restarted at half the previous rate. If the same AE appears again with the same severity at any time during the restarted infusion, the infusion should be discontinued, and no further dosing of study drug will occur without consultation with the Sponsor (or designee).

[0318] If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion, as well as every 30 minutes after the infusion for a minimum of 1 hour and until resolution of the infusion reaction.

[0319] Systemic hypersensitivity reactions should be managed under the direct supervision of a physician and according to treatment protocols in effect at the investigational site. However, in the absence of such a protocol, the standardized treatment protocol provided in Appendix 6 should be used.

#### **5.4. Blinding and Breaking the Blind**

[0320] Blinding and breaking the blind are not applicable as this is an open-label study.

#### **5.5. Drug Accountability**

[0321] The Investigator or appropriately qualified staff is responsible for maintaining accurate study drug accountability records throughout the study.

[0322] The Investigator is responsible for returning all unused study drug to the Sponsor (or designee), and must verify that no remaining supplies are in the Investigator's possession. The study site is permitted to destroy used or partially used study drug vials according to the site policy once Sponsor (or designee) approval of its documented destruction procedure has been obtained. Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be reconciled and recorded by using a drug inventory log during and on completion of the study.

#### **5.6. Investigational Product Compliance**

[0323] Only qualified trained site personnel may administer FPA008. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. FPA008 will be infused over approximately 30 minutes via a peripheral vein or central venous catheter by a trained healthcare professional. Records of study medication

administered (date, start and stop time, and dose administered relative to time of preparation) will be recorded on the patient's electronic case report form (eCRF).

### 5.7. Concomitant Medication and Treatment

[0324] All concomitant medications including herbal and other non-traditional remedies are to be captured on the eCRF. The following parameters will be collected: generic name, route of administration, start date, stop date, dosage, frequency, and indication. Any changes in the dosage or regimen of a concomitant medication also must be recorded on the eCRF.

[0325] At Screening, patients will be asked what medications they have taken during the previous 28 days. At each subsequent study visit, patients will be asked about any changes in concomitant medications since the previous visit.

[0326] Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care *except* for the following:

- Other experimental drugs or devices
- Other systemic medication for treatment of PVNS such as imatinib or nilotinib
- Chronic daily corticosteroids  $\geq 10$  mg/kg prednisone (or equivalent)

[0327] If a patient uses a prohibited medication or undergoes tumor resection, the Sponsor should be consulted for a decision on whether the patient should be withdrawn from the study.

[0328] Patients may initiate or continue pain medications as dictated by standard clinical practice. Transfusions are permitted as needed.

[0329] No routine premedication will be administered for the initial FPA008 dose. If a patient develops nausea, vomiting, or other infusion-related AEs, the patient may be pre-medicated with antiemetics, steroids, or antihistamines prior to subsequent infusions of FPA008 at the discretion of the Investigator. The treatment will be administered according to the institution's standard practice, and should be captured on the patient's eCRF.

## 6. Parameters and Methods of Assessment

[0330] Safety of FPA008 will be assessed by monitoring AEs and changes in physical examinations (including weight), vital signs, 12-lead ECGs, disease related signs and symptoms, and clinical laboratory measurements. Blood samples will be evaluated for immunogenicity.

### 6.1. Tumor Response Parameters

[0331] MRI will be performed at Screening (within 28 days prior to first dose), 4, 8, and 16 weeks following the start of treatment (Appendix 1). MRIs should be completed within 1 week of dose administration when re-imaging is scheduled. All patients should have tumor response parameters assessed at the 30 days ( $\pm 7$  days) and 90 days ( $\pm 7$  days) End of Treatment Follow-up Visits, unless a tumor assessment has been performed within the previous 6 weeks or if tumor progression was previously determined.

[0332] Clinical assessment of health outcomes (function, symptoms) will be done at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks or until treatment is discontinued.

[0333] Patients who have not progressed after the End of Treatment Follow-up Period are to be followed every 14 weeks ( $\pm 2$  weeks) (see section 7.2.10) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

[0334] Response will be evaluated using RECIST 1.1 (Eisenhauer, 2009) and the Total Volume Score (Tap, 2014) for radiologically measurable disease. MRI will be used for radiologic measurement of tumor.

[0335] Linear measurements of diffuse PVNS are complicated by a number of factors. Since the tumors are characteristically amorphous and can fluctuate in shape, correlation of serial linear measurements with changes in tumor volume depends on where the measurements are made. However, poor contrast between the tumor and adjacent tissue in certain locations limits where these measurements can be made accurately. Additionally, linear measurements are highly vulnerable to variations in the plane of section on serially acquired images. Nevertheless, given the longstanding tradition of RECIST in oncology clinical trials, linear measurements of up to two measurable tumor locations per joint or tendon sheath, as per RECIST 1.1 guidelines, will be used in this study as a reference.

[0336] Radiologic response will also be assessed by the TVS. The TVS has been used in a recent study of PVNS that showed a treatment effect of a CSF1R tyrosine kinase inhibitor.

[0337] The clinical impact of PVNS is believed to stem primarily from the mass effect and local structural damage caused by tumor growth within limited articular and peri-articular spaces. Tumor growth interferes with joint flexion and can also destroy the structural and functional integrity of joints as tumor invades local bones and soft tissues. The goals of imaging in clinical trials of PVNS are thus to monitor changes in the volume of the tumor and to monitor

any associated damage to local tissues.

[0338] Volumetric quantification of diffuse PVNS is complicated by irregular shape of the tumor, heterogeneous contrast between the tumor and its surrounding structures, and variable enhancement by intravenous gadolinium-based contrast agents. Tumor margins are thus difficult to delineate in certain locations, making automated segmentation unreliable and manual segmentation subjective. Hemosiderin deposition usually does not improve contrast substantially, as the distribution of hemosiderin is variable, heterogeneous, and not always confined to the tumor. Additionally, discriminating viable tumor from inactive scar tissue or intra- and perilesional fluid collections can be difficult. Under such circumstances, visual scoring using semi-quantitative ordinal scales is usually more reliable than volumetric quantification, as has been the experience with synovial thickening assessments in clinical trials of arthritis. Trials employing MRI for evaluation of anti-inflammatory therapy for arthritis have been based on semi-quantitative scoring.

[0339] The TVS scale is based on 10% increments of the estimated volume of the maximally distended synovial cavity, which varies from joint to joint, or of the maximally distended tendon sheath (assumed to be three times the diameter of the involved tendon). Thus, a tumor that is equal to the volume of a maximally distended synovial cavity or tendon sheath would be scored 10, whereas a tumor that was 70% of that volume would be scored 7, and a tumor twice that volume would be scored 20.

[0340] Individual patient outcomes by TVS are classified according to the following criteria:

- Complete Response (CR): lesion completely gone
- Partial Response (PR):  $\geq 50\%$  decrease in volume score relative to baseline
- Progressive Disease (PD):  $\geq 30\%$  increase in volume relative to lowest score during the study whether at baseline or some other visit
- Stable Disease (SD): does not meet any of the prior criteria based on score during study.

**Note:** Tumor assessments performed as part of the patient's standard of care within 28 days (4 weeks) of the first dose of FPA008 do not need to be repeated during Screening.

## **6.2. Safety Parameters**

### **6.2.1. Laboratory Parameters**

[0341] Laboratory assessments will be performed locally at each study site's laboratory by means of their established methods. Before starting the study, the Investigator will provide the Sponsor (and/or designee) with a list of the normal ranges and units of measurement.

[0342] Blood samples should be taken using standard venipuncture techniques. The following laboratory parameters (Table 5) will be determined in accordance with the Schedule of Assessments (Appendix 1):

**Table 5: Laboratory Assessments**

<b>Hematology:</b> Complete blood cell (CBC) with differential: white blood cells (WBC) ANC neutrophils (%) eosinophils (%) basophils (%) lymphocytes (%) monocytes (%) platelets hemoglobin hematocrit red blood cells (RBC) RBC indices: mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC)	
<b>Urinalysis:</b> Dipstick (appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood) If dipstick is positive (2+ or greater) for blood or protein, perform a microscopic examination.	
<b>Clinical chemistry:</b> albumin glucose lactate dehydrogenase (LDH) Troponins (cardiac and skeletal) blood urea nitrogen (BUN) calcium chloride carbon dioxide (CO <sub>2</sub> ) creatinine direct bilirubin phosphate alkaline phosphatase ALT (SGPT) AST (SGOT) CK isoenzymes (if CK abnormal) potassium sodium total bilirubin total cholesterol total protein uric acid CK (creatinine kinase)	
<b>Other chemistry tests:</b> Magnesium	
<b>Coagulation:</b> INR PT APTT	
<b>Serum pregnancy test:</b> For females of childbearing potential only.	
<b>Other test:</b> <b>Antinuclear antibodies (ANA)</b>	

[0343] Abnormal laboratory results that lead to a change in patient treatment



management (e.g., dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE page of the eCRF. Values meeting SAE criteria must be reported as SAEs.

[0344] The Investigator's determination of relationship of the AE to drug therapy and counter measures undertaken will be documented and noted on the eCRF.

#### **6.2.2. Vital Signs**

[0345] Vital signs will include sitting blood pressure, pulse, respiration rate, and temperature. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Vital signs will be performed in accordance with the Schedule of Assessments (Appendix 1).

#### **6.2.3. Electrocardiograms**

[0346] Twelve-lead ECGs will be performed in accordance with the Schedule of Assessments (Appendix 1). The Investigator must review the ECG, document this review in the source documents, and record any clinically significant changes that occur during the study as an AE in the eCRF.

#### **6.2.4. Pregnancy**

[0347] Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. A negative serum pregnancy test fewer than 5 days prior to first dosing with FPA008 treatment is mandatory. Patients of reproductive potential (males and females) must practice 2 effective contraception methods (Section 4.2). during the study and for 6 months after last treatment.

#### **6.2.5. Physical Examinations**

[0348] Physical examinations will be performed in accordance with the Schedule of Assessments (Appendix 1).

[0349] A complete physical examination including height and weight will be performed at Screening. Complete physical examinations should be conducted per the Schedule of Events (Appendix 1).

#### **6.2.6. Immunogenicity**

[0350] Immunogenicity, defined as an immune response to FPA008, will be assessed by measurement of total anti-FPA008 antibodies from all patients. Immunogenicity testing will

consist of screening, confirmation, and titration.

[0351] Samples for immunogenicity assessment will be drawn from each patient at the time points designated in Appendix 2. Samples for immunogenicity testing will be collected and processed according to the instruction provided in the Laboratory Manual.

#### **6.2.7. ECOG Performance Status**

[0352] ECOG performance status will be assessed at Screening, within 72 hours prior to dosing, and through the End of Treatment Follow-up Period (Appendix 1).

#### **6.3. Pharmacokinetic Parameters**

[0353] In this study, samples for the determination of serum FPA008 will be collected as outlined in Appendix 2. The sampling will allow determination of the exposure (AUC),  $C_{\max}$ ,  $C_{\min}$  (trough concentration), CL, and  $V_{ss}$ . Other PK parameters, such as accumulation ratio and half-life, may also be calculated as data allow.

[0354] These samples will be collected and processed according to the instructions provided in a separate Laboratory Manual.

#### **6.4. Pharmacodynamic Parameters**

[0355] The following exploratory endpoints will be assessed (Appendix 2):

- Serum: CSF1 and IL34 ligand concentration, CTx, and TRAP5b bone resorption marker concentrations
- Whole blood – CD14<sup>+</sup>/CD16<sup>+</sup> monocyte subsets levels

[0356] The following procedures (see Appendix 1) only apply to patients who sign the applicable Optional Research Informed Consent Form; the purpose of these procedures is to understand the impact of FPA008 on changes in local biomarkers of inflammation (synovium and synovial fluid) and distribution of FPA008 to the involved joint (synovial fluid):

- Synovium (optional)
  - Evaluate synovial biopsy for *CSF1* gene translocation (if not previously done) at pretreatment
  - Baseline and on treatment synovial biopsy, IHC for:
    - CSF1 and CSF1R
    - CD68

- Synovial fluid (optional)
- FPA008 concentration; cellular component for above markers by IHC.

### 6.5. Patient and Clinician Reported Outcome Measures

[0357] Clinical assessment of health outcomes (function, symptoms) will be done at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks or until treatment is discontinued, and through the End of Treatment Follow-up Period. Patients who have not progressed and enter Long-Term Follow-up are to be followed every 14 weeks ( $\pm 2$  weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. The following tools will be used to collect exploratory endpoint data on symptom and functional outcomes:

- Ogilvie-Harris (OH) Scale (Appendix 4): This tool was developed specifically for patients with PVNS (Ogilvie-Harris, 1992) and has been used in other PVNS publications (De Ponti, 2003; Rhee, 2010). Characteristics of this tool include the following:
  - It is a clinician reported outcome (CRO) measure
  - It is based on a 0–3 interval scale for each of the 4 domains:
    - Pain
    - Synovitis/effusion
    - Range of motion
    - Functional capacity
  - It uses lower end of the scale (score min = 0) indicating severe disability, pain and functional loss and the higher values (score max = 12) indicating no disability. Scores can be summed and classified as follows:
    - Poor condition (0 – 3 points)
    - Fair condition (4 – 6 points)
    - Good condition (7 – 9 points)
    - Excellent condition (10 – 12 points)

- Is selected for this study relative to other location-specific outcome measures (such as the WOMAC, KOOS, etc.) because:
  - It can be used in any joint affected by PVNS
  - It is specific to the disease of PVNS by addressing the symptomology of PVNS (pain and synovitis/effusion)
  - It has a low respondent burden – 4 “questions”
- Has, however, only been published in patients with PVNS of the knee and has not been validated against a gold-standard outcomes measure such as the SF-36 or EQ-5D-5L scales. Thus the EQ-5D-5L scale (a patient-reported outcome) will also be used in this study.
- EQ-5D-5L (Appendix 5): This is a well-known generic measure of health status originally published in 2001(Rabin) which includes the following characteristics:
  - Has been used in numerous diseases and chronic conditions in multiple countries
  - Is a patient reported outcome (PRO) measure
  - Is used as a functional assessment in an active PVNS clinical trial (MCS110, Novartis)
  - Is based on a 0–5 interval scale for each of the 5 domains with the lower end of the scale (score min = 0) anchored at death (or worse than death) health state and the higher values (score max = 100) anchored at perfect health state:
    - (1) Mobility
    - (2) Self-care
    - (3) Usual activities
    - (4) Pain/discomfort
    - (5) Anxiety/depression
  - It also uses a VAS to measure the responders current health on a 20-cm vertical line with 0 = “worst imaginable health” and 100 = “best imaginable health”
  - It has been validated in multiple countries and is available in 119 languages. It has a low respondent burden with only 6 questions and is available in several media (paper, web, and tablet).

## **7. Study Conduct**

### **7.1. Overview of Patient Assessments**

[0358] After an initial Screening period of up to 28 days (4 weeks), patients will be treated with FPA008 every 2 weeks ( $\pm$  3 days) in 28-day cycles, and FPA008 will be administered over approximately 30 minutes. All time points of assessments should be completed in the timeframe stated. Assessments performed prior to the patient signing the informed consent are acceptable only if confirmed to have been standard of care.

[0359] The schedule of detailed patient assessments is shown in Appendix 1 and Appendix 2. Instructions for the sampling and processing of PK, PD, and immunogenicity data are described in a separate, protocol-specific laboratory manual.

### **7.2. Study Assessments and Procedures by Visit**

#### **7.2.1. Screening Period (Day –28 to Day 0)**

[0360] Patients who have fully consented to participation in the study will undergo Screening assessments within 28 days (4 weeks) prior to administration of the first infusion of FPA008 (unless otherwise stated). To determine if the patient meets all the inclusion criteria and does not violate the exclusion criteria, the following procedures will be performed (Appendix 1):

- Written, signed informed consent must be collected prior to any study-specific procedures
- Complete medical and disease history
- Demographic and baseline characteristics
- Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [°C] after 5 minutes rest)
- Complete physical examination, including height and weight
- ECOG performance status evaluation
- 12-lead ECG (required at Screening, and if clinically indicated during the study)
- AE reporting, if applicable
- Document prior and concurrent medications
- Quantiferon test (for latent TB)
- Clinical safety labs as outlined in Table 5 (including ANA)
- Ogilvie-Harris and EQ-5D-5L assessments
- Optional archival tissue
- Optional synovial biopsy
- Optional synovial fluid aspirate
- Serum pregnancy test (beta-human chorionic gonadotropin [ $\beta$ -HCG]),  $\leq$  5 days prior to Cycle 1, Day 1, for women of childbearing potential
- Radiological imaging: MRI of the involved joint(s) is to be performed within 28 days prior to the first infusion of FPA008. If the MRI is performed as part of the patient's standard of care within 28 days of the first study infusion it does not need to be repeated if the documentation of results is provided and is adequate for an assessment.

[0361] **Note:** A protocol-specific patient registration form must be submitted to the Sponsor (or designee) to confirm patient eligibility prior to initiation of study treatment.

**7.2.2. Treatment Allocation (Dosing Assignment)**

[0362] This is an open-label study. Enrollment numbers will be faxed or emailed to the Investigator (or designee). The Sponsor (or designee) will maintain records of the number of patients treated within a specific cohort and will determine to which treatment cohort newly enrolled patients will be assigned.

**7.2.3. Phases 1 and 2: Cycle 1, Day 1**

[0363] The following procedures will be performed:

- Prior to FPA008 infusion (within  $\leq 72$  hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from Screening
  - AE reporting, if applicable
  - Review of concomitant medications
  - Record weight
  - Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [ $^{\circ}\text{C}$ ] after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 5
  - Serum  $\beta$ -hCG (evaluated by local laboratories) will be performed  $\leq 5$  days prior to the first dose of FPA008 only on women of childbearing potential
  - PK, ADA, serum biomarkers and  $\text{CD14}^{+}/\text{CD16}^{+}$  monocytes sample collections (within  $\leq 4$  hours) as outlined in Appendix 2.
- Study drug administration: Administer FPA008, by IV infusion over approximately 30 minutes
- Post FPA008 administration:
  - PK, serum biomarkers and  $\text{CD14}^{+}/\text{CD16}^{+}$  monocytes sample collections ( $\pm 5$  min) as outlined in Appendix 2.

- Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes, 15 minutes, 30 minutes, and 1 hour
- AE reporting, if applicable
- Review of concomitant medications

#### **7.2.4. Phases 1 and 2: Cycle 1, Day 2**

[0364] PK, serum biomarkers, and CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections as outlined in Appendix 2.

[0365] AE reporting, if applicable

[0366] Review of concomitant medications

#### **7.2.5. Phases 1 and 2: Cycle 1, Day 8**

[0367] Study patients will return to the study center on Day 8 ( $\pm$  2 days). No treatment will be administered.

[0368] The following assessments will be completed:

- Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [°C] after 5 minutes rest)
- Clinical safety labs with the exception of ANA, as outlined in Table 5
- PK, serum biomarkers, CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections as outlined in Appendix 2.
- AE reporting, if applicable
- Review of concomitant medications

#### **7.2.6. Phases 1 and 2: Cycle 1, Day 15**

[0369] Study patients will return to the study center on Day 15, and the following assessments will be completed.

- Prior to FPA008 infusion (within  $\leq$  72 hours unless otherwise stated):
  - Record weight



- Vital signs (sitting blood pressure, heart rate, respiration rate, and temperature [°C] after 5 minutes rest)
  - Clinical safety labs with exception of urinalysis and ANA as outlined in Table 5
  - Ogilvie-Harris and EQ-5D-5L assessments
  - PK, ADA, serum biomarkers and CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections (within ≤ 4 hours) as outlined in Appendix 2
  - Update medical and disease history
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Administer FPA008, by IV infusion over 30 minutes
  - Post FPA008 administration:
    - PK sample collection 15 minutes (±5 min) after end of infusion (as outlined in Appendix 2)
    - Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
      - 5 minutes, 15 minutes, 30 minutes, and 1 hour
    - 12-lead ECG (within approximately 30 minutes post-dose after PK/PD sample collection)
    - AE reporting, if applicable
    - Review of concomitant medications

#### **7.2.7. Phase 1: End of Cycle 1**

[0370] For Phase 1 patients, if at the end of Cycle 1 the Investigator determines that the patient may benefit from continued dosing with FPA008, entry into the Extended Treatment Period may be offered.

[0371] If the patient is continuing onto the Extended Treatment Period (Cycle 2 and beyond), proceed to procedures outlined in Section 7.2.8.

[0372] If the patient does not qualify to receive further doses of FPA008, the patient will return to the clinic for the End of Treatment Follow-up Visits.

**7.2.8. Phase 1 Extended Treatment/Phase 2 Cycle 2 and Subsequent Cycles**

[0373] Phase 1 Extended treatment may begin on Cycle 2, Day 1. Dosing will be discontinued if the patient experiences either disease progression or unacceptable toxicity.

[0374] At each infusion visit, patients are to remain at the study site after each administration of FPA008 until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted ((Appendix 1):

**7.2.8.1. Phases 1 and 2: Cycle 2 and Subsequent Cycles, Day 1**

[0375] Prior to each infusion of study drug (within  $\leq 72$  hours unless otherwise stated):

- Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [ $^{\circ}\text{C}$ ] after 5 minutes rest)
- Complete physical examination including weight at Cycle 2, 4, and 6
- ECOG performance status evaluation
- Ogilvie-Harris and EQ-5D-5L assessments
- Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 5
- PK, ADA, serum biomarkers and CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections (within  $\leq 4$  hours) on Day 1 of Cycles 2, 3, and 5, as outlined in Appendix 2
- MRI of the involved joint(s) using the same physical or radiologic parameter(s) used to evaluate baseline tumor measurements are to be done within 1 week of C2D1, C3D1, and C5D1
- Optional synovial biopsy up to -2 days prior to dose administration (Cycle 2 only) as outlined in Appendix 1
- Optional synovial fluid aspirate up to -2 days prior to dose administration (Cycle 2 only) as outlined in Appendix 1
- AE reporting, if applicable
- Review of concomitant medications

[0376] Study drug administration: Administer FPA008, by IV infusion over approximately 30 minutes

[0377] Post study drug administration:

- Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
- 5 minutes, 15 minutes, 30 minutes, and 1 hour
- PK sample collection 15 minutes ( $\pm 5$  min) after end of infusion on Day 1 of Cycles 3, and 5 (Appendix 1).
- AE reporting, if applicable
- Review of concomitant medication

**7.2.8.2. Phases 1 and 2: Cycle 2 and Subsequent Cycles, Day 15**

[0378] Prior to each infusion of study drug (within  $\leq 72$  hours unless otherwise stated):

- Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest)
- Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 5
- AE reporting, if applicable
- Review of concomitant medications

[0379] Study drug administration:

- Administer FPA008, by IV infusion over approximately 30 minutes

[0380] Post study drug administration:

- Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes, 15 minutes, 30 minutes, and 1 hour
- 12-lead ECG (within approximately 30 minutes post-dose after PK/PD sample collection)
- AE reporting, if applicable
- Review of concomitant medication

**7.2.9. End of Treatment Follow-Up Period**

[0381] Patients will return to the study center three times, approximately 30 days ( $\pm 7$  days), 60 days ( $\pm 7$  days), and 90 days ( $\pm 7$  days) after their last infusion of FPA008, to complete

the End of Treatment Follow-up Period.

[0382] The following assessments will be performed:

- Vital signs (sitting pulse, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest)
- 12-lead ECG at the 30 days ( $\pm 7$  days) End of Treatment Follow-up Visit only
- Complete physical examination at the 30 days ( $\pm 7$  days) End of Treatment Follow-up Visit only. Weight is to be recorded at all visits
- ECOG performance status evaluation
- Clinical safety labs as outlined in Table 5 (including ANA at the 30 days ( $\pm 7$  days) End of Treatment Follow-up Visit only)
- PK, ADA, serum biomarkers and CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections as outlined in Appendix 2
- Serum  $\beta$ -hCG (evaluated by local laboratories) in women of child-bearing potential
- MRI of the involved joint(s), Ogilvie-Harris, and EQ-5D-5L assessments at the 30 days ( $\pm 7$  days) and 90 days ( $\pm 7$  days) End of Treatment Follow-up Visits. These can be omitted if performed within 6 weeks prior or if tumor progression was previously determined.) Patients who have not progressed at treatment discontinuation and agree to continue participation in the study are to be followed every 14 ( $\pm 2$ ) weeks until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.
- AE reporting, if applicable
- Review of concomitant medications

#### **7.2.10. Long-Term Follow Up Period**

[0383] Patients who have not progressed should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period. Patients will be followed every 14 weeks ( $\pm 2$  weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

[0384] The following assessments will be performed:

- Clinical safety labs with the exception of urinalysis and ANA
- PK, ADA, serum biomarkers and CD14<sup>+</sup>/CD16<sup>+</sup> monocytes sample collections as outlined in Appendix 2
- MRI of the involved joint(s), Ogilvie-Harris, and EQ-5D-5L assessments
- AE reporting for ongoing adverse events thought to be related to study treatment, if applicable
- Reporting of concomitant medications (local therapy (e.g., resection, radiation) or a new systemic therapy only)

## **8. Statistical Methods**

[0385] Before database lock, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

[0386] Any deviations from the planned analyses will be described and justified in the final integrated study report.

### **8.1. Study Patients**

#### **8.1.1. Disposition of Patients**

[0387] The number and percentage of patients evaluable for DLT, safety, efficacy, PK and PD will be presented. Reasons for withdrawal will also be summarized.

#### **8.1.2. Protocol Deviations**

[0388] A summary of the number and percentage of patients with protocol deviations by type of deviation will be provided. Deviations will be defined in the SAP prior to database lock.

#### **8.1.3. Analysis Populations**

[0389] The following analysis populations are defined for the study:

- Safety Population—all patients who have received any portion of at least one dose of FPA008.
- DLT-Evaluable Population—all patients enrolled into Phase 1 of the study who received at least 2 doses of FPA008 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.

- PK-Evaluable Population—all patients who have received at least one dose of FPA008 and have had adequate PK assessments drawn for determination of the PK profile.
- Efficacy-Evaluable Population—all patients who met eligibility criteria, received at least 1 dose of FPA008, have measurable tumor lesions at baseline, and have at least 1 post-baseline disease assessment.
- Intent-to-Treat Population (ITT)—all enrolled patients. Patient without post-baseline disease assessment will be considered as non-responder.

## **8.2. General Considerations**

[0390] All analyses will be descriptive and will be presented by dose group and overall as appropriate. Patient data from Phase 2 will be summarized as a separate group. All patients dosed at the RD will also be summarized. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of valid cases, arithmetic mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

[0391] A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

## **8.3. Demographics, Baseline Characteristics, and Concomitant Medications**

[0392] Demographic data, medical history, other baseline characteristics, concomitant disease, and concomitant medication will be summarized by cohort and overall. To determine whether the criteria for study conduct are met, corresponding tables and listings will be provided. These will include an assessment of protocol deviations, study drug accountability, and other data that may impact the general conduct of the study.

## **8.4. Treatment Compliance**

[0393] Treatment administration will be summarized by cohort including dose administration, dose modifications or delays, cumulative dose, average dose, number of infusions, and the duration of therapy.

### 8.5. Analyses of Tumor Response

[0394] Patients will be classified according to their best overall tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]).

Frequencies, proportions, and exact 95% CI of patients, when appropriate, stratified by their best overall tumor response will be calculated. Patients with a best overall tumor response of CR or PR with duration of at least 4 weeks (28 days) will be further classified as having an objective tumor response. Listing of patients with an objective tumor response will be presented.

[0395] Patients will be classified for response by RECIST 1.1 and the Total Volume Score. The Tumor Volume Score classifies response according to the following definitions: Complete Response [(CR) lesion completely gone by the end of the study], Partial Response [(PR)  $\geq 50\%$  decrease in volume score relative to baseline], Progressive Disease [(PD)  $\geq 30\%$  increase in volume relative to lowest score during the study whether at baseline or some other visit] or Stable Disease [(SD) does not meet any of the prior criteria based on score during study].

[0396] In addition to local review, all MRI scans will be centrally reviewed, and concordance between the local and central assessments of tumor response will be determined.

[0397] Duration of response will be calculated as the number of days from the first documentation of overall response (CR or PR) to the first documentation of disease progression or death, whichever comes first. Patients who are alive and progression-free at the time of data analysis will be censored at the time of their last assessment for tumor response.

[0398] In patients who respond adequately such that a decision is made to resect residual disease, the duration of response will be censored at the time of the surgical procedure.

### 8.6. Safety Analyses

[0399] Safety analyses will be performed separately within both phases of the study and for all patients combined. Data from all patients that receive any portion of at least 1 dose of FPA008 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized.

[0400] AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Version 4.03 Grade 3 or higher AEs.

[0401] Weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized

categorically and descriptively.

[0402] Shift tables displaying patient counts and percentages classified by baseline grade and maximum grade on treatment will be provided for laboratory data by cohort and overall. A marked laboratory change is defined as a shift from a baseline Grade 0 to Grade 3 (non-hematologic) or Grade 4 (hematologic) on treatment, or a shift from a baseline Grade 1 to Grade 4 on treatment. The number and percentage of patients with marked laboratory changes will be tabulated by cohort and overall.

### **8.7. Efficacy Analysis**

[0403] Efficacy analyses will be descriptive. The overall response rate will be summarized with frequencies and percentages. The duration of response for CR and PR patients will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, median, minimum, and maximum) as well as categorically. Response and duration of response will be determined using RECIST 1.1. Kaplan-Meier methodology will be used to summarize duration of response and PFS.

### **8.8. Pharmacokinetic Analyses**

[0404] Individual and mean ( $\pm$ SD) serum FPA008 concentration-time data will be tabulated and plotted by dose level. FPA008 PK parameters will be calculated from the serum drug concentration-time data using a non-compartmental analysis (NCA) method with intravenous infusion input in Phoenix WinNonLin ( Certara LP, St. Louis, MO). Alternative methods may be considered. Estimated individual and mean ( $\pm$ SD) PK parameters will be tabulated and summarized by dose level. Other descriptive statistics might be reported for serum FPA008 concentration-time data and estimated PK parameters. Dose proportionality, drug accumulation, and attainment of steady state will be evaluated whenever it is possible.

[0405] The impact of immunogenicity on FPA008 exposure will be assessed.

### **8.9. Interim Analyses**

[0406] No formal interim analysis is planned.

[0407] Safety data will be reviewed on a routine basis by the Sponsor and CRO. In Phase 1, the Sponsor (and/or designee) and Investigator(s) will review safety data from each dose cohort prior to dose escalation or de-escalation. Adverse event data from the extended treatment period will be presented to the medical monitors when available.



**8.10. Determination of Sample Size**

[0408] Three patients per dose group, with a sample size increase to 6 in the case of DLT, is generally accepted as adequate to determine the safety of escalating doses of novel oncologic drugs. If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue until 2 of 3–6 patients treated at a dose level experience a DLT. The MTD is defined as the maximum dose at which  $< 33\%$  of patients experience a DLT during Cycle 1. After the MTD is determined, additional patients may be recruited at that dose level to further characterize the safety, PK, PD, and preliminary efficacy of FPA008. It is anticipated that 12-15 patients may be enrolled in Phase 1.

[0409] For the objective of estimating the ORR of FPA008 in patients with PVNS/dt-TGCT, it is estimated that approximately 30 patients will be enrolled in Phase 2. In addition, a total of approximately 33 to 36 patients will be enrolled at the RD overall. The following Table 6 displays the corresponding 95% CI and the precision for various sample sizes and observed response rates (Agresti, 1998).

**Table 6: Probability of Responders**

Sample Size	Observed Response Rate	95% CI	Precision (longest one-sided CI length)
30	15/30 (50%)	33.2% to 66.9%	~17%
	16/30 (53%)	36.1% to 69.8%	~17%
	17/30 (57%)	39.2% to 72.6%	~18%
	18/30 (60%)	42.3% to 75.4%	~18%
	19/30 (63%)	45.5% to 78.2%	~17%
	20/30 (67%)	48.7% to 80.9%	~18%
	21/30 (70%)	52.0% to 83.5%	~18%
	22/30 (73%)	55.4% to 86.0%	~18%
	23/30 (77%)	58.8% to 88.5%	~18%
	24/30 (80%)	62.3% to 90.9%	~18%
35	17/35 (49%)	33.0% to 64.4%	~16%
	18/35 (51%)	35.6% to 67.0%	~16%
	19/35 (54%)	38.2% to 69.5%	~16%
	20/35 (57%)	40.8% to 72.0%	~16%
	21/35 (60%)	43.5% to 74.5%	~16%
	22/35 (63%)	46.3% to 76.9%	~17%
	23/35 (66%)	49.1% to 79.2%	~17%
	24/35 (69%)	51.9% to 81.6%	~17%
	25/35 (71%)	54.8% to 83.8%	~16%
	26/35 (74%)	57.8% to 86.0%	~16%
	27/35 (77%)	60.7% to 88.2%	~16%
	28/35 (80%)	63.8% to 90.3%	~16%
40	20/40 (50%)	35.2% to 64.8%	~15%
	21/40 (53%)	37.5% to 67.1%	~15%
	22/40 (55%)	39.8% to 69.3%	~15%
	23/40 (58%)	42.2% to 71.5%	~16%
	24/40 (60%)	44.6% to 73.7%	~15%
	25/40 (63%)	47.0% to 75.8%	~16%
	26/40 (65%)	49.5% to 77.9%	~16%
	27/40 (68%)	51.9% to 80.0%	~16%
	28/40 (70%)	54.5% to 82.0%	~16%
	29/40 (73%)	57.0% to 84.0%	~16%
	30/40 (75%)	59.6% to 86.0%	~16%
	31/40 (78%)	62.3% to 87.9%	~16%
	32/40 (80%)	65.0% to 89.8%	~15%

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List of Abbreviations and Definitions

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC	Area under serum concentration-time curve
$\beta$ -HCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CK	Creatinine kinase
C <sub>max</sub>	Maximum serum concentration
C <sub>min</sub>	Minimum serum concentration
CL	Clearance
CO <sub>2</sub>	Carbon dioxide (bicarbonate)
CR	Complete response
CRC	Cohort Review Committee
CRO	Clinician reported outcome
CRO	Contract research organization
CSF1	Colony stimulating factor-1
CT	Computed tomography
CTx	Collagen-type I C-terminal telopeptide
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
dt-TGCT	Diffuse type tenosynovial giant cell tumor
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FNA	Fine needle aspiration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NTX	N-terminal telopeptide
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive disease
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcome
PS	Performance status

PT	Prothrombin time
PTT	Partial thromboplastin time
PVNS	Pigmented villonodular synovitis
QTc	Corrected QT interval
RBC	Red blood cell
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
$t_{1/2}$	Half-life
TB	Tuberculosis
TRAP5b	Tartrate resistant acid phosphatase 5b
TVS	Tumor volume score
ULN	Upper limit of normal
$V_{ss}$	Volume of distribution at steady state
WBC	White blood cell

Appendix 1: Schedule of Assessments

	Screening	Phases 1 and 2: Cycle 1					Phase 1 Extended Treatment Period / Phase 2 Cycle 2 and Subsequent Cycles			End of Treatment Follow-up Period <sup>s</sup>	Long- Term Follow Up Period <sup>t</sup>
		Day -28 to Day 0	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15			
			Week 1		Week 2	Week 3			≥ Week 4		
Procedure <sup>a, b</sup>	×										
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ADA Sampling <sup>o</sup>			X					X			X	X	X
PK and Serum Biomarkers Sampling <sup>o</sup>			X	X				X			X	X	X
CD14 <sup>+</sup> /16 <sup>+</sup> Monocyte Sampling <sup>p</sup>			X		X			X			X		X
Antinuclear Antibody (ANA) <sup>q</sup>	X										X		
FPA008 Study Drug Administration <sup>r</sup>			X					X			X		
Adverse events	X	-----X-----											X <sup>t</sup>
Prior/Concomitant Medications	X	-----X-----											X <sup>u</sup>

### Notes for Schedule of Assessments

- a. Unless specified, procedure is to be completed within  $\pm 72$  hours of scheduled time point and to be synchronized with administration day of FPA008 infusion.
- b. Any clinical assessment, laboratory study, or additional non-specified tests may be obtained at any time, if clinically indicated.
- c. Complete physical examination will be performed at Screening, Day 1 of Cycle 2, 4, 6, at the 30 days ( $\pm 7$  days) End of Treatment Follow-up Visit, and as determined by the Investigator, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow up on AE reports.
- d. Height is only required to be recorded at Screening. Weight is to be recorded Cycle 1, Days 1 and 15, and on Day 1 of subsequent cycles and at the End of Treatment Follow-up Visits.
- e. Vital signs include pulse, blood pressure, respiration rate, and temperature in the sitting position. Measure prior to dose and after completion of the IV infusion at the following time points: 5 minutes, 15 minutes, 30 minutes, and 1 h post-dose.
- f. Screening labs to include the Quantiferon test (for latent TB), and all women of childbearing potential (including those who have had a tubal ligation  $< 6$  months of first dose of FPA008) will have a serum pregnancy test.

### g. Clinical Safety Labs (Table 5):

**Hematology** including CBC with differential, platelets, hemoglobin, hematocrit, RBC, and RBC indices.

**Chemistry** includes CK (creatinine kinase), AST (aspartate transaminase), ALT (alanine transaminase), troponins (cardiac and skeletal), CK isoenzymes, carbon dioxide, bilirubin (direct and total), BUN (blood urea nitrogen), calcium, chloride, creatinine, glucose, LDH (lactate dehydrogenase), phosphate, potassium, sodium, magnesium, and, if applicable, serum pregnancy. Additional tests may be obtained at any time, if clinically indicated.

**Urinalysis** will only be done at Screening and at the End of Treatment Follow-up Visits, and may be repeated at any time if clinically indicated.

**Coagulation** including INR, PTT and APTT.

- h. Obtain ECG records at Screening, approximately 30 minutes post-dose on Day 15 for all cycles, and at the 30 days ( $\pm 7$  days) End of Treatment Follow-up Visit. Additional ECGs should be obtained at any time, and/or if serum CK or cardiac troponin is elevated; if abnormal (excluding sinus tachycardia), ECGs should be obtained (if clinically indicated), until the abnormality is resolved or clinically stable. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for approximately  $\geq 5$  minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.
- i. MRI of the affected joint(s) will be performed during Screening and within 7 days of the following: 4 (C2D1), 8 (C3D1), and 16 (C5D1) weeks. Patients should have an MRI done at the 30 days ( $\pm 7$  days) and 90 days ( $\pm 7$  days) End of Treatment Follow-up Visits, unless it was already performed within the previous 6 weeks or if tumor progression was previously determined. Patients who have not progressed and enter Long-Term Follow-up should have MRI performed every 14 weeks ( $\pm 2$  weeks) for duration of response until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review.
- j. All women of childbearing potential (including those who have had a tubal ligation  $< 6$  months of first dose of FPA008) will have a serum pregnancy test  $\epsilon$  Screening and at End of Treatment Follow-up Visits.
- k. The Ogilvie-Harris and EQ-5D-5L assessments will be performed at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks, or until treatment is discontinued. These can be omitted if performed within 6 weeks prior to the End of Treatment Follow-up Visits. Patients who have not progressed and enter Long-Term Follow-up are to be followed every 14 weeks ( $\pm 2$  weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

- l. Optional archival tumor tissue will be collected at Screening, if available.
- m. Optional synovial biopsies will be collected at Screening and up to -2 days prior to the C2D1 dose administration.
- n. Optional synovial fluid aspirate will be extracted at Screening and up to -2 days prior to the C2D1 dose administration.
- o. Blood samples will be collected for PK, ADA, and PD. Refer to Appendix 2 for collection times.
- p. Whole blood will be collected and shipped overnight to the testing facility for analysis of CD14<sup>+</sup>/16<sup>+</sup> monocytes. Refer to Appendix 2 for collection times.
- q. ANA testing will be performed at Screening and at the 30 days ( $\pm$  7 days) End of Treatment Follow-up Visit.
- r. FPA008 study drug will be administered every 2 weeks ( $\pm$  3 days) in 28-day cycles for 24 weeks. The Cycle 2, Day 1 infusion of FPA008 can only be administered after completion of the 28-day DLT window. All subsequent infusions can be administered with a  $\pm$ 3 day window. Patients should not have 2 doses of FPA008 within 7 days. The first dose of each cycle is considered Day 1 of each cycle, cycles will repeat every 28 days unless there is a treatment delay. Patients can have treatment delay of Day 1 of the subsequent cycle as long as the Day 1 treatment is within 6 weeks of the last treatment. FPA008 will be administered over approximately 30 minutes.
- s. Performed at 30 days ( $\pm$  7 days), 60 days ( $\pm$  7 days) and 90 days ( $\pm$  7 days) after the last dose of study treatment for all patients who complete the treatment period or who terminate early. All adverse events (including serious adverse events), regardless of attribution, will be recorded until 90 days after the last dose of study treatment. Ongoing adverse events will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient withdraws consent.
- t. Patients who have not progressed should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period. Patients are to be followed every 14 weeks ( $\pm$  2 weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated for up to 52 weeks following CID1.
- u. Only ongoing adverse events thought to be related to study treatment should be followed during the Long-Term Follow-up Period.
- v. Only local therapy (e.g., resection, radiation) or a new systemic therapy will be recorded during the Long-Term Follow-up Period.

**Appendix 2: Study Flowchart for Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collections**

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 1	Day 1 (First Dose)	$\leq 4$ hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
		15 minutes after end of infusion ( $\pm 5$ minutes)	FPA008 PK (serum)
			Serum Biomarkers (serum)
		4 hours after end of infusion ( $\pm 5$ minutes)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
	Day 2	24 hours after infusion ( $\pm 2$ hours)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
	Day 8	168 hours after infusion ( $\pm 24$ hours)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
	Day 15 (Second Dose)	$\leq 4$ hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
		15 minutes after end of infusion ( $\pm 5$ minutes)	FPA008 PK (serum)
Cycle 2	Day 1 (First Dose)	$\leq 4$ hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
Cycle 3, and	Day 1 (First Dose)	$\leq 4$ hours Prior to infusion	FPA008 PK (serum)

Study Cycle	Study Day	Time Point	Type of Sample
5*			ADA (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)
		15 minutes after end of infusion (±5 minutes)	FPA008 PK (serum)
End of Treatment Follow-up and Long-Term Follow Up	Not applicable	Not applicable	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			CD14 <sup>+</sup> /CD16 <sup>+</sup> (whole blood)

\*The 15-minute post infusion PK blood draw is not required if FPA008 is not administered.

**Appendix 3: ECOG Performance Status**

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

**Appendix 4: Ogilvie-Harris Score for PVNS**

- Pain
  - ☐ Severe (0 point)
  - ☐ Moderate (1 point)
  - ☐ Slight (2 points)
  - ☐ None (3 points)
- Synovitis/effusion
  - ☐ Severe (0 point)
  - ☐ Moderate (1 point)
  - ☐ Slight (2 points)
  - ☐ None (3 points)
- Range of Motion (\*Normal = 150°)
  - ☐ > 20% loss (0 point)
  - ☐ 10%-20% loss (1 point)
  - ☐ 0% – 10% loss (2 points)
  - ☐ No Loss (3 points)

\*Example: loss of 15° flexion or extension = loss of 10%  $(150 - (150 - 15) / 150) = 10\%$
- Functional capacity
  - ☐ Minimal activity (0 point)
  - ☐ Some activity (1 point)
  - ☐ Most activities (2 points)
  - ☐ All activities (3 points)

**Appendix 5: EQ-5D-5L**

**Under each heading, please tick the ONE box that best describes your health TODAY**

**MOBILITY**

I have no problems in walking about

I have slight problems in walking about

I have moderate problems in walking about

I have severe problems in walking about

I am unable to walk about



**SELF-CARE**

I have no problems washing or dressing myself

I have slight problems washing or dressing myself

I have moderate problems washing or dressing myself

I have severe problems washing or dressing myself

I am unable to wash or dress myself

**USUAL ACTIVITIES** (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

**PAIN / DISCOMFORT**

I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

## **Appendix 6: Management of Systemic Hypersensitivity Reactions**

[0410] Staff administering study drug are required to closely monitor all patients for possible systemic hypersensitivity reactions (e.g., generalized exanthema, urticaria, paraesthesia, bronchoconstriction, palpitations) over the first 180 minutes after infusion, paying particular attention to those patients with a history of asthma or systemic reactions to allergenic injections.

[0411] All systemic hypersensitivity manifestations will be captured on the appropriate eCRF page(s) and identified as being due to a hypersensitivity reaction.

[0412] Systemic hypersensitivity reactions will be managed according to treatment protocols in effect at the investigational site. In the absence of such a protocol, the following standardized treatment protocol will be used:

- Clinically mild reactions (e.g., generalized rash or itching, hives) are treated as soon as possible with Benadryl® (diphenhydramine hydrochloride) 25 to 50 mg, orally or IV at the Investigator's discretion. The period of observation is extended beyond 3 hours, as necessary, until symptoms and signs have resolved or stabilized. Patients who have experienced a clinically mild reaction may continue to have study drug administered.
- Clinically moderate reactions (e.g., hypotension, shortness of breath, facial edema) are treated immediately and supportive care measures instituted as medically indicated (e.g., IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). Vital signs are monitored at 10-minute intervals until they have normalized. The period of observation is extended beyond 3 hours, if necessary, until symptoms and signs have resolved. In the event of a clinically moderate reaction, the patient should receive no further treatment with study drug.

- Clinically severe reactions (e.g., marked hypotension, syncope, severe bronchoconstriction, tongue or throat swelling, significant angioedema) are treated immediately, under the direct supervision of the investigator, and supportive care measures instituted as medically indicated (e.g., IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). Vital signs and systems are monitored at a minimum of 10-minute intervals for as long as the investigator considers it necessary to ensure patient safety. In the event of a clinically severe reaction, the patient should receive no further treatment with study drug.

[0413] These clinical classifications are for the purpose of recommending treatment for patients who experience systemic hypersensitivity reactions. These classifications will not be used to grade the severity of the systemic hypersensitivity event within the eCRF. The severity of these events will be documented per the grading system presented in NCI CTCAE v4.03.

[0414] Preliminary data from this trial shows that patients under treatment with a dose as low as 1 mg/kg demonstrated clinical improvement in some parameters according to the Ogilvie-Harris Score for PVNS, including:

- 1) reducing pain, for example, from severe (0 points) to none (3 points),
- 2) enhancing range of motion, for example, from loss more than 20% to no loss, and
- 3) increasing functional capacity, for example, from capable of having some activity to capable of have all activity.

An improving effect of the treatment was also seen with EQ-5D-5L Evaluation as least some of the patients receiving the treatment had improved ability in washing and dressing and other self-care activity.

**TABLE OF SEQUENCES**

[0415] Table 5 provides certain sequences discussed herein. All polypeptide and antibody sequences are shown without leader sequences, unless otherwise indicated.

Table 5: Sequences and Descriptions

SEQ ID NO	Description	Sequence
1	hCSF1R (full-length, no leader sequence)	IPVIEPSVPE LVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPAWPWN VLAQEVVVFEE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMIS SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTNLNDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSSEQNL IQEVTVGEGE NLKVMVEAYP GLQGFNWTYL GPFSDHQPEP KLANATTKDT YRHTFTLSLP RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ SLLTVETLEH NQTYECRAHN SVGSGSWAFI PISAGATHP PDEFLLTPVV VACMSIMALL LLLLLLLLYK YKQKPKYQVR WKIIESYEGN SYTFIDPTQL PYNEKWEFPR NNLFQFGKTLG AGAFGKVVEA TAFGLGKEDA VLKVAVKMLK STAHADKEA LMSELKIMSH LGQHENVNL LGACTHGGPV LVITEYCCYG DLLNFLRRKA EAMLGPSLSP QDPEGGVVDY KNIHLEKKYV RDSGFSSQGV VDTYVEMRPV STSSNDSFSE QDLKDGEDGR LELRDLLHFS SQVAQGMFL ASKNCIHRDV AARNVLLTNG HVAKIGDFGL ARDIMNDSNY IVKGNARLPV KWMAPESIFD CVYTVQSDVW SYGILLWEIF SLGLNPYPGI LVNSKFYKLV KDGYQMAQPA FAPKNIYSIM QACWALEPTH RPTFQQICSF LQEQAQEDRR ERDYNLPSS SRSGSGSSS SELEEESSE HLTCCCEQDI AQPLLQPNNY QFC
2	hCSF1R (full-length, + leader sequence)	MGPGVLLLLL VATAWHGQGI PVIEPSVPEL VVKPGATVTL RCVGNGSVEW DGPPSPHWTL YSDGSSSILS TNNATFQNTG TYRCTEPGDP LGGSAAIHL VKDPAWPWN LAQEVVVFED QDALLPCLLT DVPVLEAGVSL VRVRGRPLMR HTNYSFSPWH GFTIHRAKFI QSQDYQCSAL MGRKVMIS IRLKVQKVIP GPPALTLVPA ELVRIRGEAA QIVCSASSVD VNFVDVFLQHN NTKLAIPQQS DFHNNRYQKV LTLNLNDQVDF QHAGNYSCVA SNVQGKHSTS MFFRVVESAY LNLSSSEQNLI QEVTVGEGLN LKVMVEAYPG LQGFNWTYLG PFSHQPEPK LANATTKDTY RHTFTLSLPR LKPSEAGRYS FLARNPGGWR ALTFELTLRY PPEVSVIWT FINGSGTLLCA ASGYPQPNVT WLQCSGHTDR CDEAQVLQVW DDPYPEVLSQ EPFHKVTVQS LLTVETLEHN QTYECRAHNS VSGSGSWAFIP ISAGATHPP DEFLLTPVVV ACMSIMALLL LLLLLLLLYKY KQKPKYQVRW KIIESYEGNS YTFIDPTQLP YNEKWEFPRN NLQFGKTLGA GAFGKVVEAT AFGLGKEDAV LKVAVKMLKS TAHADKEAL MSELKIMSHL GQHENVNLL GACTHGGPVL VITEYCCYGD LLNFLRRKAE AMLGPSLSPG QDPEGGVVDYK NIHLEKKYVR RDSGFSSQGV DTYVEMRPVS TSSNDSFSEQ DLDKEDGRPL ELRDLLHFSS QVAQGMFLA SKNCIHRDVA ARNVLLTNGH VAKIGDFGLA RDIMNDSNYI VKGNARLPVK WMAPESIFDC VYTVQSDVWS YGILLWEIFS LGLNPYPGIL VNSKFYKLVK DGYQMAQPAF APKNIYSIMQ ACWALEPTHR PTFQQICSF LQEQAQEDRR RDTNLPSSS RSGSGSSSSS ELEEESSEH LTCCEQGDIA QPLLQPNNYQ FC
5	hCSF1R ECD.506	IPVIEPSVPE LVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPAWPWN VLAQEVVVFEE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMIS SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTNLNDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSSEQNL IQEVTVGEGE NLKVMVEAYP GLQGFNWTYL GPFSDHQPEP KLANATTKDT YRHTFTLSLP

		RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ SLLTVETLEH NQTYECRAHN SVSGSGSWAFI PISAGAH
6	hCSF1R ECD.506-Fc	IPVIEPSVPE LVVVKPGATVT LRCVGNGSVE WDGPPSPHWT LYSDGSSSIL STNNATFQNT GTYRCTEPGD PLGGSAAIHL YVKDPAWPWN VLAQEVVFFE DQDALLPCLL TDPVLEAGVS LVRVRGRPLM RHTNYSFSPW HGFTIHRAKF IQSQDYQCSA LMGGRKVMIS SIRLKVQKVI PGPPALTLVP AELVRIRGEA AQIVCSASSV DVNFDVFLQH NNTKLAIPQQ SDFHNNRYQK VLTNLNDQVD FQHAGNYSCV ASNVQGKHST SMFFRVVESA YLNLSSSEQNL IQEVTVGEGL NLKVMVEAYP GLQGFNWTYL GPFSHQPEP KLANATTKDT YRHTFTLSLP RLKPSEAGRY SFLARNPGGW RALTFELTLR YPPEVSVIWT FINGSGTLLC AASGYPPQPNV TWLQCSGHTD RCDEAQVLQV WDDPYPEVLS QEPFHKVTVQ SLLTVETLEH NQTYECRAHN SVSGSGSWAFI 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)	MGPGLVLLLL VVTAWHGQGI PVIEPSGPPEL VVKPGETVTI RCVGNGSVEW DGPISPHWTL YSDGPSSVLT TTNATFQNT TYRCTEPGDP LGGSAAIHLY VKDPAWPWN 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 PPEVSVIWT INSGTLLCA ASGYPPQPNV WLQCAGHTDR CDEAQVLQVW VDPHPEVLSQ EPFQKVTVQS LLTAETLEHN QTYECRAHNS VGSGSWAFIP ISAGAR
8	cynoCSF1R ECD-Fc (with leader sequence)	MGPGLVLLLL VVTAWHGQGI PVIEPSGPPEL VVKPGETVTI RCVGNGSVEW DGPISPHWTL YSDGPSSVLT TTNATFQNT TYRCTEPGDP LGGSAAIHLY VKDPAWPWN 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 PPEVSVIWT INSGTLLCA ASGYPPQPNV WLQCAGHTDR CDEAQVLQVW VDPHPEVLSQ EPFQKVTVQS LLTAETLEHN QTYECRAHNS VGSGSWAFIP ISAGARGSEP KSSDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPE EVTCTVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
3	Light chain leader sequence	METDTLLLV LLLWVPGSTG
4	Heavy chain leader sequence	MAVLGLLLCL VTFPSCVLS
9	Fab 0301 heavy chain variable	EVQLQQSGPE LVRPGASVKM SCKASGYTFT DNYMIWVKQS HGKSLEWIGD INPYNGGTTF NQKFQKATL TVEKSSSTAY MQLNSLTSED SAVYYCARES PYFSNLYVMD YWGQGTSTVTV SS

	region	
10	Fab 0301 light chain variable region	NIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDNYMNWY QOKPGQPPKL LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCHLSNEDLS TFGGGTKLEI K
11	Fab 0302 heavy chain variable region	EIQLQQSGPE LVKPGASVKM SCKASGYTFS DFNIHWVKQK PGQGLEWIGY INPYTDVTYVY NEKFKGKATL TSDRSSSTAY MDLSSLTSED SAVYYCASYF DGTFDYALDY WQQGTSITVS S
12	Fab 0302 light chain variable region	DVVVTQTPAS LAVSLGQRAT ISCRASESVD NYGLSFMNWF QOKPGQPPKL 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 SWGKGTTTLTV SS
14	Fab 0311 light chain variable region	DIVLTQSPAS LAVSLGQRAT ISCKASQSVD YDGDSHMNWF QOKPGQPPKL LIYTASNLES GIPARFSGSG SGADFTLTIH PVEEEDAATY YCQQGNEDPW TFGGGTRLEI K
15	0301 heavy chain CDR1	GYTFDNYMI
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	YINPYTDVTYV YNEKFKG
23	0302 heavy chain CDR3	YFDGTFDYAL DY
24	0302 light chain CDR1	RASESVDNYG LSFMN
25	0302 light chain CDR2	TASNLES
26	0302 light chain CDR3	QQSKELPWT
27	0311 heavy chain CDR1	GYIFTDYNMH

28	0311 heavy chain CDR2	EINPNNGVVV YNQKFKG
29	0311 heavy chain CDR3	ALYHSNFGWY FDS
30	0311 light chain CDR1	KASQSVDDYDG DSHMN
31	0311 light chain CDR2	TASNLES
32	0311 light chain CDR3	QQGNEDPWT
33	cAb 0301 heavy chain	EVQLQQSGPE LVRPGASVKM SCKASGYTFT DNYMIWVKQS HGKSLEWIGD INPYNGGTTF NQKFKGKATL TVEKSSSTAY MQLNSLTSED SAVYYCARES PYFSNLYVMD YWGQGTSTTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPVSSSLGT KTYTCNVDPK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVDVDSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
34	cAb 0301 light chain	NIVLTQSPAS LAVSLGQRAT ISCKASQSV DGDNYMNWY QQKPGQPPKL LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCHLSNEDLS TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLKADY EKHKVYACEV THQGLSPVT KSFNRGEC
35	cAb 0302 heavy chain	EIQLQQSGPE LVKPGASVKM SCKASGYTFS DFNHFWVKQK PGQGLEWIGY INPYTDVTYV NEKFKGKATL TSDRSSSTAY MDLSSLTSED SAVYYCASYF DGTFDYALDY WGQGTSTITVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVT SWNSGALTSG VHTFPAVLQS SGLYSLSSV VTPVSSSLGK TYTCNVDPK PSNTKVDKRV ESKYGPPCPP PAPEFLGGPS VFLFPPKPKD TLTMISRTPEV TCVVDVDSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK
36	cAb 0302 light chain	DVVVTQTPAS LAVSLGQRAT ISCRASESVD NYGLSFMNWF QQKPGQPPKL LIYTASNLES GIPARFSGSG SRTDFTLTID PVEADDAATY FCQQSKELPW TFGGGTRLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLKADY EKHKVYACEV THQGLSPVT KSFNRGEC
37	cAb 0311 heavy chain	EIQLQQSGPD LMKPGASVKM SCKASGYIFT DYNMHWVKQN QGKSLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSSSTAY MDLHSLTSED SAVYYCTRAL YHSNFGWYFD SWGKGTTTLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPVSSSLGT KTYTCNVDPK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVDVDSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
38	cAb 0311 light chain	DIVLTQSPAS LAVSLGQRAT ISCKASQSV DGDSHMNWY QQKPGQPPKL LIYTASNLES GIPARFSGSG SGADFTLTIH PVEEEDAATY YCQQGNEDPW TFGGGTRLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLKADY EKHKVYACEV THQGLSPVT KSFNRGEC

39	h0301-H0 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWQGQTLVTV SS
40	h0301-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWQGQTLVTV SS
41	h0301-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWIGD INPYNGGTTF NQKFKGRATL TVDKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWQGQTLVTV SS
42	H0302-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWMGY INPYTDVTYVY NEKFKGRVTI TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLLVTVS S
43	H0302-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWIGY INPYTDVTYVY NEKFKGRATL TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLLVTVS S
44	H0311-H1 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLLVTV SS
45	H0311-H2 heavy chain variable region	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVVY NQKFKGTTTL TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLLVTV 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	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDShMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI K



	region	
52	H0311-L1 light chain variable region	DIVLTQSPAT LSLSPGERAT LSCKASQSV D YGDGSHMNWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGADFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI K
53	h0301-H0 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPSSSLGT KTYTCNV D HK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVSVLTV 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 YWGQGTLLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPSSSLGT KTYTCNV D HK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVSVLTV 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 YWGQGTLLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPSSSLGT KTYTCNV D HK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
56	H0302-H1 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWMGY INPYTDVTYV NEKFKGRVTI TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLLTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSV VTPSSSLGTK TYTCNV D HKP SNTKVDKRV ESKYGPPCPP PAPEFLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK
57	H0302-H2 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYTFS DFNIHWVRQA PGQGLEWIGY INPYTDVTYV NEKFKGRATL TSDKSTSTAY MELSSLRSED TAVYYCASYF DGTFDYALDY WGQGTLLTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSV VTPSSSLGTK TYTCNV D HKP SNTKVDKRV ESKYGPPCPP PAPEFLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK
58	H0311-H1 heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYIFT DYNMHWVRQA PGQGLEWMGE INPNNGVVYV NQKFKGRVTI TVDKSTSTAY MELSSLRSED TAVYYCTRAL YHSNFGWYFD SWGQGTLLTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTPSSSLGT KTYTCNV D HK 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 LSCKASQSV D YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
61	h0301-L1 light chain	NIVLTQSPAT LSLSPGERAT LSCKASQSV D YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL 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 DSKDSTYSL 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 DSKDSTYSL 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 DSKDSTYSL STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
65	H0311-L0 light chain	EIVLTQSPAT LSLSPGERAT LSCKASQSV D YDGDHNMWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
66	H0311-L1 light chain	DIVLTQSPAT LSLSPGERAT LSCKASQSV D YDGDHNMWY QQKPGQAPRL LIYTASNLES GIPARFSGSG SGADFTLTIS SLEPEDFAVY YCQQGNEDPW TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSL STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
67	Human CSF1	EEVSEYCSHM IGSGLHLSLQ RLIDSQMETS CQITFEFVDQ EQLKDPVCYL KKAFLLVQDI MEDTMRFRDN TPNAIAIVQL QELSLRLKSC FTKDYEEHDK ACVRTFFYETP LQLEKVKNV FNETKNLLDK DWNIFSKNCN NSFAECSSQG HERQSEGS
68	Human IL-	NEPLEMWPLT QNEECTVTGF LRDKLQYRSR LQYMKHYFPI NYKISVPYEG VFRIANVTRL QRAQVSEREL RYLWVLVSLSATESVQDVLL EGHPSWKYLQ

	34	EVQTLNLLNVQ QGLTDVEVSP KVESVLSLLN APGPNLKLVR PKALLDNCFR VMELLYCSCC KQSSVLNWQD CEVPSPQSCS PEPSLQYAAT QLYPPPPWSP SSPPHSTGSV RVPRAQGEGL LP
69	Human acceptor A FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
70	Human acceptor A FR2	WVRQAPGQGL EWMG
71	Human acceptor A FR3	RVTITADKST STAYMELSSL RSEDNAVYYC AR
72	Human acceptor A FR4	WGQGTLLTVS S
73	Human acceptor B FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
74	Human acceptor B FR2	WVRQAPGQGL EWMG
75	Human acceptor B FR3	RVTITADKST STAYMELSSL RSEDNAVYYC AR
76	Human acceptor B FR4	WGQGTLLTVSS
77	Human acceptor C FR1	QVQLVQSGAE VKKPGSSVKV SCKAS
78	Human acceptor C FR2	WVRQAPGQGL EWMG
79	Human acceptor C FR3	RVTITADKST STAYMELSSL RSEDNAVYYC AR
80	Human acceptor C FR4	WGQGTLLTVS 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	FGGGTKVEIK

	FR4	
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 RGFIIIRKAKV LDSNTYVCKT MVNGRESTST GIWLKVN RVH PEPPQIKLEP SKLVIRGEA AQIVCSATNA EVGFNVILKR GDTKLEIPLN SDFQDNYYKK VRALSNAVD FQDAGIYSCV ASNDVGTRTA TMNFQVVESA YLNLTSQSL LQEVSVGDSL ILTVHADAYP SIQHYNWYTL GPFFEDQRKL EFITQRAIYR YTFKLFLNRV KASEAGQYFL MAQNKAGWNN LTFELTLRYP PEVSVTWMPV NGSDVLFCDV SGYPQPSVTW MECRGHTDRC DEAQALQVWN DTHPEVLSQK PFDKVI IQSQ LPIGTLKHNM TYFCKTHNSV GNSSQYFRAV SLGQSKQEPK SSDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTPPVVL 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 LPQSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTPPVLD DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK
95	Human Igk	RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC

## CLAIMS

1. Use of an antibody that binds human CSF1R in the manufacture of a medicament for reducing pain in a subject with pigmented villonodular synovitis (PVNS), wherein the antibody that binds human CSF1R is administered at a dose of 1-4 mg/kg, wherein the dose of the antibody is capable of reducing pain in PVNS subjects independently of tumor response, and wherein the antibody is selected from:

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

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

c) an antibody comprising a heavy chain comprising SEQ ID NO: 53 and a light chain comprising SEQ ID NO: 60.

2. A method of reducing pain in a subject with pigmented villonodular synovitis (PVNS), comprising administering to the subject a dose of 1-4 mg/kg of an antibody that binds human CSF1R, wherein the dose of the antibody is capable of reducing pain in PVNS subjects independently of tumor response, and wherein the antibody is selected from:

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

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

c) an antibody comprising a heavy chain comprising SEQ ID NO: 53 and a light chain comprising SEQ ID NO: 60.

3. The use of claim 1 or method of claim 2, wherein the antibody is administered once per week, once per two weeks, once per three weeks, or once per month.

4. The use or method of claim 3, wherein the antibody is administered once per two weeks.

5. The use or method of any one of claims 1 to 4, wherein the antibody is administered at a dose of 1 mg/kg.

6. The use or method of any one of claims 1 to 4, wherein the antibody is administered

at a dose of 2 mg/kg.

7. The use or method of any one of claims 1 to 4, wherein the antibody is administered at a dose of 3 mg/kg.

8. The use or method of any one of claims 1 to 4, wherein the antibody is administered at a dose of 4 mg/kg.

9. The use or method of any one of claims 1 to 8, wherein the tumor volume is reduced by at least 30% or at least 40% or at least 50% or at least 60% or at least 70% after administration of at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten doses of the antibody that binds human CSF1R.

10. The use or method of claim 9, wherein the tumor volume is tumor volume in a single joint.

11. The use or method of claim 10, wherein the single joint is selected from a hip joint and a knee joint.

12. The use or method of claim 9, wherein the tumor volume is total tumor volume in all joints affected by PVNS.

13. The use or method of any one of claims 1 to 12, wherein prior to a first dose of the antibody being administered, the subject received a first therapy selected from surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement.

14. The use or method of claim 13, wherein the PVNS recurred or progressed after the first therapy.

15. The use or method of any one of claims 1 to 12, wherein the antibody is administered prior to a therapy selected from surgical synovectomy, radiation beam therapy, radio isotope synovectomy, and joint replacement, or wherein the tumor is unresectable.

16. The use or method of any one of claims 1 to 15, wherein the subject has not received prior treatment with a CSF1R inhibitor.

17. The use or method of any one of claims 1 to 15, wherein the subject has received prior treatment with a CSF1R inhibitor.

18. The use or method of any one of claims 1 to 17, wherein the antibody blocks binding of human CSF1 and/or human IL-34 to human CSF1R.

19. The use or method of any one of claims 1 to 18, wherein the antibody inhibits ligand-induced human CSF1R phosphorylation *in vitro*.

20. The use or method of any one of claims 1 to 19, wherein the antibody is a humanized antibody.

21. The use or method of claim 20, wherein the antibody is huAb1.

22. The use or method of any one of claims 1 to 21, wherein the antibody is selected from a Fab, an Fv, an scFv, a Fab', and a (Fab')<sub>2</sub>.

23. The use or method of any one of claims 1 to 22, wherein the subject experiences (a) an increased range of motion in a joint, (b) an increase in functional capacity of a joint, or (c) both an increased range of motion in a joint and an increase in functional capacity of a joint, following at least one dose of the antibody.

24. The use or method of any one of claims 1 to 23, wherein the dose of the antibody is capable of reducing pain in PVNS subjects from severe (0 points) to none (3 points) according to Ogilvie-Harris scores for PVNS.

Ab ID	L/H chains	CDR1																				alt. CDR1																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
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Ab0301	parental	E	V	Q	L	Q	S	G	P	E	L	V	R	P	G	A	S	G	A	S	G	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A	S	G	A

FIG. 1A



Ab ID	L/H chains	CDRH2																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20								
cAb0301 human acceptor A	parental	S	L	E	N	I	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab1	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab2	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab3	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab4	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab5	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
	Ab6	G	L	E	N	M	G	D	I	N	P	Y	N	G	T	T	T	P	N	Q	K	F	K	G	G	K	K	E	L
cAb0302 human acceptor B	parental	G	L	E	N	I	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab7	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab8	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab9	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab10	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab11	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
	Ab12	G	L	E	N	M	G	Y	I	N	P	Y	T	D	V	T	V	Y	N	E	K	F	K	G	G	K	K	E	L
cAb 0311 human acceptor C	parental	S	L	E	N	M	G	E	I	N	P	N	N	G	V	V	V	Y	N	Q	K	F	K	G	G	K	K	E	L
	Ab13	G	L	E	N	M	G	E	I	N	P	N	N	G	V	V	V	Y	N	Q	K	F	K	G	G	K	K	E	L
	Ab14	G	L	E	N	M	G	E	I	N	P	N	N	G	V	V	V	Y	N	Q	K	F	K	G	G	K	K	E	L
	Ab15	G	L	E	N	M	G	E	I	N	P	N	N	G	V	V	V	Y	N	Q	K	F	K	G	G	K	K	E	L
	Ab16	G	L	E	N	M	G	E	I	N	P	N	N	G	V	V	V	Y	N	Q	K	F	K	G	G	K	K	E	L

FIG. 1B

Ab ID	L/H chains	CDRH3																Seq ID NO
		638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	
Ab0301	parental	N	S	L	T	S	R	S	E	D	S	A	V	Y	Y	C	A	9
Ab1	h0301-L0H0	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	59-72
Ab2	h0301-L0H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	39
Ab3	h0301-L0H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	40
Ab4	h0301-L1H0	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	41
Ab5	h0301-L1H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	39
Ab6	h0301-L1H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	40
Ab0302	parental	S	S	L	T	S	R	S	E	D	S	A	V	Y	Y	C	A	41
Ab7	h0302-L0H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	11
Ab8	h0302-L1H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	73-76
Ab9	h0302-L2H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	42
Ab10	h0302-L0H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	42
Ab11	h0302-L1H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	43
Ab12	h0302-L2H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	43
Ab0311	parental	H	S	L	T	S	R	S	E	D	S	A	V	Y	Y	C	A	13
Ab13	h0311-L0H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	77-80
Ab14	h0311-L1H1	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	44
Ab15	h0311-L0H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	44
Ab16	h0311-L1H2	S	S	L	R	S	E	D	S	E	D	T	A	V	Y	C	A	45

FIG. 1C

Ab ID	L/A chains	CDR3																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
CAb0301	parental	N	I	V	L	T	Q	S	P	A	S	L	A	V	S	L	P	G	E	R	A
human acceptor D		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab1	h0301-L0H0	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab2	h0301-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab3	h0301-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab4	h0301-L1H0	N	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab5	h0301-L1H1	N	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab6	h0301-L1H2	N	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
CAb0302	parental	D	V	V	L	T	Q	S	P	A	S	L	A	V	S	L	P	G	E	R	A
human acceptor E		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab7	h0302-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab8	h0302-L1H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab9	h0302-L2H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab10	h0302-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab11	h0302-L1H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab12	h0302-L2H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
CAb 0311	parental	D	I	V	L	T	Q	S	P	A	S	L	A	V	S	L	P	G	E	R	A
human acceptor F		E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab13	h0311-L0H1	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab14	h0311-L1H1	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab15	h0311-L0H2	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T
Ab16	h0311-L1H2	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T

FIG. 2A

Ab ID	L/H chains	CDRL2																					
		W	Y	Q	Q	K	P	G	Q	P	K	L	L	I	Y	A	S	N	L	E	S		
cAb0301	parental	W	Y	Q	Q	K	P	G	Q	P	K	L	L	I	Y	A	S	N	L	E	S		
human acceptor D																							
Ab1	h0301-L0H0	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
Ab2	h0301-L0H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
Ab3	h0301-L0H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
Ab4	h0301-L1H0	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
Ab5	h0301-L1H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
Ab6	h0301-L1H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	A	S	N	L	E	S	
cAb0302	parental	W	F	Q	Q	K	P	G	Q	P	K	L	L	I	Y	T	A	S	N	L	E	S	
human acceptor E																							
Ab7	h0302-L0H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab8	h0302-L1H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab9	h0302-L2H1	W	<div></div>	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab10	h0302-L0H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab11	h0302-L1H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab12	h0302-L2H2	W	<div></div>	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
cAb 0311	parental	W	Y	Q	Q	K	P	G	Q	P	K	L	L	I	Y	T	A	S	N	L	E	S	
human acceptor F																							
Ab13	h0311-L0H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab14	h0311-L1H1	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab15	h0311-L0H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S
Ab16	h0311-L1H2	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	T	A	S	N	L	E	S

FIG. 2B

Ab ID	L/H chains	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	CDRL3										89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	SEQ ID NO
Ab0301	parental	F	T	L	N	I	H	P	V	E	E	E	D	A	A	T	Y	Y	C	H	L	S	N	E	D	L	S	T	F	F	G	G	G	G	G	T	K	L	V	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	H	L	S	N	E	D	L	S	T	F	F	G	G	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	F	G	G	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	E	D	L	S	T	F	F	G	G	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	F	G	G	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	F	G	G	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	E	D	L	S	T	F	F	G	G	G	G	G	T	K	V	E	I	K	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	E	D	L	S	T	F	F	G	G	G	G	G	T	K	V	E	I	K	47							
Ab0302	parental	F	T	L	T	I	D	P	V	E	A	D	A	A	T	Y	F	C	Q	Q	S	K	E	L	P	W	T	F	F	G	G	G	G	G	T	R	L	V	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	Q	Q	S	K	E	L	P	W	T	F	F	G	G	G	G	G	T	K	V	E	I	K	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	F	G	G	G	G	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	E	L	P	W	T	F	F	G	G	G	G	G	T	K	V	E	I	K	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	E	L	P	W	T	F	F	G	G	G	G	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	F	F	G	G	G	G	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	E	L	P	W	T	F	F	G	G	G	G	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	F	F	G	G	G	G	G	T	K	V	E	I	K	50							
Ab0311	parental	F	T	L	T	I	H	P	V	E	E	E	D	A	A	T	Y	Y	C	Q	Q	G	N	E	D	P	W	T	F	F	G	G	G	G	G	T	R	L	V	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	Q	Q	G	N	E	D	P	W	T	F	F	G	G	G	G	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	F	G	G	G	G	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	F	F	G	G	G	G	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	F	G	G	G	G	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	F	G	G	G	G	G	T	K	V	E	I	K	52							

**FIG. 2C**

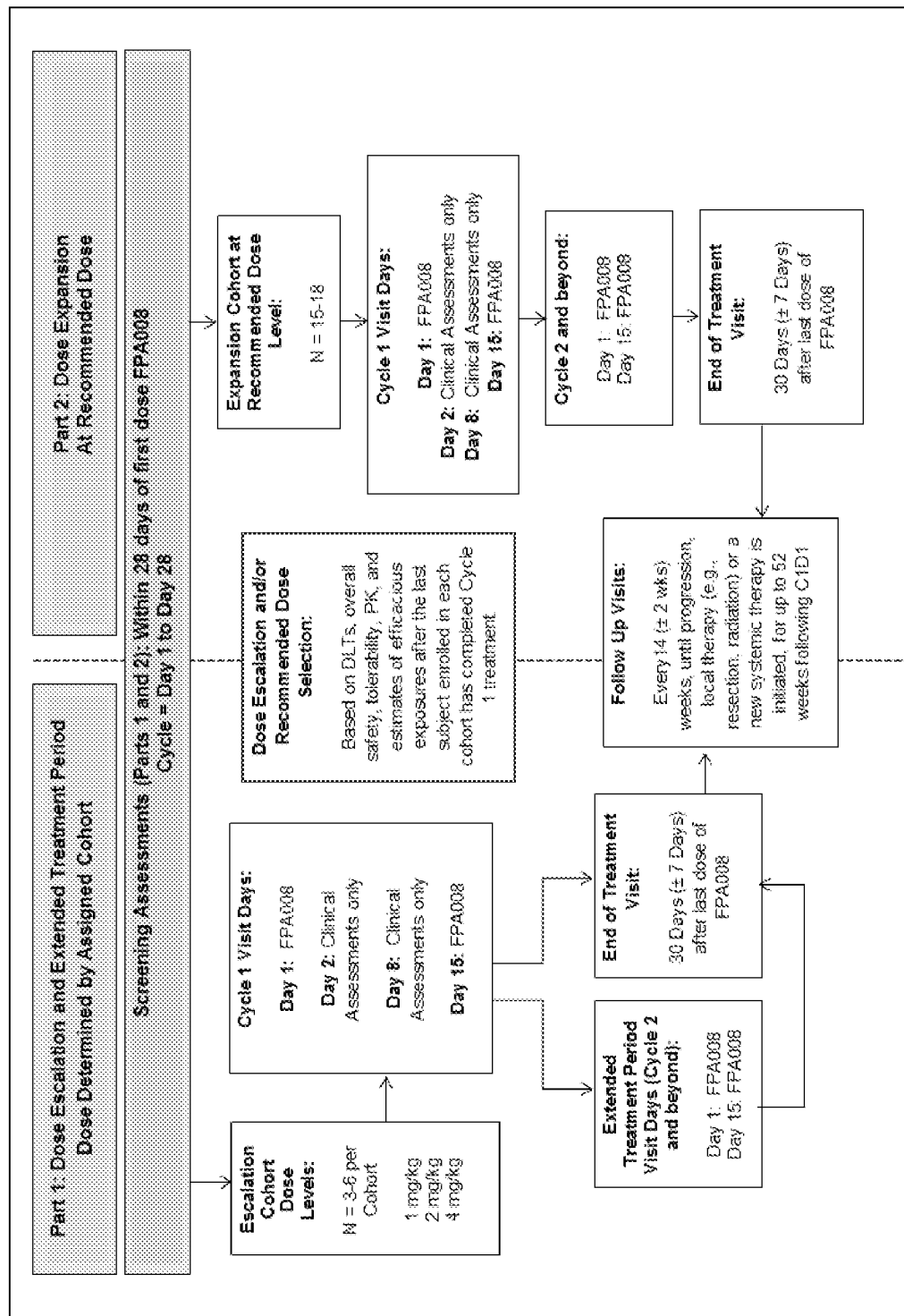


FIG. 3

2015-12-08\_01134-0037-00PCT\_SeqLi st\_ST25  
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<150> US 62/095,297  
<151> 2014-12-22  
<150> US 62/163,251  
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Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly Ser Ser Ser  
35 40 45

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr  
 435 440 445  
 Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn Gln Thr Tyr  
 450 455 460  
 Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp Ala Phe Ile  
 465 470 475 480  
 Pro Ile Ser Ala Gly Ala His Thr His Pro Pro Asp Glu Phe Leu Phe  
 485 490 495  
 Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu Leu Leu  
 500 505 510  
 Leu Leu Leu Leu Leu Tyr Lys Tyr Lys Gln Lys Pro Lys Tyr Gln  
 515 520 525  
 Val Arg Trp Lys Ile Ile Glu Ser Tyr Glu Gly Asn Ser Tyr Thr Phe  
 530 535 540  
 Ile Asp Pro Thr Gln Leu Pro Tyr Asn Glu Lys Trp Glu Phe Pro Arg  
 545 550 555 560  
 Asn Asn Leu Gln Phe Gly Lys Thr Leu Gly Ala Gly Ala Phe Gly Lys  
 565 570 575  
 Val Val Glu Ala Thr Ala Phe Gly Leu Gly Lys Glu Asp Ala Val Leu  
 580 585 590  
 Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala His Ala Asp Glu Lys  
 595 600 605  
 Glu Ala Leu Met Ser Glu Leu Lys Ile Met Ser His Leu Gly Gln His  
 610 615 620  
 Glu Asn Ile Val Asn Leu Leu Gly Ala Cys Thr His Gly Gly Pro Val  
 625 630 635 640  
 Leu Val Ile Thr Glu Tyr Cys Cys Tyr Gly Asp Leu Leu Asn Phe Leu  
 645 650 655  
 Arg Arg Lys Ala Glu Ala Met Leu Gly Pro Ser Leu Ser Pro Gly Gln  
 660 665 670  
 Asp Pro Glu Gly Gly Val Asp Tyr Lys Asn Ile His Leu Glu Lys Lys  
 675 680 685  
 Tyr Val Arg Arg Asp Ser Gly Phe Ser Ser Gln Gly Val Asp Thr Tyr  
 690 695 700

Val Glu Met Arg Pro Val Ser Thr Ser Ser Asn Asp Ser Phe Ser Glu  
 705 710 715 720  
 Gln Asp Leu Asp Lys Glu Asp Gly Arg Pro Leu Glu Leu Arg Asp Leu  
 725 730 735  
 Leu His Phe Ser Ser Gln Val Ala Gln Gly Met Ala Phe Leu Ala Ser  
 740 745 750  
 Lys Asn Cys Ile His Arg Asp Val Ala Ala Arg Asn Val Leu Leu Thr  
 755 760 765  
 Asn Gly His Val Ala Lys Ile Gly Asp Phe Gly Leu Ala Arg Asp Ile  
 770 775 780  
 Met Asn Asp Ser Asn Tyr Ile Val Lys Gly Asn Ala Arg Leu Pro Val  
 785 790 795 800  
 Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Cys Val Tyr Thr Val Gln  
 805 810 815  
 Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu Ile Phe Ser Leu  
 820 825 830  
 Gly Leu Asn Pro Tyr Pro Gly Ile Leu Val Asn Ser Lys Phe Tyr Lys  
 835 840 845  
 Leu Val Lys Asp Gly Tyr Gln Met Ala Gln Pro Ala Phe Ala Pro Lys  
 850 855 860  
 Asn Ile Tyr Ser Ile Met Gln Ala Cys Trp Ala Leu Glu Pro Thr His  
 865 870 875 880  
 Arg Pro Thr Phe Gln Gln Ile Cys Ser Phe Leu Gln Glu Gln Ala Gln  
 885 890 895  
 Glu Asp Arg Arg Glu Arg Asp Tyr Thr Asn Leu Pro Ser Ser Ser Arg  
 900 905 910  
 Ser Gly Gly Ser Gly Ser Ser Ser Glu Leu Glu Glu Glu Ser Ser  
 915 920 925  
 Ser Glu His Leu Thr Cys Cys Glu Gln Gly Asp Ile Ala Gln Pro Leu  
 930 935 940  
 Leu Gln Pro Asn Asn Tyr Gln Phe Cys  
 945 950

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Phe Leu Phe Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu  
 515 520 525  
 Leu Leu Leu Leu Leu Leu Leu Leu Tyr Lys Tyr Lys Gl n Lys Pro  
 530 535 540  
 Lys Tyr Gl n Val Arg Trp Lys Ile Ile Gl u Ser Tyr Gl u Gl y Asn Ser  
 545 550 555 560  
 Tyr Thr Phe Ile Asp Pro Thr Gl n Leu Pro Tyr Asn Gl u Lys Trp Gl u  
 565 570 575  
 Phe Pro Arg Asn Asn Leu Gl n Phe Gl y Lys Thr Leu Gl y Ala Gl y Ala  
 580 585 590  
 Phe Gl y Lys Val Val Gl u Ala Thr Ala Phe Gl y Leu Gl y Lys Gl u Asp  
 595 600 605  
 Ala Val Leu Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala Hi s Ala  
 610 615 620  
 Asp Gl u Lys Gl u Ala Leu Met Ser Gl u Leu Lys Ile Met Ser Hi s Leu  
 625 630 635 640  
 Gl y Gl n Hi s Gl u Asn Ile Val Asn Leu Leu Gl y Ala Cys Thr Hi s Gl y  
 645 650 655  
 Gl y Pro Val Leu Val Ile Thr Gl u Tyr Cys Cys Tyr Gl y Asp Leu Leu  
 660 665 670  
 Asn Phe Leu Arg Arg Lys Ala Gl u Ala Met Leu Gl y Pro Ser Leu Ser  
 675 680 685  
 Pro Gl y Gl n Asp Pro Gl u Gl y Gl y Val Asp Tyr Lys Asn Ile Hi s Leu  
 690 695 700  
 Gl u Lys Lys Tyr Val Arg Arg Asp Ser Gl y Phe Ser Ser Gl n Gl y Val  
 705 710 715 720  
 Asp Thr Tyr Val Gl u Met Arg Pro Val Ser Thr Ser Ser Asn Asp Ser  
 725 730 735  
 Phe Ser Gl u Gl n Asp Leu Asp Lys Gl u Asp Gl y Arg Pro Leu Gl u Leu  
 740 745 750  
 Arg Asp Leu Leu Hi s Phe Ser Ser Gl n Val Ala Gl n Gl y Met Ala Phe  
 755 760 765  
 Leu Ala Ser Lys Asn Cys Ile Hi s Arg Asp Val Ala Ala Arg Asn Val  
 770 775 780

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

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

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

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

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

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

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

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

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

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

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

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

<210> 3  
<211> 20  
<212> PRT  
<213> Artificial sequence

<220>  
<223> Light chain leader sequence

<400> 3

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

Gly Ser Thr Gly  
20

<210> 4

<211> 19  
 <212> PRT  
 <213> Arti fici al sequence

<220>  
 <223> Heavy chain leader sequence

<400> 4

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

Val Leu Ser

<210> 5  
 <211> 487  
 <212> PRT  
 <213> Arti fici al sequence

<220>  
 <223> hCSF1R ECD. 506

<400> 5

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

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

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

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

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

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

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

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

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

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

Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg Leu Lys Val

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



435

440

445

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

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

Pro Ile Ser Ala Gly Ala His  
 485

&lt;210&gt; 6

&lt;211&gt; 719

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; hCSF1R ECD. 506-Fc

&lt;400&gt; 6

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

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

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

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

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

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

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

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

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

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

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

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Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val Pro Ala Glu  
 180 185 190  
 Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Ser  
 195 200 205  
 Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn Asn Thr Lys  
 210 215 220  
 Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg Tyr Gln Lys  
 225 230 235 240  
 Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His Ala Gly Asn  
 245 250 255  
 Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser Thr Ser Met  
 260 265 270  
 Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln  
 275 280 285  
 Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn Leu Lys Val  
 290 295 300  
 Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp Thr Tyr Leu  
 305 310 315 320  
 Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala Asn Ala Thr  
 325 330 335  
 Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu Pro Arg Leu  
 340 345 350  
 Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg Asn Pro Gly  
 355 360 365  
 Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu  
 370 375 380  
 Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr Leu Leu Cys  
 385 390 395 400  
 Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu Gln Cys Ser  
 405 410 415  
 Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln Val Trp Asp  
 420 425 430  
 Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr  
 435 440 445

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Val Gl n Ser Leu Leu Thr Val Gl u Thr Leu Gl u Hi s Asn Gl n Thr Tyr  
 450 455 460  
 Gl u Cys Arg Al a Hi s Asn Ser Val Gly Ser Gly Ser Trp Al a Phe Ile  
 465 470 475 480  
 Pro Ile Ser Al a Gly Al a Hi s Gl u Pro Lys Ser Ser Asp Lys Thr Hi s  
 485 490 495  
 Thr Cys Pro Pro Cys Pro Al a Pro Gl u Leu Leu Gly Gly Pro Ser Val  
 500 505 510  
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr  
 515 520 525  
 Pro Gl u Val Thr Cys Val Val Val Asp Val Ser Hi s Gl u Asp Pro Gl u  
 530 535 540  
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys  
 545 550 555 560  
 Thr Lys Pro Arg Gl u Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser  
 565 570 575  
 Val Leu Thr Val Leu Hi s Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys  
 580 585 590  
 Cys Lys Val Ser Asn Lys Al a Leu Pro Al a Pro Ile Gl u Lys Thr Ile  
 595 600 605  
 Ser Lys Al a Lys Gly Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro  
 610 615 620  
 Pro Ser Arg Asp Gl u Leu Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu  
 625 630 635 640  
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Al a Val Gl u Trp Gl u Ser Asn  
 645 650 655  
 Gly Gl n Pro Gl u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser  
 660 665 670  
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg  
 675 680 685  
 Trp Gl n Gl n Gly Asn Val Phe Ser Cys Ser Val Met Hi s Gl u Al a Leu  
 690 695 700  
 Hi s Asn Hi s Tyr Thr Gl n Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 705 710 715

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

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

<400> 7

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Ala Ser Asn Ile Asp Val Asp Phe Asp Val Phe Leu Gln His Asn  
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225 230 235 240  
 Thr Thr Lys Leu Ala Ile Pro Gln Arg Ser Asp Phe His Asp Asn Arg  
 245 250 255  
 Tyr Gln Lys Val Leu Thr Leu Ser Leu Gly Gln Val Asp Phe Gln His  
 260 265 270  
 Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser  
 275 280 285  
 Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asp Leu Ser  
 290 295 300  
 Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn  
 305 310 315 320  
 Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp  
 325 330 335  
 Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala  
 340 345 350  
 Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu  
 355 360 365  
 Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg  
 370 375 380  
 Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr  
 385 390 395 400  
 Pro Pro Glu Val Ser Val Ile Trp Thr Ser Ile Asn Gly Ser Gly Thr  
 405 410 415  
 Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu  
 420 425 430  
 Gln Cys Ala Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln  
 435 440 445  
 Val Trp Val Asp Pro His Pro Glu Val Leu Ser Gln Glu Pro Phe Gln  
 450 455 460  
 Lys Val Thr Val Gln Ser Leu Leu Thr Ala Glu Thr Leu Glu His Asn  
 465 470 475 480  
 Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp  
 485 490 495  
 Ala Phe Ile Pro Ile Ser Ala Gly Ala Arg

500

505

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

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

<400> 8

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Ser 225 Ala Ser Asn Ile Asp 230 Val Asp Phe Asp 235 Val Phe Leu Gl n Hi s Asn 240  
 Thr Thr Lys Leu Ala 245 Ile Pro Gl n Arg Ser 250 Asp Phe Hi s Asp Asn 255 Arg  
 Tyr Gl n Lys Val 260 Leu Thr Leu Ser Leu 265 Gly Gl n Val Asp Phe Gl n Hi s  
 Ala Gly Asn 275 Tyr Ser Cys Val Ala 280 Ser Asn Val Gl n Gly 285 Lys Hi s Ser  
 Thr Ser 290 Met Phe Phe Arg Val 295 Val Gl u Ser Ala Tyr 300 Leu Asp Leu Ser  
 Ser 305 Gl u Gl n Asn Leu Ile 310 Gl n Gl u Val Thr Val 315 Gly Gl u Gly Leu Asn 320  
 Leu Lys Val Met Val 325 Gl u Ala Tyr Pro Gly 330 Leu Gl n Gly Phe Asn 335 Trp  
 Thr Tyr Leu Gly 340 Pro Phe Ser Asp Hi s 345 Gl n Pro Gl u Pro Lys 350 Leu Ala  
 Asn Ala Thr 355 Thr Lys Asp Thr Tyr 360 Arg Hi s Thr Phe Thr 365 Leu Ser Leu  
 Pro Arg 370 Leu Lys Pro Ser Gl u 375 Ala Gly Arg Tyr Ser 380 Phe Leu Ala Arg  
 Asn 385 Pro Gly Gly Trp Arg 390 Ala Leu Thr Phe Gl u 395 Leu Thr Leu Arg Tyr 400  
 Pro Pro Gl u Val Ser 405 Val Ile Trp Thr Ser 410 Ile Asn Gly Ser Gly 415 Thr  
 Leu Leu Cys Ala 420 Ala Ser Gly Tyr Pro Gl n Pro Asn Val Thr 430 Trp Leu  
 Gl n Cys Ala 435 Gly Hi s Thr Asp Arg 440 Cys Asp Gl u Ala Gl n 445 Val Leu Gl n  
 Val Trp 450 Val Asp Pro Hi s Pro 455 Gl u Val Leu Ser Gl n Gl u 460 Pro Phe Gl n  
 Lys 465 Val Thr Val Gl n Ser 470 Leu Leu Thr Ala Gl u 475 Thr Leu Gl u Hi s Asn 480  
 Gl n Thr Tyr Gl u Cys 485 Arg Ala Hi s Asn Ser 490 Val Gly Ser Gly Ser 495 Trp

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Pro Gly Lys  
740

<210> 9  
<211> 122  
<212> PRT



&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Fab 0301 heavy chain variable region

&lt;400&gt; 9

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

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

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

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

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

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

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

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

&lt;210&gt; 10

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Fab 0301 light chain variable region

&lt;400&gt; 10

Asn Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

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

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

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

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

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

<210> 11

<211> 121

<212> PRT

<213> Artificial sequence

<220>

<223> Fab 0302 heavy chain variable region

<400> 11

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

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

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

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

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

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

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

Gln Gly Thr Ser Ile Thr Val Ser Ser  
115 120

<210> 12

<211> 111

<212> PRT

<213> Artificial sequence

<220>

<223> Fab 0302 light chain variable region

<400> 12

Asp Val Val Val Thr Gln Thr Pro Ala Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr  
20 25 30

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

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

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

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

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

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

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

<400> 13

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

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

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

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

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

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

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

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

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

&lt;220&gt;

&lt;223&gt; Fab 0311 light chain variable region

&lt;400&gt; 14

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly  
 1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
 20 25 30

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

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

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

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

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

&lt;210&gt; 15

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; 0301 heavy chain CDR1

&lt;400&gt; 15

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

&lt;210&gt; 16

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; 0301 heavy chain CDR

&lt;400&gt; 16

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

Gly

&lt;210&gt; 17

&lt;211&gt; 13

&lt;212&gt; PRT

<213> Artificial sequence

<220>

<223> 0301 heavy chain CDR3

<400> 17

Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr  
1 5 10

<210> 18

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> 0301 light chain CDR1

<400> 18

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

<210> 19

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> 0301 light chain CDR2

<400> 19

Ala Ala Ser Asn Leu Glu Ser  
1 5

<210> 20

<211> 9

<212> PRT

<213> Artificial sequence

<220>

<223> 0301 light chain CDR3

<400> 20

His Leu Ser Asn Glu Asp Leu Ser Thr  
1 5

<210> 21

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> 0302 heavy chain CDR1

<400> 21

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

<210> 22

<211> 17  
 <212> PRT  
 <213> Arti fi ci al sequence

<220>  
 <223> 0302 heavy chain CDR2

<400> 22

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

Gly

<210> 23  
 <211> 12  
 <212> PRT  
 <213> Arti fi ci al sequence

<220>  
 <223> 0302 heavy chain CDR3

<400> 23

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

<210> 24  
 <211> 15  
 <212> PRT  
 <213> Arti fi ci al sequence

<220>  
 <223> 0302 light chain CDR1

<400> 24

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

<210> 25  
 <211> 7  
 <212> PRT  
 <213> Arti fi ci al sequence

<220>  
 <223> 0302 light chain CDR2

<400> 25

Thr Ala Ser Asn Leu Glu Ser  
 1 5

<210> 26  
 <211> 9  
 <212> PRT  
 <213> Arti fi ci al sequence

<220>  
 <223> 0302 light chain CDR3

<400> 26

Gln Gln Ser Lys Glu Leu Pro Trp Thr  
1 5

<210> 27  
<211> 10  
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<220>  
<223> 0311 heavy chain CDR1

<400> 27

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

<210> 28  
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<400> 28

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

Gly

<210> 29  
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<400> 29

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

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<400> 30

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

<210> 31  
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<220>

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<400> 31

Thr Ala Ser Asn Leu Glu Ser  
1 5

<210> 32

<211> 9

<212> PRT

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<220>

<223> 0311 light chain CDR3

<400> 32

Gln Gln Gly Asn Glu Asp Pro Trp Thr  
1 5

<210> 33

<211> 449

<212> PRT

<213> Artificial sequence

<220>

<223> cAb 0301 heavy chain

<400> 33

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

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

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

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

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
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Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
195 200 205

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser  
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
260 265 270

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

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val  
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
Page 27

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
435 440 445

Lys

<210> 34  
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<213> Artificial sequence

<220>  
<223> cAb 0301 light chain

<400> 34

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

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

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

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

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

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

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

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

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala  
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val  
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala  
165 170 175

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Val	Leu	Gln	Ser 180	Ser	Gly	Leu	Tyr	Ser 185	Leu	Ser	Ser	Val	Val 190	Thr	Val		
Pro	Ser	Ser 195	Ser	Leu	Gly	Thr	Lys 200	Thr	Tyr	Thr	Cys	Asn 205	Val	Asp	His		
Lys	Pro 210	Ser	Asn	Thr	Lys	Val 215	Asp	Lys	Arg	Val	Glu 220	Ser	Lys	Tyr	Gly		
Pro 225	Pro	Cys	Pro	Pro	Cys 230	Pro	Ala	Pro	Glu	Phe 235	Leu	Gly	Gly	Pro	Ser 240		
Val	Phe	Leu	Phe	Pro 245	Pro	Lys	Pro	Lys	Asp 250	Thr	Leu	Met	Ile	Ser 255	Arg		
Thr	Pro	Glu	Val 260	Thr	Cys	Val	Val	Val 265	Asp	Val	Ser	Gln	Glu 270	Asp	Pro		
Glu	Val	Gln 275	Phe	Asn	Trp	Tyr	Val 280	Asp	Gly	Val	Glu	Val 285	His	Asn	Ala		
Lys	Thr 290	Lys	Pro	Arg	Glu	Glu 295	Gln	Phe	Asn	Ser	Thr 300	Tyr	Arg	Val	Val		
Ser 305	Val	Leu	Thr	Val	Leu	His 310	Gln	Asp	Trp	Leu 315	Asn	Gly	Lys	Glu	Tyr 320		
Lys	Cys	Lys	Val	Ser 325	Asn	Lys	Gly	Leu	Pro 330	Ser	Ser	Ile	Glu	Lys 335	Thr		
Ile	Ser	Lys	Ala 340	Lys	Gly	Gln	Pro	Arg 345	Glu	Pro	Gln	Val	Tyr 350	Thr	Leu		
Pro	Pro	Ser 355	Gln	Glu	Glu	Met	Thr 360	Lys	Asn	Gln	Val	Ser 365	Leu	Thr	Cys		
Leu	Val 370	Lys	Gly	Phe	Tyr	Pro 375	Ser	Asp	Ile	Ala	Val 380	Glu	Trp	Glu	Ser		
Asn 385	Gly	Gln	Pro	Glu	Asn 390	Asn	Tyr	Lys	Thr	Thr 395	Pro	Pro	Val	Leu	Asp 400		
Ser	Asp	Gly	Ser	Phe 405	Phe	Leu	Tyr	Ser	Arg 410	Leu	Thr	Val	Asp	Lys 415	Ser		
Arg	Trp	Gln	Glu 420	Gly	Asn	Val	Phe	Ser 425	Cys	Ser	Val	Met	His 430	Glu	Ala		
Leu	His 435	Asn	His	Tyr	Thr	Gln	Lys 440	Ser	Leu	Ser	Leu	Ser 445	Leu	Gly	Lys		

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<220>  
 <223> cAb 0302 heavy chain

<400> 35

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

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

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

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

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

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

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

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

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala  
 130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val  
 145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala  
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val  
 180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His  
 195 200 205

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

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser

225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg  
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro  
260 265 270

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

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val  
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr  
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr  
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu  
340 345 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys  
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser  
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp  
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser  
405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala  
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys  
435 440 445

<210> 36

<211> 218

<212> PRT

<213> Artificial sequence

<220>

<223> cAb 0302 light chain

<400> 36

Asp Val Val Val Thr Gln Thr Pro Ala Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

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Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr  
20 25 30

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

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

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

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

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 37

<211> 449

<212> PRT

<213> Artificial sequence

<220>

<223> cAb 0311 heavy chain

<400> 37

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr  
Page 32

Asn Met His Trp Val Lys Gln Asn Gln Gly Lys Ser Leu Glu Trp Met  
 35 40 45  
 Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe  
 50 55 60  
 Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr  
 65 70 75 80  
 Met Asp Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys  
 85 90 95  
 Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp  
 100 105 110  
 Gly Lys Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro  
 115 120 125  
 Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
 130 135 140  
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
 145 150 155 160  
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
 165 170 175  
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
 180 185 190  
 Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
 195 200 205  
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr  
 210 215 220  
 Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
 225 230 235 240  
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser  
 245 250 255  
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
 260 265 270  
 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn  
 275 280 285  
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val

290

295

300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
435 440 445

Lys

&lt;210&gt; 38

&lt;211&gt; 218

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; cAb 0311 light chain

&lt;400&gt; 38

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly  
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

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

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



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

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

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 39  
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<223> h0301-H0 heavy chain variable region

<400> 39

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

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

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

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

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
Page 35

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

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

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

&lt;210&gt; 40

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-H1 heavy chain variable region

&lt;400&gt; 40

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

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

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

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

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

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

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

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

&lt;210&gt; 41

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-H2 heavy chain variable region

&lt;400&gt; 41

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn  
 20 25 30  
 Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile  
 35 40 45  
 Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe  
 50 55 60  
 Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp  
 100 105 110  
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120  
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 <213> Artificial sequence  
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 <223> H0302-H1 heavy chain variable region  
 <400> 42  
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Phe  
 20 25 30  
 Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 Gly Tyr Ile Asn Pro Tyr Thr Asp Val Thr Val Tyr Asn Glu Lys Phe  
 50 55 60  
 Lys Gly Arg Val Thr Ile Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Ser Tyr Phe Asp Gly Thr Phe Asp Tyr Ala Leu Asp Tyr Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 43  
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<212> PRT  
<213> Artificial sequence

<220>  
<223> H0302-H2 heavy chain variable region

<400> 43

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

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

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

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

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

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

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

Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 44  
<211> 122  
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<220>  
<223> H0311-H1 heavy chain variable region

<400> 44

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

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

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

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

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

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

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

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

<210> 45

<211> 122

<212> PRT

<213> Artificial sequence

<220>

<223> H0311-H2 heavy chain variable region

<400> 45

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

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

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

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

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

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

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

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

<210> 46

<211> 111

<212> PRT

<213> Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-L0 light chain variable region

&lt;400&gt; 46

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

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
 20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Leu Ser Asn  
 85 90 95

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

&lt;210&gt; 47

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-L1 light chain variable region

&lt;400&gt; 47

Asn Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
 20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Leu Ser Asn  
 85 90 95

Glu Asp Leu Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100

105

110

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 <212> PRT  
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<220>  
 <223> H0302-L0 light chain variable region  
 <400> 48

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

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

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
 35 40 45

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

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

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

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

<210> 49  
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 <213> Artificial sequence

<220>  
 <223> H0302-L1 light chain variable region  
 <400> 49

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

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

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
 35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser  
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65

70

75

80

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

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105 110

&lt;210&gt; 50

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; H0302-L2 light chain variable region

&lt;400&gt; 50

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

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

Gly Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro  
35 40 45

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

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

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

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105 110

&lt;210&gt; 51

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; H0311-L0 light chain variable region

&lt;400&gt; 51

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

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

Gly Asp Ser His Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro



35

40

45

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn  
 85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

&lt;210&gt; 52

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; H0311-L1 light chain variable region

&lt;400&gt; 52

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
 20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn  
 85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 100 105 110

&lt;210&gt; 53

&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-H0 heavy chain

&lt;400&gt; 53

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn  
 20 25 30  
 Tyr Met Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 Gly Asp Ile Asn Pro Tyr Asn Gly Gly Thr Thr Phe Asn Gln Lys Phe  
 50 55 60  
 Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Glu Ser Pro Tyr Phe Ser Asn Leu Tyr Val Met Asp Tyr Trp  
 100 105 110  
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro  
 115 120 125  
 Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
 130 135 140  
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
 145 150 155 160  
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
 165 170 175  
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
 180 185 190  
 Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
 195 200 205  
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr  
 210 215 220  
 Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
 225 230 235 240  
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser  
 245 250 255  
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
 260 265 270  
 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn  
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275

280

285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val  
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
 435 440 445

Lys

&lt;210&gt; 54

&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-H1 heavy chain

&lt;400&gt; 54

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

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

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

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Gly	Asp	Ile	Asn	Pro	Tyr	Asn	Gly	Gly	Thr	Thr	Phe	Asn	Gln	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Val	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Ser	Pro	Tyr	Phe	Ser	Asn	Leu	Tyr	Val	Met	Asp	Tyr	Trp
			100					105					110		
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
		115					120					125			
Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
	130					135					140				
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
145					150					155					160
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
			165						170					175	
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
			180					185					190		
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
		195					200					205			
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
	210					215					220				
Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
225					230					235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245					250					255	
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
			260					265					270		
Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275					280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
	290					295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
435 440 445

Lys

<210> 55

<211> 449

<212> PRT

<213> Artificial sequence

<220>

<223> h0301-H2 heavy chain

<400> 55

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

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

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

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
195 200 205

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser  
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
260 265 270

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

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val  
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr

355

360

365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
 435 440 445

Lys

&lt;210&gt; 56

&lt;211&gt; 448

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; H0302-H1 heavy chain

&lt;400&gt; 56

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

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

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

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

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

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

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

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

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Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
	130					135					140				
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
145					150					155					160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165					170					175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
			180					185					190		
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
		195					200					205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
	210					215					220				
Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser
225					230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245					250					255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
			260					265					270		
Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
		275					280					285			
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290					295					300				
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
305					310					315					320
Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325					330					335	
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340					345					350		
Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		355					360					365			
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	370					375					380				
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
385					390					395					400



Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser  
405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala  
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys  
435 440 445

<210> 57

<211> 448

<212> PRT

<213> Artificial sequence

<220>

<223> H0302-H2 heavy chain

<400> 57

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

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

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

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

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

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

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

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

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala  
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val  
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala  
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180

185

190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp Hi s  
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Gl u Ser Lys Tyr Gly  
210 215 220

Pro Pro Cys Pro Pro Cys Pro Al a Pro Gl u Phe Leu Gly Gly Pro Ser  
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg  
245 250 255

Thr Pro Gl u Val Thr Cys Val Val Val Asp Val Ser Gl n Gl u Asp Pro  
260 265 270

Gl u Val Gl n Phe Asn Trp Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a  
275 280 285

Lys Thr Lys Pro Arg Gl u Gl u Gl n Phe Asn Ser Thr Tyr Arg Val Val  
290 295 300

Ser Val Leu Thr Val Leu Hi s Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr  
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Gl u Lys Thr  
325 330 335

Ile Ser Lys Al a Lys Gly Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu  
340 345 350

Pro Pro Ser Gl n Gl u Gl u Met Thr Lys Asn Gl n Val Ser Leu Thr Cys  
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Al a Val Gl u Trp Gl u Ser  
370 375 380

Asn Gly Gl n Pro Gl u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp  
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser  
405 410 415

Arg Trp Gl n Gl u Gly Asn Val Phe Ser Cys Ser Val Met Hi s Gl u Al a  
420 425 430

Leu Hi s Asn Hi s Tyr Thr Gl n Lys Ser Leu Ser Leu Ser Leu Gly Lys  
435 440 445

&lt;210&gt; 58

<211> 449  
 <212> PRT  
 <213> Arti f i c i a l    s e q u e n c e

<220>  
 <223> H0311-H1 heavy chain

<400> 58

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

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

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

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

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

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

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

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
 195 200 205

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
 225 230 235 240

Ser Val Phe Leu Phe 245 Pro Pro Lys Pro Lys 250 Asp Thr Leu Met Ile Ser 255

Arg Thr Pro Glu 260 Val Thr Cys Val Val 265 Val Asp Val Ser Gln Glu Asp 270

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

Ala Lys 290 Thr Lys Pro Arg Glu 295 Glu Gln Phe Asn Ser 300 Thr Tyr Arg Val

Val 305 Ser Val Leu Thr Val 310 Leu His Gln Asp Trp 315 Leu Asn Gly Lys Glu 320

Tyr Lys Cys Lys Val 325 Ser Asn Lys Gly Leu 330 Pro Ser Ser Ile Glu 335 Lys

Thr Ile Ser Lys 340 Ala Lys Gly Gln Pro 345 Arg Glu Pro Gln Val 350 Tyr Thr

Leu Pro Pro 355 Ser Gln Glu Glu Met 360 Thr Lys Asn Gln Val 365 Ser Leu Thr

Cys Leu Val 370 Lys Gly Phe Tyr 375 Pro Ser Asp Ile Ala 380 Val Glu Trp Glu

Ser 385 Asn Gly Gln Pro Glu 390 Asn Asn Tyr Lys Thr 395 Thr Pro Pro Val Leu 400

Asp Ser Asp Gly 405 Ser Phe Phe Leu Tyr Ser 410 Arg Leu Thr Val Asp 415 Lys

Ser Arg Trp Gln 420 Glu Gly Asn Val Phe 425 Ser Cys Ser Val Met 430 His Glu

Ala Leu His 435 Asn His Tyr Thr Gln 440 Lys Ser Leu Ser Leu 445 Ser Leu Gly

Lys

<210> 59  
 <211> 449  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> H0311-H2 heavy chain

<400> 59

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 Page 54

1 5 10 15  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr  
 20 25 30  
 Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 Gly Glu Ile Asn Pro Asn Asn Gly Val Val Val Tyr Asn Gln Lys Phe  
 50 55 60  
 Lys Gly Thr Thr Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr  
 65 70 75 80  
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Thr Arg Ala Leu Tyr His Ser Asn Phe Gly Trp Tyr Phe Asp Ser Trp  
 100 105 110  
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro  
 115 120 125  
 Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr  
 130 135 140  
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr  
 145 150 155 160  
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro  
 165 170 175  
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr  
 180 185 190  
 Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp  
 195 200 205  
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr  
 210 215 220  
 Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro  
 225 230 235 240  
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser  
 245 250 255  
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
 260 265 270  
 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn  
 Page 55

275

280

285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val  
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys  
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu  
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly  
 435 440 445

Lys

&lt;210&gt; 60

&lt;211&gt; 218

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; h0301-L0 light chain

&lt;400&gt; 60

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

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
 20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Leu Ser Asn  
85 90 95

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 61

<211> 218

<212> PRT

<213> Artificial sequence

<220>

<223> h0301-L1 light chain

<400> 61

Asn Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

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

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala  
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Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Leu Ser Asn  
85 90 95

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 62

<211> 218

<212> PRT

<213> Artificial sequence

<220>

<223> H0302-L0 light chain

<400> 62

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

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

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
35 40 45

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



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

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

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 63  
<211> 218  
<212> PRT  
<213> Artificial sequence  
  
<220>  
<223> H0302-L1 light chain  
  
<400> 63

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

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

Gly Leu Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser  
Page 59

65 70 75 80

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

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 64  
<211> 218  
<212> PRT  
<213> Artificial sequence

<220>  
<223> H0302-L2 light chain

<400> 64

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

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

Gly Leu Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro  
35 40 45

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

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

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

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 65  
<211> 218  
<212> PRT  
<213> Artificial sequence

<220>  
<223> H0311-L0 light chain

<400> 65

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

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn  
Page 61

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 66  
<211> 218  
<212> PRT  
<213> Artificial sequence

<220>  
<223> H0311-L1 light chain

<400> 66

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp  
20 25 30

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Asn  
85 90 95

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln  
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr  
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser  
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215

<210> 67  
<211> 158  
<212> PRT  
<213> Homo sapiens

<220>  
<221> MISC\_FEATURE  
<222> (1)..(158)  
<223> Human CSF1

<400> 67

Glu Glu Val Ser Glu Tyr Cys Ser His Met Ile Gly Ser Gly His Leu  
1 5 10 15

Gln Ser Leu Gln Arg Leu Ile Asp Ser Gln Met Glu Thr Ser Cys Gln  
20 25 30

Ile Thr Phe Glu Phe Val Asp Gln Glu Gln Leu Lys Asp Pro Val Cys  
35 40 45

Tyr Leu Lys Lys Ala Phe Leu Leu Val Gln Asp Ile Met Glu Asp Thr  
50 55 60

Met Arg Phe Arg Asp Asn Thr Pro Asn Ala Ile Ala Ile Val Gln Leu  
65 70 75 80

Gln Glu Leu Ser Leu Arg Leu Lys Ser Cys Phe Thr Lys Asp Tyr Glu  
85 90 95

Glu His Asp Lys Ala Cys Val Arg Thr Phe Tyr Glu Thr Pro Leu Gln  
100 105 110

Leu Leu Glu Lys Val Lys Asn Val Phe Asn Glu Thr Lys Asn Leu Leu  
115 120 125

Asp Lys Asp Trp Asn Ile Phe Ser Lys Asn Cys Asn Asn Ser Phe Ala  
130 135 140

Glu Cys Ser Ser Gln Gly His Glu Arg Gln Ser Glu Gly Ser  
145 150 155

<210> 68  
<211> 222  
<212> PRT  
<213> Homo sapiens

<220>  
<221> MI SC\_FEATURE  
<222> (1)..(222)  
<223> Human IL-34

<400> 68

Asn Glu Pro Leu Glu Met Trp Pro Leu Thr Gln Asn Glu Glu Cys Thr  
1 5 10 15

Val Thr Gly Phe Leu Arg Asp Lys Leu Gln Tyr Arg Ser Arg Leu Gln  
20 25 30

Tyr Met Lys His Tyr Phe Pro Ile Asn Tyr Lys Ile Ser Val Pro Tyr  
35 40 45

Glu Gly Val Phe Arg Ile Ala Asn Val Thr Arg Leu Gln Arg Ala Gln  
50 55 60

Val Ser Glu Arg Glu Leu Arg Tyr Leu Trp Val Leu Val Ser Leu Ser  
65 70 75 80

Ala Thr Glu Ser Val Gln Asp Val Leu Leu Glu Gly His Pro Ser Trp  
85 90 95

Lys Tyr Leu Gln Glu Val Gln Thr Leu Leu Leu Asn Val Gln Gln Gly  
100 105 110

Leu Thr Asp Val Glu Val Ser Pro Lys Val Glu Ser Val Leu Ser Leu  
115 120 125

Leu Asn Ala Pro Gly Pro Asn Leu Lys Leu Val Arg Pro Lys Ala Leu  
130 135 140

Leu Asp Asn Cys Phe Arg Val Met Glu Leu Leu Tyr Cys Ser Cys Cys  
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145 150 155 160

Lys Gln Ser Ser Val Leu Asn Trp Gln Asp Cys Glu Val Pro Ser Pro  
165 170 175

Gln Ser Cys Ser Pro Glu Pro Ser Leu Gln Tyr Ala Ala Thr Gln Leu  
180 185 190

Tyr Pro Pro Pro Pro Trp Ser Pro Ser Ser Pro Pro His Ser Thr Gly  
195 200 205

Ser Val Arg Pro Val Arg Ala Gln Gly Glu Gly Leu Leu Pro  
210 215 220

<210> 69  
<211> 25  
<212> PRT  
<213> Artificial sequence

<220>  
<223> Human acceptor A FR1

<400> 69

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

Ser Val Lys Val Ser Cys Lys Ala Ser  
20 25

<210> 70  
<211> 14  
<212> PRT  
<213> Artificial sequence

<220>  
<223> Human acceptor A FR2

<400> 70

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly  
1 5 10

<210> 71  
<211> 32  
<212> PRT  
<213> Artificial sequence

<220>  
<223> Human acceptor A FR3

<400> 71

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu  
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg  
20 25 30

<210> 72  
 <211> 11  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor A FR4

<400> 72

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 1 5 10

<210> 73  
 <211> 25  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor B FR1

<400> 73

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

Ser Val Lys Val Ser Cys Lys Ala Ser  
 20 25

<210> 74  
 <211> 14  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor B FR2

<400> 74

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly  
 1 5 10

<210> 75  
 <211> 32  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor B FR3

<400> 75

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu  
 1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg  
 20 25 30

<210> 76  
 <211> 11  
 <212> PRT



<213> Arti f i c i a l   s e q u e n c e

<220>

<223> Human acceptor B FR4

<400> 76

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
1 5 10

<210> 77

<211> 25

<212> PRT

<213> Arti f i c i a l   s e q u e n c e

<220>

<223> Human acceptor C FR1

<400> 77

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

Ser Val Lys Val Ser Cys Lys Ala Ser  
20 25

<210> 78

<211> 14

<212> PRT

<213> Arti f i c i a l   s e q u e n c e

<220>

<223> Human acceptor C FR2

<400> 78

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly  
1 5 10

<210> 79

<211> 32

<212> PRT

<213> Arti f i c i a l   s e q u e n c e

<220>

<223> Human acceptor C FR3

<400> 79

Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu  
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg  
20 25 30

<210> 80

<211> 11

<212> PRT

<213> Arti f i c i a l   s e q u e n c e

<220>

<223> Human acceptor C FR4

&lt;400&gt; 80

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 1 5 10

&lt;210&gt; 81

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Human acceptor D FR1

&lt;400&gt; 81

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

Glu Arg Ala Thr Leu Ser Cys  
 20

&lt;210&gt; 82

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Human acceptor D FR2

&lt;400&gt; 82

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr  
 1 5 10 15

&lt;210&gt; 83

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Human acceptor D FR3

&lt;400&gt; 83

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr  
 1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys  
 20 25 30

&lt;210&gt; 84

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Human acceptor D FR4

&lt;400&gt; 84

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

1

5

10

<210> 85  
 <211> 23  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> Human acceptor E FR1

<400> 85

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

Glu Arg Ala Thr Leu Ser Cys  
 20

<210> 86  
 <211> 15  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> Human acceptor E FR2

<400> 86

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr  
 1 5 10 15

<210> 87  
 <211> 32  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> Human acceptor E FR3

<400> 87

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr  
 1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys  
 20 25 30

<210> 88  
 <211> 10  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> Human acceptor E FR4

<400> 88

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 1 5 10

<210> 89

<211> 23  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor F FR1

<400> 89

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

Glu Arg Ala Thr Leu Ser Cys  
 20

<210> 90  
 <211> 15  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor F FR2

<400> 90

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr  
 1 5 10 15

<210> 91  
 <211> 32  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor F FR3

<400> 91

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr  
 1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys  
 20 25 30

<210> 92  
 <211> 10  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

<220>  
 <223> Human acceptor F FR4

<400> 92

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
 1 5 10

<210> 93  
 <211> 719  
 <212> PRT  
 <213> Arti f i c i a l   s e q u e n c e

&lt;220&gt;

&lt;223&gt; mCSF1R ECD-Fc

&lt;400&gt; 93

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

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

Gly Pro Ile Ser Pro Tyr Trp Thr Leu Asp Pro Glu Ser Pro Gly Ser  
35 40 45

Thr Leu Thr Thr Arg Asn Ala Thr Phe Lys Asn Thr Gly Thr Tyr Arg  
50 55 60

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

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

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

Pro Ala Leu Lys Asp Ser Val Ser Leu Met Arg Glu Gly Gly Arg Gln  
115 120 125

Val Leu Arg Lys Thr Val Tyr Phe Phe Ser Pro Trp Arg Gly Phe Ile  
130 135 140

Ile Arg Lys Ala Lys Val Leu Asp Ser Asn Thr Tyr Val Cys Lys Thr  
145 150 155 160

Met Val Asn Gly Arg Glu Ser Thr Ser Thr Gly Ile Trp Leu Lys Val  
165 170 175

Asn Arg Val His Pro Glu Pro Pro Gln Ile Lys Leu Glu Pro Ser Lys  
180 185 190

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

Asn Ala Glu Val Gly Phe Asn Val Ile Leu Lys Arg Gly Asp Thr Lys  
210 215 220

Leu Glu Ile Pro Leu Asn Ser Asp Phe Gln Asp Asn Tyr Tyr Lys Lys  
225 230 235 240

Val Arg Ala Leu Ser Leu Asn Ala Val Asp Phe Gln Asp Ala Gly Ile  
245 250 255

Tyr Ser Cys Val Ala Ser Asn Asp Val Gly Thr Arg Thr Ala Thr Met  
 260 265 270  
 Asn Phe Gln Val Val Glu Ser Ala Tyr Leu Asn Leu Thr Ser Glu Gln  
 275 280 285  
 Ser Leu Leu Gln Glu Val Ser Val Gly Asp Ser Leu Ile Leu Thr Val  
 290 295 300  
 His Ala Asp Ala Tyr Pro Ser Ile Gln His Tyr Asn Trp Thr Tyr Leu  
 305 310 315 320  
 Gly Pro Phe Phe Glu Asp Gln Arg Lys Leu Glu Phe Ile Thr Gln Arg  
 325 330 335  
 Ala Ile Tyr Arg Tyr Thr Phe Lys Leu Phe Leu Asn Arg Val Lys Ala  
 340 345 350  
 Ser Glu Ala Gly Gln Tyr Phe Leu Met Ala Gln Asn Lys Ala Gly Trp  
 355 360 365  
 Asn Asn Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu Val Ser  
 370 375 380  
 Val Thr Trp Met Pro Val Asn Gly Ser Asp Val Leu Phe Cys Asp Val  
 385 390 395 400  
 Ser Gly Tyr Pro Gln Pro Ser Val Thr Trp Met Glu Cys Arg Gly His  
 405 410 415  
 Thr Asp Arg Cys Asp Glu Ala Gln Ala Leu Gln Val Trp Asn Asp Thr  
 420 425 430  
 His Pro Glu Val Leu Ser Gln Lys Pro Phe Asp Lys Val Ile Ile Gln  
 435 440 445  
 Ser Gln Leu Pro Ile Gly Thr Leu Lys His Asn Met Thr Tyr Phe Cys  
 450 455 460  
 Lys Thr His Asn Ser Val Gly Asn Ser Ser Gln Tyr Phe Arg Ala Val  
 465 470 475 480  
 Ser Leu Gly Gln Ser Lys Gln Glu Pro Lys Ser Ser Asp Lys Thr His  
 485 490 495  
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val  
 500 505 510  
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr  
 515 520 525

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

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

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

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

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

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

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

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

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

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg  
675 680 685

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

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

<210> 94

<211> 327

<212> PRT

<213> Artificial sequence

<220>

<223> Human IgG4 S241P

<400> 94

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

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr  
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser  
Page 73

35

40

45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser  
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys  
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp  
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe  
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu  
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys  
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser  
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser



305

310

315

320

Leu Ser Leu Ser Leu Gly Lys  
325

<210> 95  
<211> 107  
<212> PRT  
<213> Homo sapiens

<220>  
<221> MI SC\_FEATURE  
<222> (1)..(107)  
<223> Human Ig-kappa  
  
<400> 95

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu  
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe  
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln  
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser  
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu  
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser  
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
100 105