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(54) **COMBINATION THERAPY OF ANTIBODIES
AGAINST HUMAN CSF-1R AND
ANTIBODIES AGAINST HUMAN PD-L1**

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Sep. 12, 2014.

(57) **ABSTRACT**

The present invention relates to the combination therapy of
specific antibodies which bind human CSF-1R with specific
antibodies which bind human PD-L1.

Fig. 1a

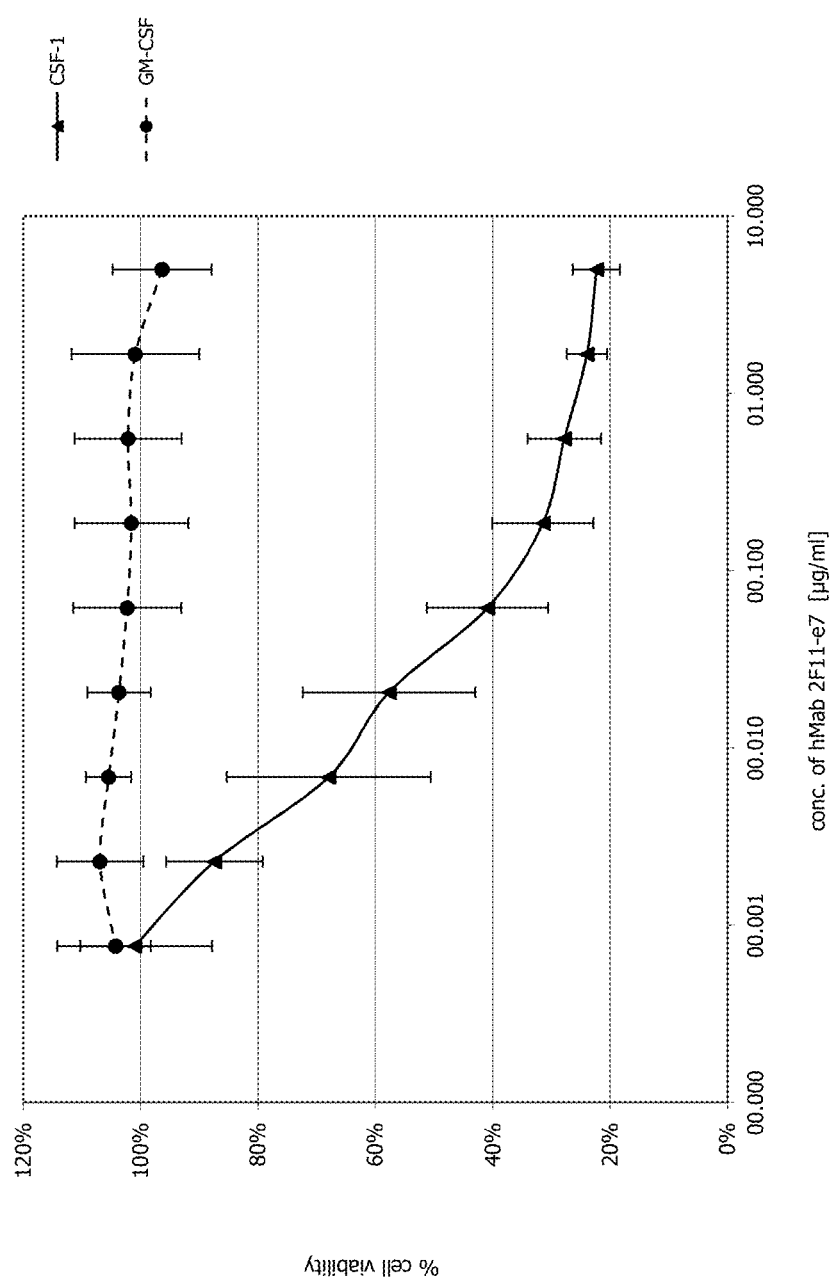


Fig. 1b

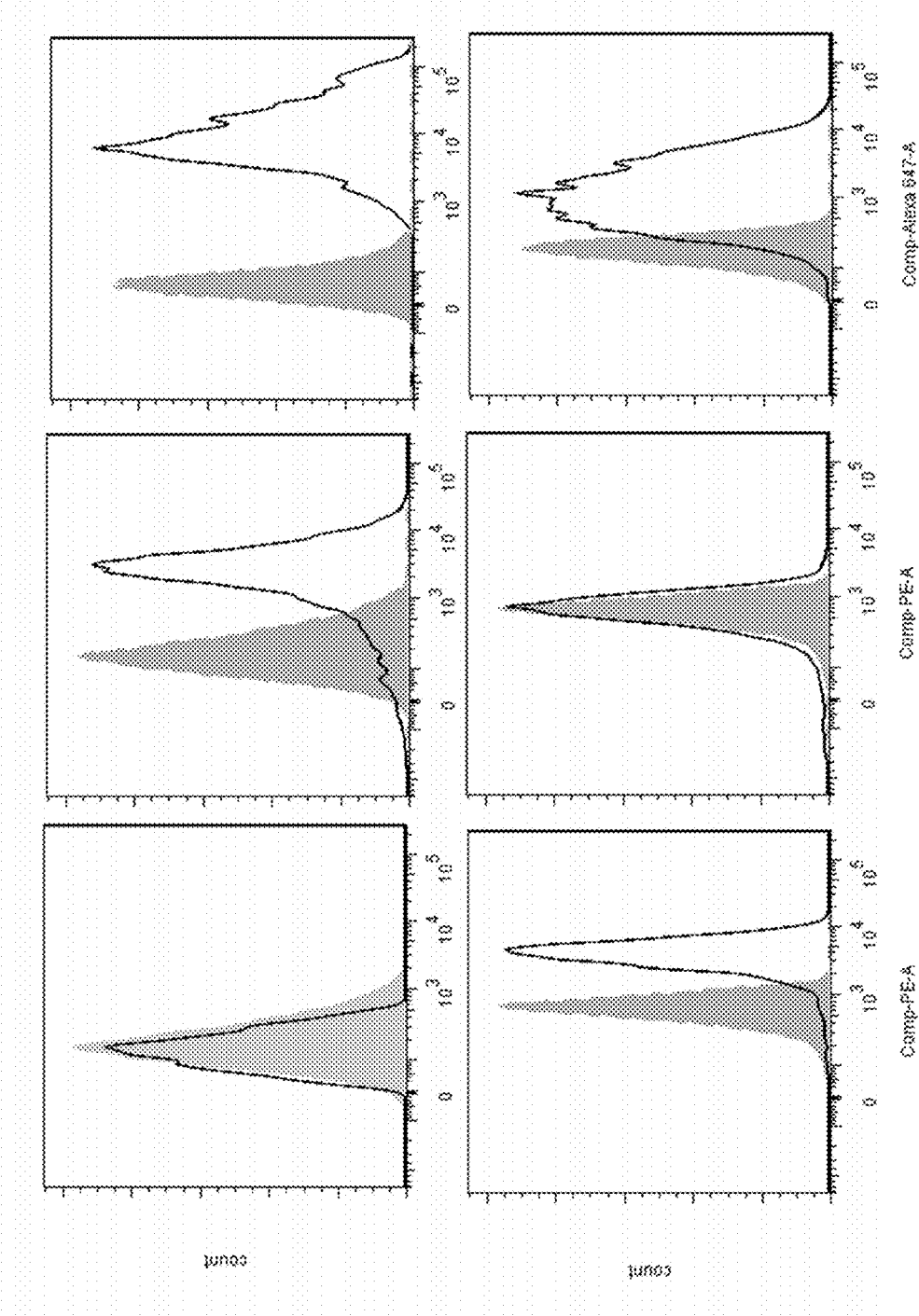


Fig. 2a

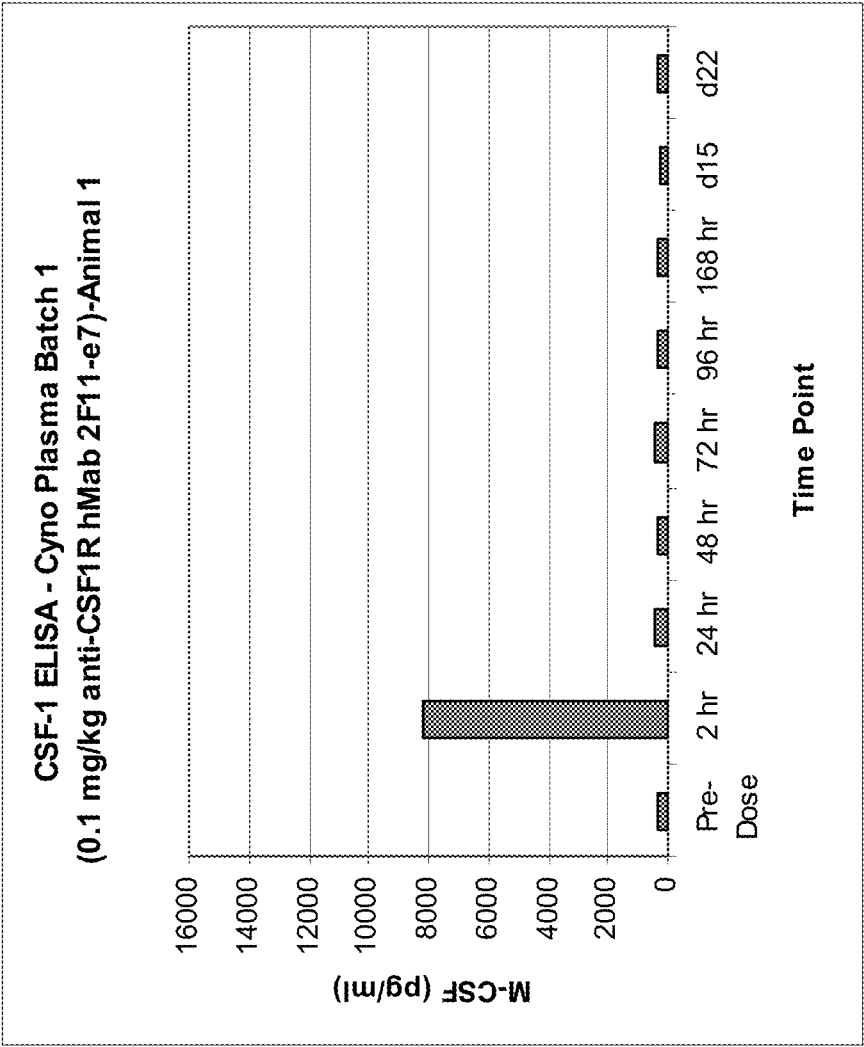


Fig. 2b

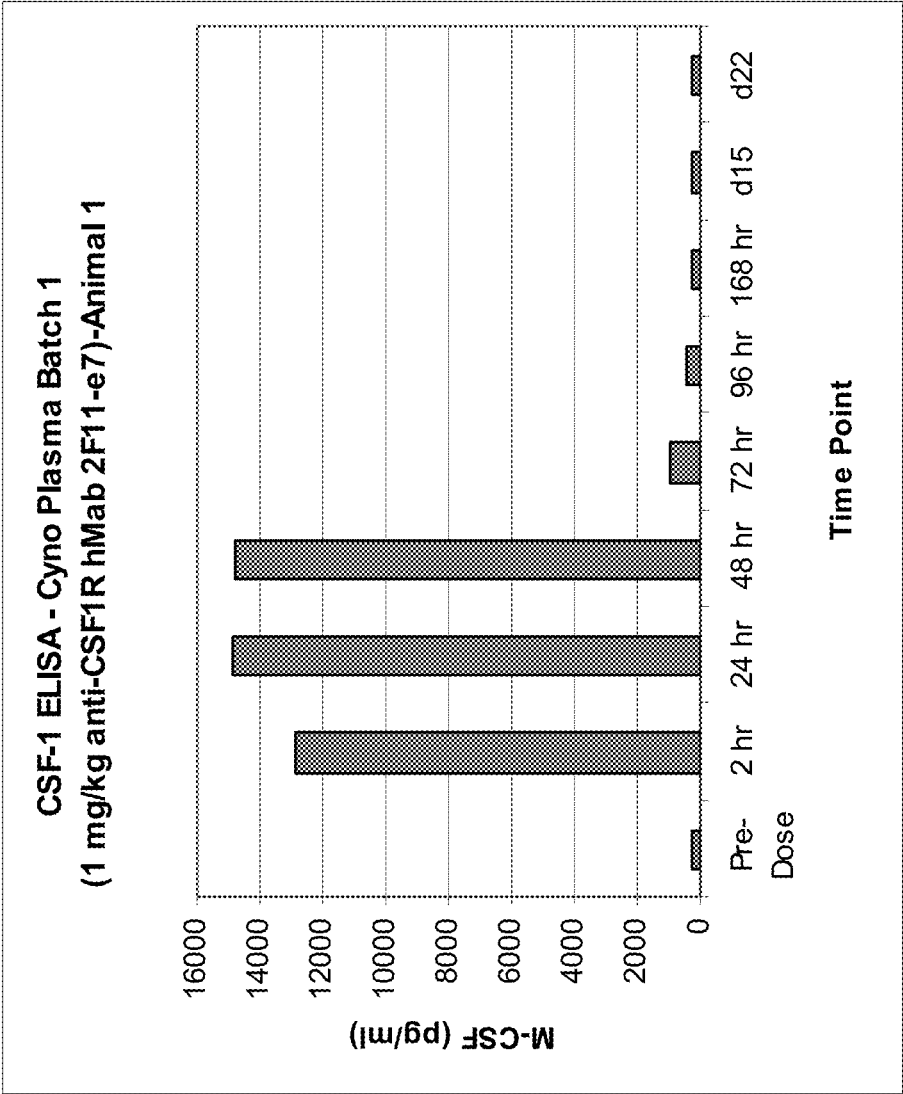


Fig. 2c

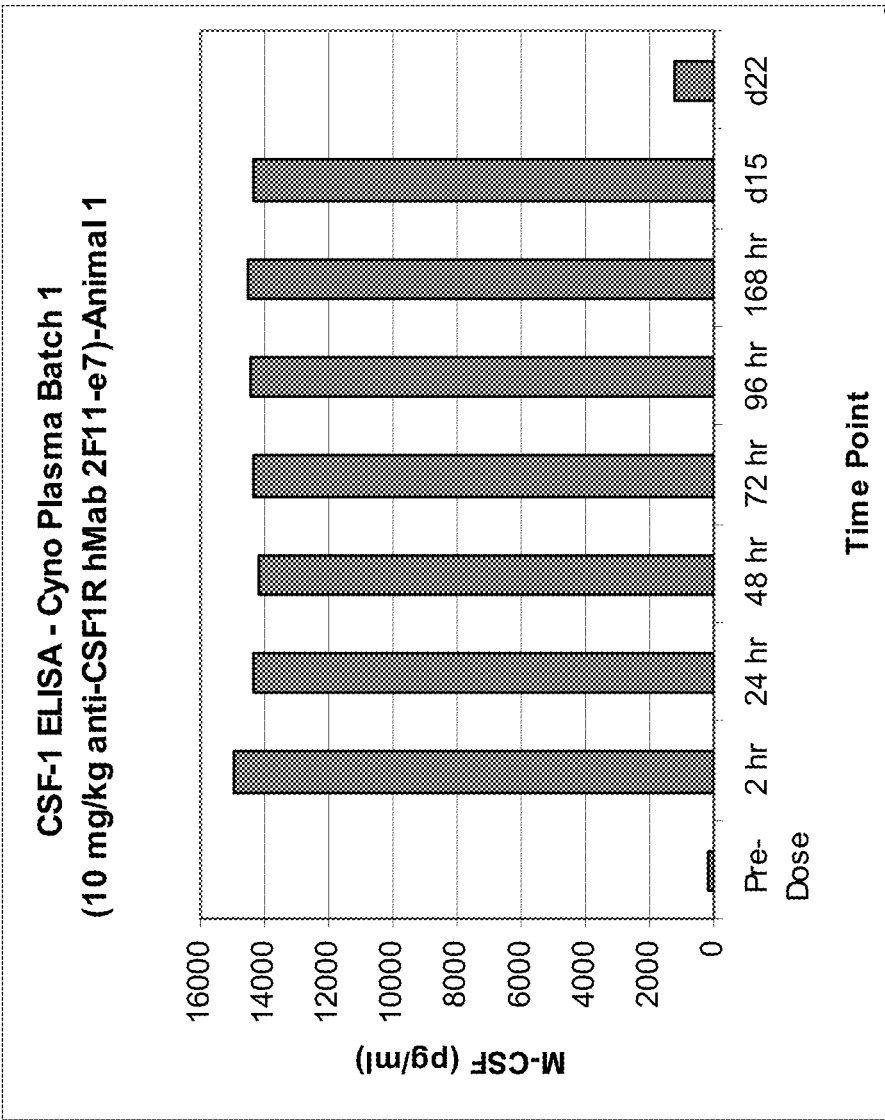


Fig. 2d

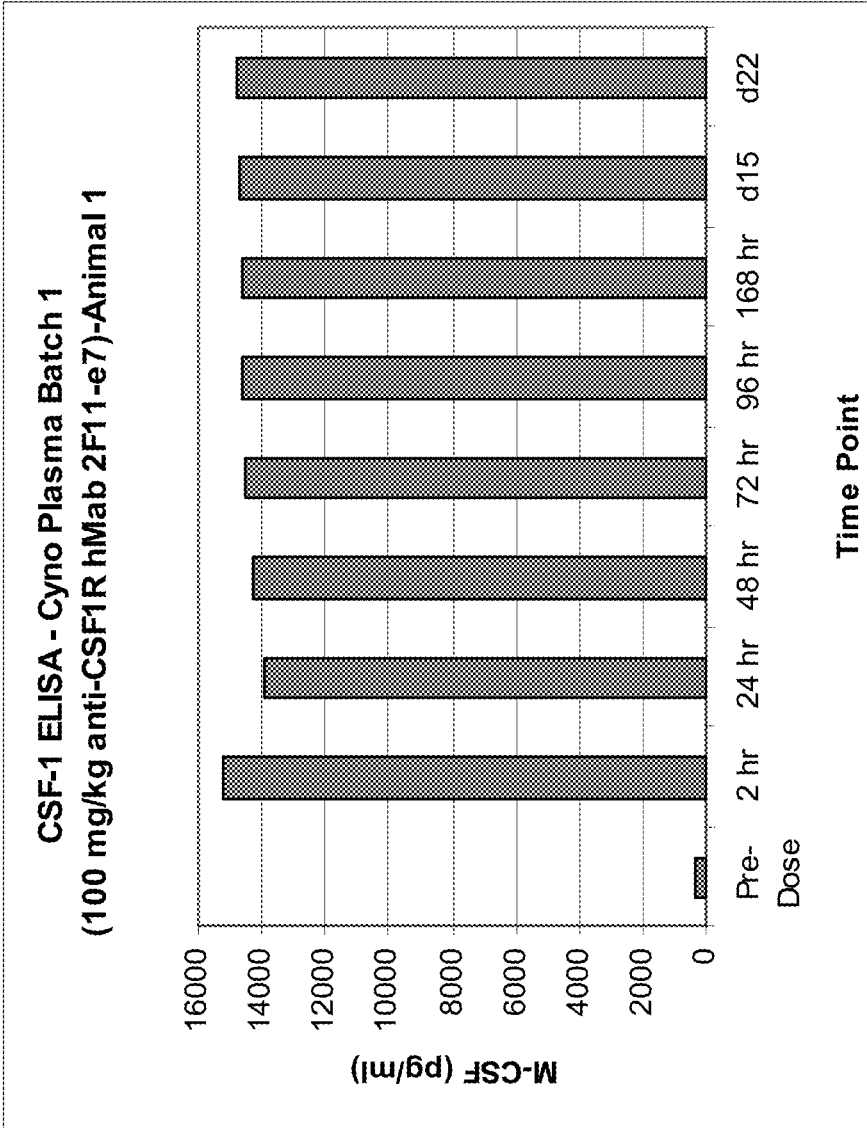


Fig. 3

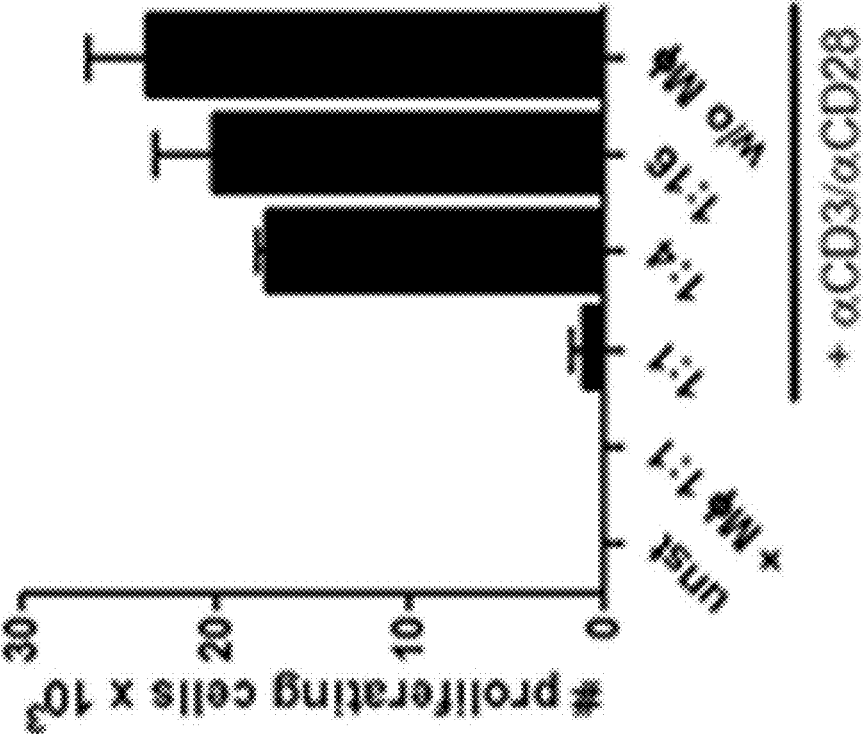


Fig. 4

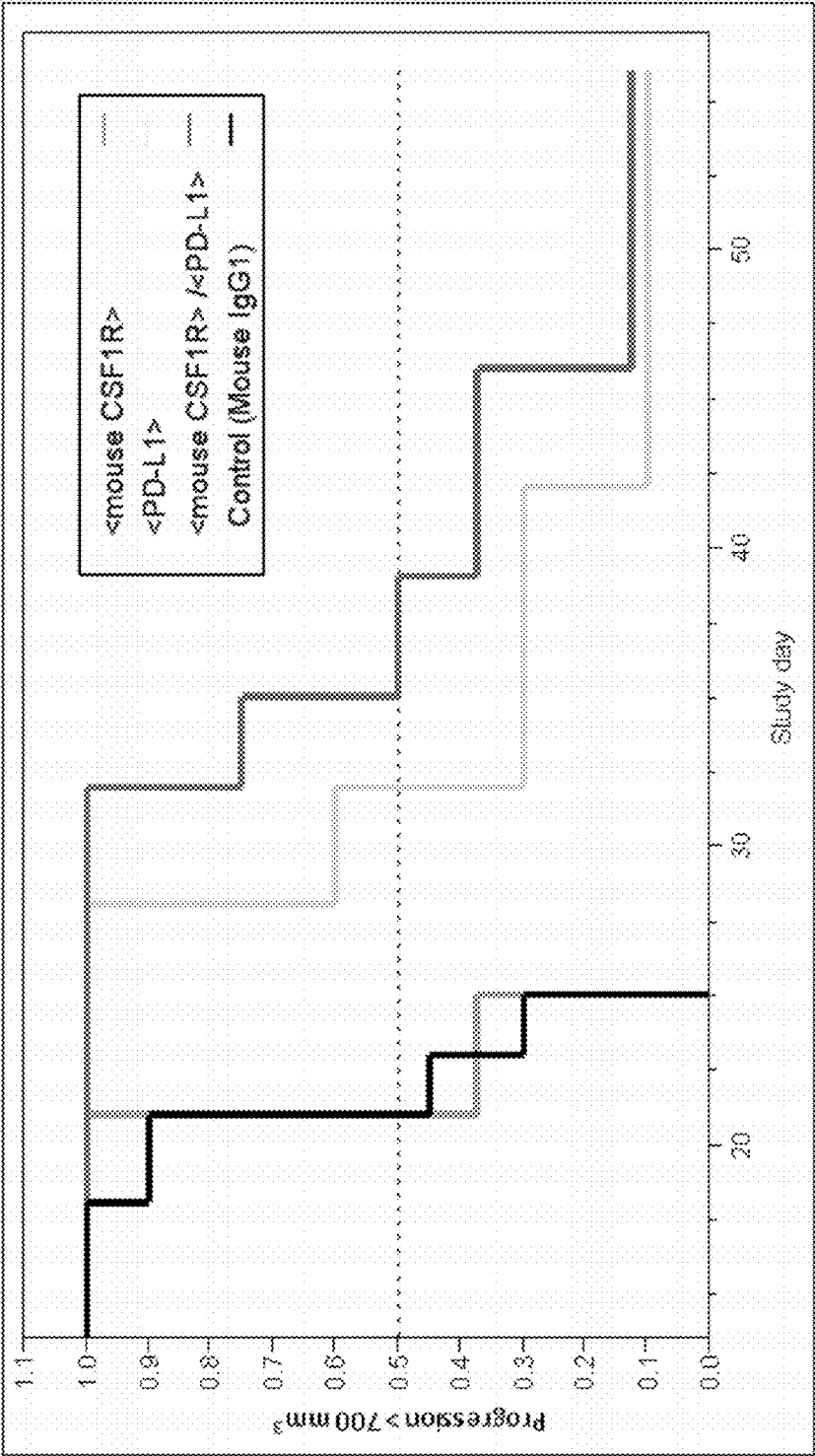
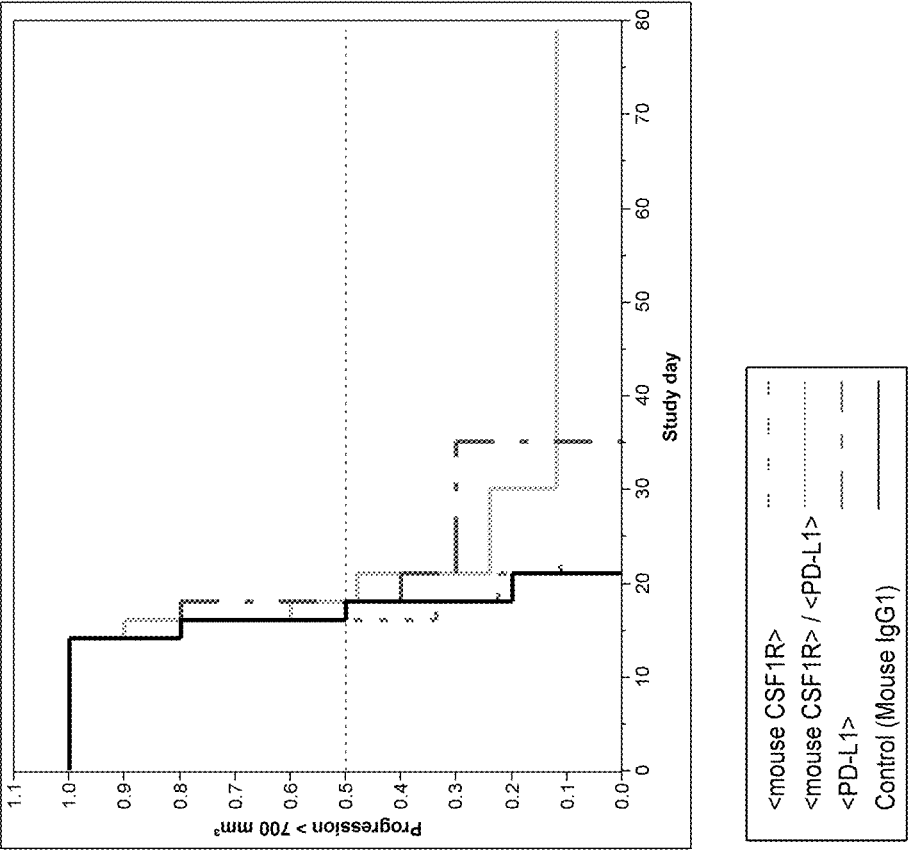


Fig. 5



COMBINATION THERAPY OF ANTIBODIES AGAINST HUMAN CSF-1R AND ANTIBODIES AGAINST HUMAN PD-L1

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 14/485,140 filed Sep. 12, 2014, which claims the benefit of EP Patent Application No. 13184120.7, filed on Sep. 12, 2013, the entire disclosures of which are expressly incorporated by reference herein.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 146392030201SeqList.txt, date recorded: Jul. 28, 2016, size: 98 KB).

[0003] The present invention relates to the combination therapy of specific antibodies which bind human CSF-1R with specific antibodies which bind human PD-L1.

BACKGROUND OF THE INVENTION

CSF-1R and CSF-1R Antibodies

[0004] The human CSF-1 receptor (CSF-1R; colony stimulating factor 1 receptor; synonyms: M-CSF receptor; Macrophage colony-stimulating factor 1 receptor, Fms proto-oncogene, c-fms, SEQ ID NO: 62) is known since 1986 (Coussens, L., et al., *Nature* 320 (1986) 277-280). CSF-1R is a growth factor and encoded by the c-fms proto-oncogene (reviewed e.g. in Roth, P., and Stanley, E. R., *Curr. Top. Microbiol. Immunol.* 181 (1992) 141-167).

[0005] CSF-1R is the receptor for CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage colony-stimulating factor) and mediates the biological effects of this cytokine (Sherr, C. J., et al., *Cell* 41 (1985) 665-676). The cloning of the colony stimulating factor-1 receptor (CSF-1R) (also called c-fms) was described for the first time in Roussel, M. F., et al., *Nature* 325 (1987) 549-552. In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee, P. S., et al., *Embo J.* 18 (1999) 3616-3628). Recently a second ligand for CSF-1R termed interleukin-34 (IL-34) was identified (Lin, H., et al., *Science* 320 (2008) 807-811).

[0006] Currently two CSF-1R ligands that bind to the extracellular domain of CSF-1R are known. The first one is CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage; SEQ ID NO: 86) and is found extracellularly as a disulfide-linked homodimer (Stanley, E. R. et al., *Journal of Cellular Biochemistry* 21 (1983) 151-159; Stanley, E. R. et al., *Stem Cells* 12 Suppl. 1 (1995) 15-24). The second one is IL-34 (Human IL-34; SEQ ID NO: 87) (Hume, D. A., et al., *Blood* 119 (2012) 1810-1820). The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of hematopoietic precursor cells to the macrophage lineage (including osteoclast). Activation of CSF-1R is mediated by its CSF-1R ligands, CSF-1 (M-CSF) and IL-34. Binding of CSF-1

(M-CSF) to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Li, W. et al., *EMBO Journal*. 10 (1991) 277-288; Stanley, E. R., et al., *Mol. Reprod. Dev.* 46 (1997) 4-10).

[0007] The biologically active homodimer CSF-1 binds to the CSF-1R within the subdomains D1 to D3 of the extracellular domain of the CSF-1 receptor (CSF-1R-ECD). The CSF-1R-ECD comprises five immunoglobulin-like subdomains (designated D1 to D5). The subdomains D4 to D5 of the extracellular domain (CSF-1R-ECD) are not involved in the CSF-1 binding (Wang, Z., et al. *Molecular and Cellular Biology* 13 (1993) 5348-5359). The subdomain D4 is involved in dimerization (Yeung, Y.-G., et al. *Molecular & Cellular Proteomics* 2 (2003) 1143-1155; Pixley, F. J., et al., *Trends Cell Biol.* 14 (2004) 628-638).

[0008] Further signaling is mediated by the p85 subunit of PI3K and Grb2 connecting to the PI3K/AKT and Ras/MAPK pathways, respectively. These two important signaling pathways can regulate proliferation, survival and apoptosis. Other signaling molecules that bind the phosphorylated intracellular domain of CSF-1R include STAT1, STAT3, PLC γ , and Cbl (Bourette, R. P. and Rohrschneider, L. R., *Growth Factors* 17 (2000) 155-166).

[0009] CSF-1R signaling has a physiological role in immune responses, in bone remodeling and in the reproductive system. The knockout animals for either CSF-1 (Polard, J. W., *Mol. Reprod. Dev.* 46 (1997) 54-61) or CSF-1R (Dai, X. M., et al., *Blood* 99 (2002) 111-120) have been shown to have osteopetrotic, hematopoietic, tissue macrophage, and reproductive phenotypes consistent with a role for CSF-1R in the respective cell types.

[0010] Sherr, C. J., et al., *Blood* 73 (1989) 1786-1793 relates to some antibodies against CSF-1R that inhibit the CSF-1 activity. Ashmun, R. A., et al., *Blood* 73 (1989) 827-837 relates to CSF-1R antibodies. Lenda, D., et al., *Journal of Immunology* 170 (2003) 3254-3262 relates to reduced macrophage recruitment, proliferation, and activation in CSF-1-deficient mice results in decreased tubular apoptosis during renal inflammation. Kitaura, H., et al., *Journal of Dental Research* 87 (2008) 396-400 refers to an anti-CSF-1 antibody which inhibits orthodontic tooth movement. WO 2001/030381 mentions CSF-1 activity inhibitors including antisense nucleotides and antibodies while disclosing only CSF-1 antisense nucleotides. WO 2004/045532 relates to metastases and bone loss prevention and treatment of metastatic cancer by a CSF-1 antagonist disclosing as antagonist anti-CSF-1-antibodies only. WO 2005/046657 relates to the treatment of inflammatory bowel disease by anti-CSF-1-antibodies. US 2002/0141994 relates to inhibitors of colony stimulating factors. WO 2006/096489 relates to the treatment of rheumatoid arthritis by anti-CSF-1-antibodies. WO 2009/026303 and WO 2009/112245 relate to certain anti-CSF-1R antibodies binding to CSF-1R within the first three subdomains (D1 to D3) of the Extracellular Domain (CSF-1R-ECD). WO2011/123381(A1) relates to antibodies against CSF-1R. WO2011/070024 relate to certain anti-CSF-1R antibodies binding to CSF-1R within the dimerization domain (D4 to D5).

PD-L1 and PD-L1 Antibodies

[0011] Co-stimulation or the provision of two distinct signals to T-cells is a widely accepted model of lymphocyte

activation of resting T lymphocytes by antigen-presenting cells (APCs). Lafferty et al., *Aust. J. Exp. Biol. Med. Sci.* 53: 27-42 (1975).

[0012] This model further provides for the discrimination of self from non-self and immune tolerance. Bretscher et al., *Science* 169: 1042-1049 (1970); Bretscher, P. A., *P.N.A.S. USA* 96: 185-190 (1999); Jenkins et al., *J. Exp. Med.* 165: 302-319 (1987). The primary signal, or antigen specific signal, is transduced through the T-cell receptor (TCR) following recognition of foreign antigen peptide presented in the context of the major histocompatibility-complex (MHC). The second or co-stimulatory signal is delivered to T-cells by co-stimulatory molecules expressed on antigen-presenting cells (APCs), and induce T-cells to promote clonal expansion, cytokine secretion and effector function. Lenschow et al., *Ann. Rev. Immunol.* 14:233 (1996). In the absence of co-stimulation, T-cells can become refractory to antigen stimulation, do not mount an effective immune response, and further may result in exhaustion or tolerance to foreign antigens.

[0013] The simple two-signal model can be an oversimplification because the strength of the TCR signal actually has a quantitative influence on T-cell activation and differentiation. Viola et al., *Science* 273: 104-106 (1996); Sloan-Lancaster, *Nature* 363: 156-159 (1993). Moreover, T-cell activation can occur even in the absence of co-stimulatory signal if the TCR signal strength is high. More importantly, T-cells receive both positive and negative secondary co-stimulatory signals. The regulation of such positive and negative signals is critical to maximize the host's protective immune responses, while maintaining immune tolerance and preventing autoimmunity.

[0014] Negative secondary signals seem necessary for induction of T-cell tolerance, while positive signals promote T-cell activation. While the simple two-signal model still provides a valid explanation for naive lymphocytes, a host's immune response is a dynamic process, and co-stimulatory signals can also be provided to antigen-exposed T-cells.

[0015] The mechanism of co-stimulation is of therapeutic interest because the manipulation of co-stimulatory signals has shown to provide a means to either enhance or terminate cell-based immune response. Recently, it has been discovered that T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). As a result, therapeutic targeting PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) are an area of intense interest. The inhibition of PD-L1 signaling has been proposed as a means to enhance T cell immunity for the treatment of cancer (e.g., tumor immunity) and infection, including both acute and chronic (e.g., persistent) infection. However, as an optimal therapeutic directed to a target in this pathway has yet to be commercialized, a significant unmet medical need exists. Antibodies against PD-L1 are described e.g. in WO 2010/077634.

SUMMARY OF THE INVENTION

[0016] The invention comprises the combination therapy of an antibody which binds to human CSF-1R with an antibody which binds to human PD-L1 for use in the treatment of cancer, for use in the prevention or treatment of metastasis, for use in the treatment inflammatory diseases,

for use in the treatment of bone loss, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity.

[0017] The invention further comprises the use of antibody which binds to human CSF-1R for the manufacture of a medicament for use in the treatment of cancer, for use in the treatment inflammatory diseases, for use in the treatment of bone loss, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity, wherein the antibody is administered in combination with an antibody which binds to human PD-L1.

[0018] The antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0019] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

[0020] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

[0021] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

[0022] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

[0023] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0024] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or

[0025] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

[0026] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0027] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0028] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0029] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or light chain variable domain VL of SEQ ID NO:98, or

[0030] h) heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or

[0031] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

[0032] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

[0033] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- [0034] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0035] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0036] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0037] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0038] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0039] In one embodiment the antibody is for use in the treatment of cancer.
- [0040] In one embodiment the antibody is for use in the prevention or treatment of metastasis.
- [0041] In one embodiment the antibody is, for use in the treatment of bone loss.
- [0042] In one embodiment the antibody is for use in the treatment of inflammatory diseases.
- [0043] In one embodiment the antibody is for use in treating or delaying progression of an immune related disease such as tumor immunity.
- [0044] In one embodiment the antibody is for use in stimulating an immune response or function, such as T cell activity.
- [0045] The invention further comprises antibody which binds to human CSF-1R wherein the antibody is administered in combination with an antibody which binds to human PD-L1 for use in
- [0046] i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R expressing tumor cells;
- [0047] ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
- [0048] iii) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or
- [0049] iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;
- [0050] wherein the antibody is administered in combination with an antibody which binds to human PD-L1;
- [0051] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0052] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0053] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0054] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0055] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0056] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0057] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0058] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0059] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0060] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- [0061] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- [0062] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- [0063] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- [0064] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- [0065] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- [0066] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- [0067] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- [0068] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- [0069] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0070] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0071] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0072] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0073] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0074] The invention further comprised an antibody which binds to human CSF-1R, for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand and wherein the anti-CSF-1R antibody is administered in combination with an antibody which binds to human PD-L1,
- [0075] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

- [0076] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0077] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0078] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0079] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0080] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0081] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0082] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0083] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0084] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- [0085] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- [0086] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- [0087] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- [0088] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- [0089] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- [0090] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- [0091] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- [0092] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- [0093] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0094] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0095] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0096] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0097] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0098] In one embodiment the antibodies are of human IgG1 subclass or human IgG4 subclass.
- [0099] The invention further comprises:
- [0100] A) a method for
- [0101] i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;
- [0102] ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
- [0103] iii) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or
- [0104] iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;
- [0105] wherein an antibody which binds to human CSF-1R, is administered in combination with an antibody which binds to human PD-L1,
- [0106] or
- [0107] B) a method of treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand and wherein an antibody which binds to human CSF-1R is administered in combination with an antibody which binds to human PD-L1,
- [0108] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0109] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0110] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0111] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0112] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0113] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0114] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0115] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0116] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0117] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0118] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0119] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0120] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

[0121] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or

[0122] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or

[0123] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

[0124] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

[0125] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

[0126] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or

[0127] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or

[0128] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

[0129] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or

[0130] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0131] The term “ligand independent” as used herein refers to a ligand-independent signaling through the extracellular ECD (and does not include the ligand independent signaling mediated by activating point mutations in the intracellular kinase domain). In one embodiment CSF-1R ligand in this context refers a CSF-1R ligand selected from human CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)).

[0132] The invention comprises the combination treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand (in one embodiment the CSF-1R ligand is selected from human CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)) (detectable in serum, urine or tumor biopsies), wherein an antibody which binds to human CSF-1R as described herein is administered in combination with an anti-PD-L1 antibody as described herein. The term “increase of CSF-1R ligand” refers to the overexpression of human CSF-1R ligand (in one embodiment the CSF-1R ligand is selected from human

CSF-1 (SEQ ID No: 86) and human IL-34 (SEQ ID No: 87); in one embodiment the CSF-1R ligand is human CSF-1 (SEQ ID No: 86); in one embodiment the CSF-1R ligand is human IL-34 (SEQ ID No: 87)) (compared to normal tissue) before treatment or overexpression of human CSF-1R ligand induced by treatment with anti-CSF-1R antibody (and compared to the expression levels before treatment). In certain embodiments, the term “increase” or “above” refers to a level above the reference level or to an overall increase of 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 100% or greater, in CSF-1R ligand level detected by the methods described herein, as compared to the CSF-1R ligand level from a reference sample. In certain embodiments, the term increase refers to the increase in CSF-1R ligand level wherein, the increase is at least about 1.5-, 1.75-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 30-, 40-, 50-, 60-, 70-, 75-, 80-, 90-, or 100-fold higher as compared to the CSF-1R ligand level e.g. predetermined from a reference sample. In one preferred embodiment the term increased level relates to a value at or above a reference level.

[0133] The combination therapies of the antibodies described herein show benefits for patients in need of a CSF-1R targeting therapy. The specific anti-CSF-1R antibodies according to the invention show efficient antiproliferative activity against ligand-independent and ligand-dependent proliferation and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific anti-PD-L1 antibodies described herein.

DESCRIPTION OF THE FIGURES

[0134] FIG. 1a-b 1a: Human Monocytes differentiated into macrophages with coculture of GM-CSF or CSF-1 (100 ng/ml ligand). After 6 days differentiation addition of hMab 2F11-e7. Cell viability was measured at day 7 of antibody treatment in a CTG Viability Assay (CellTiterGlo® Promega). Calculation of % cell viability: RLU signals from treated cells divided by RLU signal from untreated control without antibody, (n=4).

[0135] 1b: Human Monocytes differentiated into macrophages with GM-CSF (M1) or M-CSF (M2) for 7 days. Phenotype analyzed by indirect fluorescence analysis—staining with anti CD163-PE, anti CD80-PE or anti HLA-DR/DQ/DP-Zenon-Alexa647 labeled. The number in each histogram corresponds to mean ratio fluorescence intensity (MRFI); calculated ratio between mean fluorescence intensity (MFI) of cells stained with the selected antibody (empty histogram) and of corresponding isotype control (negative control; gray filled histogram) (mean+SD; n>5).

[0136] FIG. 2a-d CSF-1 levels in Cynomolgus monkey after application of different dosages of anti-CSF-1R antibody hMab 2F11-e7.

[0137] FIG. 3 In the presence of TAMs, T cell expansion induced by activation of CD3 and CD28 was suppressed: TAM were isolated from MC38 tumors and co-cultured at the ratios indicated with CFSE-labeled CD8+ T cells in the presence of CD3/CD28 stimulation. T cell proliferation was analyzed after 3 days using bead quantification of CFSE low dividing cells. One representative experiment out of two is depicted as means+SEM of triplicate wells.

[0138] FIG. 4 Anti tumor Efficacy of <mouse CSF1R> antibody/<PD-L1> antibody combination in the MC38

mouse CRC in vivo model (Kaplan-Meier Plot for Progression of tumor volume >700 mm³).

[0139] FIG. 5 Anti tumor Efficacy of <mouse CSF1R> antibody/<PD-L1> antibody combination in the subcutaneous syngeneic CT26.WT colon carcinoma in vivo model (Kaplan-Meier Plot for Progression of tumor volume >700 mm³).

DETAILED DESCRIPTION OF THE INVENTION

[0140] Many tumors are characterized by a prominent immune cell infiltrate, including macrophages. Initially, the immune cells were thought to be part of a defense mechanism against the tumor, but recent data support the notion that several immune cell populations including macrophages may, in fact, promote tumor progression. Macrophages are characterized by their plasticity. Depending on the cytokine microenvironment, macrophages can exhibit so-called M1 or M2-subtypes. M2 macrophages are engaged in the suppression of tumor immunity. They also play an important role in tissue repair functions such as angiogenesis and tissue remodeling which are coopted by the tumor to support growth. In contrast to tumor promoting M2 macrophages, M1 macrophages exhibit antitumor activity via the secretion of inflammatory cytokines and their engagement in antigen presentation and phagocytosis (Mantovani, A. et al., *Curr. Opin. Immunol.* 2 (2010) 231-237).

[0141] By secreting various cytokines such as colony stimulating factor 1 (CSF-1) and IL-10, tumor cells are able to recruit and shape macrophages into the M2-subtype, whereas cytokines such as granulocyte macrophage colony stimulating factor (GM-CSF), IFN-gamma program macrophages towards the M1 subtype. Using immunohistochemistry, it is possible to distinguish between a macrophage subpopulation co-expressing CD68 and CD163, which is likely to be enriched for M2 Macrophages, and a subset showing the CD68+/MHC II+, or CD68+/CD80+ immunophenotype, likely to include M1 macrophages. Cell shape, size, and spatial distribution of CD68 and CD163 positive macrophages is consistent with published hypotheses on a tumor-promoting role of M2 macrophages, for example by their preferential location in tumor intersecting stroma, and vital tumor areas. In contrast, CD68+/MHC class II+ macrophages are ubiquitously found. Their hypothetical role in phagocytosis is reflected by clusters of the CD68+/MHC class II+, but CD163-immunophenotype near apoptotic cells and necrotic tumor areas.

[0142] The subtype and marker expression of different macrophage subpopulations is linked with their functional state. M2 macrophages can support tumorigenesis by:

[0143] a) enhancing angiogenesis via the secretion of angiogenic factors such as VEGF or bFGF,

[0144] b) supporting metastasis formation via secretion of matrix metalloproteinases (MMPs), growth factors and migratory factors guiding the tumor cells to the blood stream and setting up the metastatic niche (Wyckoff, J. et al., *Cancer Res.* 67 (2007) 2649-2656),

[0145] c) playing a role in building an immunosuppressive milieu by secreting immunosuppressive cytokines such as IL-4, IL-13, IL-1ra and IL-10, which in turn regulate T regulatory cell function. Conversely CD4 positive T cells have been shown to enhance the activity of tumor promoting macrophages in preclinical

models (Mantovani, A. et al., *Eur. J. Cancer* 40 (2004) 1660-1667; DeNardo, D. et al., *Cancer Cell* 16 (2009) 91-102).

[0146] Accordingly, in several types of cancer (e.g. breast, ovarian, Hodgkin's lymphoma) the prevalence of M2 subtype tumor associated macrophages (TAMs) has been associated with poor prognosis (Bingle, L. et al., *J. Pathol.* 3 (2002) 254-265; One, M., and Rogers, P. A., *Gynecol. Oncol.* 1 (1999) 47-50; Steidl, C. et al., *N. Engl. J. Med.* 10 (2010) 875-885). Recent data show a correlation of CD163 positive macrophage infiltrate in tumors and tumor grade (Kawamura, K. et al., *Pathol. Int.* 59 (2009) 300-305). TAMs isolated from patient tumors had a tolerant phenotype and were not cytotoxic to tumor cells (Mantovani, A. et al., *Eur. J. Cancer* 40 (2004) 1660-1667). However, infiltration of TAMs in the presence of cytotoxic T cells correlates with improved survival in non small cell lung cancer and hence reflects a more prominent M1 macrophage infiltrate in this tumor type (Kawai, O. et al., *Cancer* 6 (2008) 1387-1395).

[0147] Recently, a so-called immune signature comprising high numbers of macrophages and CD4 positive T cells, but low numbers of cytotoxic CD8 positive T cells was shown to correlate with reduced overall survival (OS) in breast cancer patients and to represent an independent prognostic factor (DeNardo, D. et al., *Cancer Discovery* 1 (2011) 54-67).

[0148] Consistent with a role for CSF-1 in driving the pro-tumorigenic function of M2 macrophages, high CSF-1 expression in rare sarcomas or locally aggressive connective tissue tumors, such as pigmented villonodular synovitis (PVNS) and tenosynovial giant cell tumor (TGCT) due in part to a translocation of the CSF-1 gene, leads to the accumulation of monocytes and macrophages expressing the receptor for CSF-1, the colony-stimulating factor 1 receptor (CSF-1R) forming the majority of the tumor mass (West, R. B. et al., *Proc. Natl. Acad. Sci. USA* 3 (2006) 690-695). These tumors were subsequently used to define a CSF-1 dependent macrophage signature by gene expression profiling. In breast cancer and leiomyosarcoma patient tumors this CSF-1 response gene signature predicts poor prognosis (Espinosa, I. et al., *Am. J. Pathol.* 6 (2009) 2347-2356; Beck, A. et al., *Clin. Cancer Res.* 3 (2009) 778-787).

[0149] CSF-1R belongs to the class III subfamily of receptor tyrosine kinases and is encoded by the *c-fms* proto-oncogene. Binding of CSF-1 or IL-34 induces receptor dimerization, followed by autophosphorylation and activation of downstream signaling cascades. Activation of CSF-1R regulates the survival, proliferation and differentiation of monocytes and macrophages (Xiong, Y. et al., *J. Biol. Chem.* 286 (2011) 952-960).

[0150] In addition to cells of the monocytic lineage and osteoclasts, which derive from the same hematopoietic precursor as the macrophage, CSF-1R/*c-fms* has also been found to be expressed by several human epithelial cancers such as ovarian and breast cancer and in leiomyosarcoma and TGCT/PVNS, albeit at lower expression levels compared to macrophages. As with TGCT/PVNS, elevated levels of CSF-1, the ligand for CSF-1R, in serum as well as ascites of ovarian cancer patients have been correlated with poor prognosis (Scholl, S. et al., *Br. J. Cancer* 62 (1994) 342-346; Price, F. et al., *Am. J. Obstet. Gynecol.* 168 (1993) 520-527). Furthermore, a constitutively active mutant form

of CSF 1R is able to transform NIH3T3 cells, one of the properties of an oncogene (Chambers, S., *Future Oncol* 5 (2009) 1429-1440).

[0151] Preclinical models provide validation of CSF-1R as an oncology target. Blockade CSF-1 as well as CSF-1R activity results in reduced recruitment of TAMs. Chemotherapy resulted in elevated CSF-1 expression in tumor cells leading to enhanced TAM recruitment. Blockade of CSF-1R in combination with paclitaxel resulted in activation of CD8 positive cytotoxic T cells leading to reduced tumor growth and metastatic burden in a spontaneous transgenic breast cancer model (DeNardo, D. et al., *Cancer Discovery* 1 (2011) 54-67).

[0152] The human CSF-1R (CSF-1 receptor; synonyms: M-CSF receptor; Macrophage colony-stimulating factor 1 receptor, *Fms* proto-oncogene, *c-fms*, SEQ ID NO: 22) is known since 1986 (Coussens, L., et al., *Nature* 320 (1986) 277-280). CSF-1R is a growth factor and encoded by the *c-fms* proto-oncogene (reviewed e.g. in Roth, P. and Stanley, E. R., *Curr. Top. Microbiol. Immunol.* 181 (1992) 141-167).

[0153] CSF-1R is the receptor for the CSF-1R ligands CSF-1 (macrophage colony stimulating factor, also called M-CSF) (SEQ ID No.: 86) and IL-34 (SEQ ID No.: 87) and mediates the biological effects of these cytokines (Sherr, C. J., et al., *Cell* 41 (1985) 665-676; Lin, H., et al., *Science* 320 (2008) 807-811). The cloning of the colony stimulating factor-1 receptor (also called *c-fms*) was described for the first time in Roussel, M. F., et al., *Nature* 325 (1987) 549-552. In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee, P. S., et al., *Embo J.* 18 (1999) 3616-3628).

[0154] CSF-1R is a single chain, transmembrane receptor tyrosine kinase (RTK) and a member of the family of immunoglobulin (Ig) motif containing RTKs characterized by 5 repeated Ig-like subdomains D1-D5 in the extracellular domain (ECD) of the receptor (Wang, Z., et al *Molecular and Cellular Biology* 13 (1993) 5348-5359). The human CSF-1R Extracellular Domain (CSF-1R-ECD) (SEQ ID NO: 64) comprises all five extracellular Ig-like subdomains D1-D5. The human CSF-1R fragment delD4 (SEQ ID NO: 65) comprises the extracellular Ig-like subdomains D1-D3 and D5, but is missing the D4 subdomain. The human CSF-1R fragment D1-D3 (SEQ ID NO: 66) comprises the respective subdomains D1-D3. The sequences are listed without the signal peptide MGSGPGVLLLL LLVATAWHGQ G (SEQ ID NO: 67). The human CSF-1R fragment D4-D3 (SEQ ID NO: 85) comprises the respective subdomains D4-D3.

[0155] Currently two CSF-1R ligands that bind to the extracellular domain of CSF-1R are known. The first one is CSF-1 (colony stimulating factor 1, also called M-CSF, macrophage; human CSF-1, SEQ ID NO: 86) and is found extracellularly as a disulfide-linked homodimer (Stanley, E. R. et al., *Journal of Cellular Biochemistry* 21 (1983) 151-159; Stanley, E. R. et al., *Stem Cells* 12 Suppl. 1 (1995) 15-24). The second one is IL-34 (human IL-34; SEQ ID NO: 87) (Hume, D. A., et al, *Blood* 119 (2012) 1810-1820). Thus in one embodiment the term "CSF-1R ligand" refers to human CSF-1 (SEQ ID NO: 86) and/or human IL-34 (SEQ ID NO: 87).

[0156] For experiments often the active 149 amino acid (aa) fragment of human CSF-1 (aa 33-181 of SEQ ID NO:

86) is used. This active 149 aa fragment of human CSF-1 (aa 33-181 of SEQ ID NO: 86) is contained in all 3 major forms of CSF-1 and is sufficient to mediate binding to CSF-1R (Hume, D. A., et al, *Blood* 119 (2012) 1810-1820).

[0157] The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of hematopoietic precursor cells to the macrophage lineage (including osteoclast). Activation of CSF-1R is mediated by its CSF-1R ligands, CSF-1 (M-CSF) and IL-34. Binding of CSF-1 (M-CSF) to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Li, W. et al, *EMBO Journal.* 10 (1991) 277-288; Stanley, E. R., et al., *Mol. Reprod. Dev.* 46 (1997) 4-10).

[0158] The intracellular protein tyrosine kinase domain is interrupted by a unique insert domain that is also present in the other related RTK class III family members that include the platelet derived growth factor receptors (PDGFR), stem cell growth factor receptor (*c-Kit*) and *fms*-like cytokine receptor (FLT3). In spite of the structural homology among this family of growth factor receptors, they have distinct tissue-specific functions.

[0159] CSF-1R is mainly expressed on cells of the monocytic lineage and in the female reproductive tract and placenta. In addition expression of CSF-1R has been reported in Langerhans cells in skin, a subset of smooth muscle cells (Inaba, T., et al., *J. Biol. Chem.* 267 (1992) 5693-5699), B cells (Baker, A. H., et al., *Oncogene* 8 (1993) 371-378) and microglia (Sawada, M., et al., *Brain Res.* 509 (1990) 119-124). Cells with mutant human CSF-1R ((SEQ ID NO: 23) are known to proliferate independently of ligand stimulation.

[0160] As used herein, "binding to human CSF-1R" or "specifically binding to human CSF-1R" or "which binds to human CSF-1R" or "anti-CSF-1R antibody" refers to an antibody specifically binding to the human CSF-1R antigen with a binding affinity of KD-value of 1.0×10^{-8} mol/l or lower, in one embodiment of a KD-value of 1.0×10^{-9} mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BIAcore®, GE-Healthcare Uppsala, Sweden). Thus an "antibody binding to human CSF-1R" as used herein refers to an antibody specifically binding to the human CSF-1R antigen with a binding affinity of KD 1.0×10^{-8} mol/l or lower (in one embodiment 1.0×10^{-8} mol/l- 1.0×10^{-13} mol/l), in on embodiment of a KD 1.0×10^{-9} mol/l or lower (in one embodiment 1.0×10^{-9} mol/l- 1.0×10^{-13} mol/l).

PD-1/PD-L1/PD-L2 Pathway:

[0161] An important negative co-stimulatory signal regulating T cell activation is provided by programmed death-1 receptor (PD-1)(CD279), and its ligand binding partners PD-L1 (B7-H1, CD274; SEQ ID NO: 88) and PD-L2 (B7-DC, CD273). The negative regulatory role of PD-1 was revealed by PD-1 knock outs (*Pdcd1*-/-), which are prone to autoimmunity. Nishimura et al., *Immunity* 11: 141-51 (1999); Nishimura et al., *Science* 291: 319-22 (2001). PD-1 is related to CD28 and CTLA-4, but lacks the membrane proximal cysteine that allows homodimerization. The cytoplasmic domain of PD-1 contains an immunoreceptor tyrosine-based inhibition motif (ITIM, V/IxYxxL/V). PD-1 only binds to PD-L1 and PD-L2. Freeman et al., *J. Exp. Med.* 192: 1-9 (2000); Dong et al., *Nature Med.* 5: 1365-1369

(1999); Latchman et al., *Nature Immunol.* 2: 261-268 (2001); Tseng et al., *J. Exp. Med.* 193: 839-846 (2001).

[0162] PD-1 can be expressed on T cells, B cells, natural killer T cells, activated monocytes and dendritic cells (DCs). PD-1 is expressed by activated, but not by unstimulated human CD4⁺ and CD8⁺ T cells, B cells and myeloid cells. This stands in contrast to the more restricted expression of CD28 and CTLA-4. Nishimura et al., *Int. Immunol.* 8: 773-80 (1996); Boettler et al., *J. Virol.* 80: 3532-40 (2006). There are at least 4 variants of PD-1 that have been cloned from activated human T cells, including transcripts lacking (i) exon 2, (ii) exon 3, (iii) exons 2 and 3 or (iv) exons 2 through 4. Nielsen et al., *Cell. Immunol.* 235: 109-16 (2005). With the exception of PD-1 Aex3, all variants are expressed at similar levels as full length PD-1 in resting peripheral blood mononuclear cells (PBMCs). Expression of all variants is significantly induced upon activation of human T cells with anti-CD3 and anti-CD28. The PD-1 Aex3 variant lacks a transmembrane domain, and resembles soluble CTLA-4, which plays an important role in autoimmunity. Ueda et al., *Nature* 423: 506-11 (2003). This variant is enriched in the synovial fluid and sera of patients with rheumatoid arthritis. Wan et al., *J. Immunol.* 177: 8844-50 (2006).

[0163] The two PD-1 ligands differ in their expression patterns. PD-L1 is constitutively expressed on mouse T and B cells, CD8, macrophages, mesenchymal stem cells and bone marrow-derived mast cells. Yamazaki et al., *J. Immunol.* 169: 5538-45 (2002). PD-L1 is expressed on a wide range of nonhematopoietic cells (e.g., cornea, lung, vascular epithelium, liver nonparenchymal cells, mesenchymal stem cells, pancreatic islets, placental syncytiotrophoblasts, keratinocytes, etc.) [Keir et al., *Annu Rev. Immunol.* 26: 677-704 (2008)], and is upregulated on a number of cell types after activation. Both type I and type II interferons (IFN's) upregulate PD-L1. Eppihimer et al., *Microcirculation* 9: 133-45 (2002); Schreiner et al., *J. Neuroimmunol.* 155: 172-82 (2004). PD-L1 expression in cell lines is decreased when MyD88, TRAF6 and MEK are inhibited. Liu et al., *Blood* 110: 296-304 (2007). JAK2 has also been implicated in PD-L1 induction. Lee et al., *FEBS Lett.* 580: 755-62 (2006); Liu et al., *Blood* 110: 296-304 (2007). Loss or inhibition of phosphatase and tensin homolog (PTEN), a cellular phosphatase that modified phosphatidylinositol 3-kinase (PI3K) and Akt signaling, increased post-transcriptional PD-L1 expression in cancers. Parsa et al., *Nat. Med.* 13: 84-88 (2007).

[0164] PD-L2 expression is more restricted than PD-L1. PD-L2 is inducibly expressed on DCs, macrophages, and bone marrow-derived mast cells. PD-L2 is also expressed on about half to two-thirds of resting peritoneal B1 cells, but not on conventional B2 B cells. Zhong et al., *Eur. J. Immunol.* 37: 2405-10 (2007). PD-L2+B1 cells bind phosphatidylcholine and may be important for innate immune responses against bacterial antigens. Induction of PD-L2 by IFN- γ is partially dependent upon NF- κ B. Liang et al., *Eur. J. Immunol.* 33: 2706-16 (2003). PD-L2 can also be induced on monocytes and macrophages by GM-CSF, IL-4 and IFN- γ . Yamazaki et al., *J. Immunol.* 169: 5538-45 (2002); Loke et al., *PNAS* 100:5336-41 (2003).

[0165] PD-1 signaling typically has a greater effect on cytokine production than on cellular proliferation, with significant effects on IFN- γ , TNF- α and IL-2 production. PD-1 mediated inhibitory signaling also

depends on the strength of the TCR signaling, with greater inhibition delivered at low levels of TCR stimulation. This reduction can be overcome by costimulation through CD28 [Freeman et al., *J. Exp. Med.* 192: 1027-34 (2000)] or the presence of IL-2 [Carter et al., *Eur. J. Immunol.* 32: 634-43 (2002)].

[0166] Evidence is mounting that signaling through PD-L1 and PD-L2 may be bidirectional. That is, in addition to modifying TCR or BCR signaling, signaling may also be delivered back to the cells expressing PD-L1 and PD-L2. While treatment of dendritic cells with a naturally human anti-PD-L2 antibody isolated from a patient with Waldenström's macroglobulinemia was not found to upregulate MHC II or B7 costimulatory molecules, such cells did produce greater amount of proinflammatory cytokines, particularly TNF- α and IL-6, and stimulated T cell proliferation. Nguyen et al., *J. Exp. Med.* 196: 1393-98 (2002). Treatment of mice with this antibody also (1) enhanced resistance to transplanted b16 melanoma and rapidly induced tumor-specific CTL. Radhakrishnan et al., *J. Immunol.* 170: 1830-38 (2003); Radhakrishnan et al., *Cancer Res.* 64: 4965-72 (2004); Heckman et al., *Eur. J. Immunol.* 37: 1827-35 (2007); (2) blocked development of airway inflammatory disease in a mouse model of allergic asthma. Radhakrishnan et al., *J. Immunol.* 173: 1360-65 (2004); Radhakrishnan et al., *J. Allergy Clin. Immunol.* 116: 668-74 (2005).

[0167] Further evidence of reverse signaling into dendritic cells ("DC's") results from studies of bone marrow derived DC's cultured with soluble PD-1 (PD-1 EC domain fused to Ig constant region—"s-PD-1"). Kuipers et al., *Eur. J. Immunol.* 36: 2472-82 (2006). This sPD-1 inhibited DC activation and increased IL-10 production, in a manner reversible through administration of anti-PD-1.

[0168] Additionally, several studies show a receptor for PD-L1 or PD-L2 that is independent of PD-1. B7.1 has already been identified as a binding partner for PD-L1. Butte et al., *Immunity* 27: 111-22 (2007). Chemical crosslinking studies suggest that PD-L1 and B7.1 can interact through their IgV-like domains. B7.1:PD-L1 interactions can induce an inhibitory signal into T cells. Ligation of PD-L1 on CD4⁺ T cells by B7.1 or ligation of B7.1 on CD4⁺ T cells by PD-L1 delivers an inhibitory signal. T cells lacking CD28 and CTLA-4 show decreased proliferation and cytokine production when stimulated by anti-CD3 plus B7.1 coated beads. In T cells lacking all the receptors for B7.1 (i.e., CD28, CTLA-4 and PD-L1), T cell proliferation and cytokine production were no longer inhibited by anti-CD3 plus B7.1 coated beads. This indicates that B7.1 acts specifically through PD-L1 on the T-cell in the absence of CD28 and CTLA-4. Similarly, T cells lacking PD-1 showed decreased proliferation and cytokine production when stimulated in the presence of anti-CD3 plus PD-L1 coated beads, demonstrating the inhibitory effect of PD-L1 ligation on B7.1 on T cells. When T cells lacking all known receptors for PD-L1 (i.e., no PD-1 and B7.1), T cell proliferation was no longer impaired by anti-CD3 plus PD-L1 coated beads. Thus, PD-L1 can exert an inhibitory effect on T cells either through B7.1 or PD-1.

[0169] The direct interaction between B7.1 and PD-L1 suggests that the current understanding of costimulation is incomplete, and underscores the significance to the expression of these molecules on T cells. Studies of PD-L1^{-/-} T cells indicate that PD-L1 on T cells can downregulate T cell

cytokine production. Latchman et al., Proc. Natl. Acad. Sci. USA 101: 10691-96 (2004). Because both PD-L1 and B7.1 are expressed on T cells, B cells, DCs and macrophages, there is the potential for directional interactions between B7.1 and PD-L1 on these cells types. Additionally, PD-L1 on non-hematopoietic cells may interact with B7.1 as well as PD-1 on T cells, raising the question of whether PD-L1 is involved in their regulation. One possible explanation for the inhibitory effect of B7.1:PD-L1 interaction is that T cell PD-L1 may trap or segregate away APC B7.1 from interaction with CD28.

[0170] As a result, the antagonism of signaling through PD-L1, including blocking PD-L1 from interacting with either PD-1, B7.1 or both, thereby preventing PD-L1 from sending a negative co-stimulatory signal to T-cells and other antigen presenting cells is likely to enhance immunity in response to infection (e.g., acute and chronic) and tumor immunity. In addition, the anti-PD-L1 antibodies of the present invention, may be combined with antagonists of other components of PD-1:PD-L1 signaling, for example, antagonist anti-PD-1 and anti-PD-L2 antibodies.

[0171] The term “human PD-L1” refers to the human protein PD-L1 (SEQ ID NO: 88, PD-1 signaling typically). As used herein, “binding to human PD-L1” or “specifically binding to human PD-L1” or “which binds to human PD-L1” or “anti-PD-L1 antibody” refers to an antibody specifically binding to the human PD-L1 antigen with a binding affinity of KD-value of 1.0×10^{-8} mol/l or lower, in one embodiment of a KD-value of 1.0×10^{-9} mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BIAcore®, GE-Healthcare Uppsala, Sweden). Thus an “antibody binding to human PD-L1” as used herein refers to an antibody specifically binding to the human PD-L1 antigen with a binding affinity of KD 1.0×10^{-8} mol/l or lower (in one embodiment 1.0×10^{-8} mol/l- 1.0×10^{-13} mol/l), in one embodiment of a KD 1.0×10^{-9} mol/l or lower (in one embodiment 1.0×10^{-9} mol/l- 1.0×10^{-13} mol/l).

[0172] In one embodiment the antibody which binds to human CSF-1R used in the combination therapy described herein is selected from the group consisting of hMab 2F11-c11, hMab 2F11-d8, hMab 2F11-e7, hMab 2F11412, and hMab 2F11-g1.

[0173] These antibodies are described in WO2011/070024 and are characterized in comprising the following VH and VL sequences as described herein:

TABLE 1

anti-CSF-1R antibody	amino acid sequence of the heavy chain variable domain VH, SEQ ID NO:	amino acid sequence of the light chain variable domain VL, SEQ ID NO:
hMab 2F11-c11	23	24
hMab 2F11-d8	31	32
hMab 2F11-e7	39	40
hMab 2F11-f12	47	48
hMab 2F11-g1	55	56

[0174] In one embodiment the antibody which binds to human PD-L1 used in the combination therapy described herein is selected from the group consisting of:

[0175] 243.55.S70, 243.55.H1, 243.55.H12, 243.55.H37, 243.55.H70, 243.55.H89, 243.55.S1, 243.55.5, 243.55.8, 243.55.30, 243.55.34, 243.55.S37, 243.55.49, 243.55.51, 243.55.62, and 243.55.84.

[0176] These antibodies are described in WO 2010/77634 (sequences are shown in FIG. 11 of WO 2010/77634) and are characterized in comprising the following VH and VL sequences as described herein:

TABLE 2

anti-PD-L1 antibody	amino acid sequence of the heavy chain variable domain VH, SEQ ID NO:	amino acid sequence of the light chain variable domain VL, SEQ ID NO:
243.55.S70	89	92
243.55.H1	90	93
243.55.H12	90	94
243.55.H37	90	95
243.55.H70	90	96
243.55.H89	90	97
243.55.S1	90	98
243.55.5	90	99
243.55.8	90	100
243.55.30	90	101
243.55.34	90	102
243.55.S37	90	103
243.55.49	90	104
243.55.51	90	105
243.55.62	90	106
243.55.84	91	107

[0177] In one embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is characterized in comprising

[0178] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

[0179] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

[0180] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

[0181] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

[0182] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56; and

the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0183] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or

[0184] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

[0185] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0186] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0187] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0188] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106.

[0222] In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0223] In one preferred embodiment of the invention the antibody which binds to human CSF-1R used in the combination therapy described herein is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, and

the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92.

[0224] The term “epitope” denotes a protein determinant of human CSF-1R or PD-L1 capable of specifically binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually epitopes have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0225] The “variable domain” (light chain variable domain VL, heavy chain variable domain VH) as used herein denotes each of the pair of light and heavy chain domains which are involved directly in binding the antibody to the antigen. The variable light and heavy chain domains have the same general structure and each domain comprises four framework (FR) regions whose sequences are widely conserved, connected by three “hypervariable regions” (or complementary determining regions, CDRs). The framework regions adopt a beta-sheet conformation and the CDRs may form loops connecting the beta-sheet structure. The CDRs in each chain are held in their three-dimensional structure by the framework regions and form together with the CDRs from the other chain the antigen binding site. The antibody’s heavy and light chain CDR3 regions play a particularly important role in the binding specificity/affinity of the antibodies according to the invention and therefore provide a further object of the invention.

[0226] The term “antigen-binding portion of an antibody” when used herein refer to the amino acid residues of an antibody which are responsible for antigen-binding. The antigen-binding portion of an antibody comprises amino acid residues from the “complementary determining regions” or “CDRs”, “Framework” or “FR” regions are those variable domain regions other than the hypervariable region residues as herein defined. Therefore, the light and heavy chain variable domains of an antibody comprise from N- to C-terminus the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Especially, CDR3 of the heavy chain is the region which contributes most to antigen binding and defines the antibody’s properties. CDR and FR regions are determined according to the standard definition of Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th ed., Public Health Service, National Institutes of Health, Bethesda, Md. (1991) and/or those residues from a “hypervariable loop”.

[0227] The terms “nucleic acid” or “nucleic acid molecule”, as used herein, are intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

[0228] The term “amino acid” as used within this application denotes the group of naturally occurring carboxy alpha-amino acids comprising alanine (three letter code: ala, one letter code: A), arginine (arg, R), asparagine (asn, N), aspartic acid (asp, D), cysteine (cys, C), glutamine (gln, Q), glutamic acid (glu, E), glycine (gly, G), histidine (his, H), isoleucine (ile, I), leucine (leu, L), lysine (lys, K), methionine (met, M), phenylalanine (phe, F), proline (pro, P), serine (ser, S), threonine (thr, T), tryptophan (trp, W), tyrosine (tyr, Y), and valine (val, V).

[0229] The “Fc part” of an antibody is not involved directly in binding of an antibody to an antigen, but exhibit various effector functions. A “Fc part of an antibody” is a term well known to the skilled artisan and defined on the basis of papain cleavage of antibodies. Depending on the amino acid sequence of the constant region of their heavy chains, antibodies or immunoglobulins are divided in the classes: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG1, IgG2, IgG3, and IgG4, IgA1, and IgA2. According to the heavy chain constant regions the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively. The Fc part of an antibody is directly involved in ADCC (antibody-dependent cell-mediated cytotoxicity) and CDC (complement-dependent cytotoxicity) based on complement activation, C1q binding and Fc receptor binding. Complement activation (CDC) is initiated by binding of complement factor C1q to the Fc part of most IgG antibody subclasses. While the influence of an antibody on the complement system is dependent on certain conditions, binding to C1q is caused by defined binding sites in the Fc part. Such binding sites are known in the state of the art and described e.g. by Boackle, R. J., et al., *Nature* 282 (1979) 742-743; Lukas, T. J., et al., *J. Immunol.* 127 (1981) 2555-2560; Brunhouse, R., and Cebra, J. J., *Mol. Immunol.* 16 (1979) 907-917; Burton, D. R., et al., *Nature* 288 (1980) 338-344; Thommesen, J. E., et al., *Mol. Immunol.* 37 (2000) 995-1004; Idusogie, E. E., et al., *J. Immunol.* 164 (2000) 4178-4184; Hezareh, M., et al., *J. Virology* 75 (2001) 12161-12168; Morgan, A., et al., *Immunology* 86 (1995) 319-324; EP 0 307 434. Such binding sites are e.g. L234, L235, D270, N297, E318, K320, K322, P331 and P329 (numbering according to EU index of Kabat, E. A., see below). Antibodies of subclass IgG1, IgG2 and IgG3 usually show complement activation and C1q and C3 binding, whereas IgG4 do not activate the complement system and do not bind C1q and C3.

[0230] In one embodiment the antibody according to the invention comprises an Fc part derived from human origin and preferably all other parts of the human constant regions. As used herein the term “Fc part derived from human origin” denotes a Fc part which is either a Fc part of a human antibody of the subclass IgG1, IgG2, IgG3 or IgG4, preferably a Fc part from human IgG1 subclass, a mutated Fc part from human IgG1 subclass (in one embodiment with a mutation on L234A+L235A), a Fc part from human IgG4 subclass or a mutated Fc part from human IgG4 subclass (in one embodiment with a mutation on S228P). In one preferred embodiment the human heavy chain constant region is SEQ ID NO: 58 (human IgG1 subclass), in another

preferred embodiment the human heavy chain constant region is SEQ ID NO: 59 (human IgG1 subclass with mutations L234A and L235A), in another preferred embodiment the human heavy chain constant region is SEQ ID NO: 60 (human IgG4 subclass), and in another preferred embodiment the human heavy chain constant region is SEQ ID NO: 61 (human IgG4 subclass with mutation S228P). In one embodiment said antibodies have reduced or minimal effector function. In one embodiment the minimal effector function results from an effectorless Fc mutation. In one embodiment the effectorless Fc mutation is L234A/L235A or L234A/L235A/P329G or N297A or D265A/N297A. In one embodiment the effectorless Fc mutation is selected for each of the antibodies independently of each other from the group comprising (consisting of) L234A/L235A, L234A/L235A/P329G, N297A and D265A/N297A.

[0231] In one embodiment the antibodies described herein are of human IgG class (i.e. of IgG1, IgG2, IgG3 or IgG4 subclass).

[0232] In a preferred embodiment the antibodies described herein are of human IgG1 subclass or of human IgG4 subclass. In one embodiment the described herein are of human IgG1 subclass. In one embodiment the antibodies described herein are of human IgG4 subclass.

[0233] In one embodiment the antibody described herein is characterized in that the constant chains are of human origin. Such constant chains are well known in the state of the art and e.g. described by Kabat, E. A., (see e.g. Johnson, G. and Wu, T. T., *Nucleic Acids Res.* 28 (2000) 214-218). For example, a useful human heavy chain constant region comprises an amino acid sequence of SEQ ID NO: 58. For example, a useful human light chain constant region comprises an amino acid sequence of a kappa-light chain constant region of SEQ ID NO: 57.

[0234] The invention comprises a method for the treatment of a patient in need of therapy, characterized by administering to the patient a therapeutically effective amount of an antibody according to the invention.

[0235] The invention comprises the use of an antibody according to the invention for the described therapy.

[0236] One preferred embodiment of the invention are the CSF-1R antibodies of the present invention for use in the treatment of "CSF-1R mediated diseases" or the CSF-1R antibodies of the present invention for use for the manufacture of a medicament in the treatment of "CSF-1R mediated diseases", which can be described as follows:

[0237] There are 3 distinct mechanisms by which CSF-1R signaling is likely involved in tumor growth and metastasis. The first is that expression of CSF-ligand and receptor has been found in tumor cells originating in the female reproductive system (breast, ovarian, endometrium, cervical) (Scholl, S. M., et al., *J. Natl. Cancer Inst.* 86 (1994) 120-126; Kacinski, B. M., *Mol. Reprod. Dev.* 46 (1997) 71-74; Ngan, H. Y., et al., *Eur. J. Cancer* 35 (1999) 1546-1550; Kirma, N., et al., *Cancer Res* 67 (2007) 1918-1926) and the expression has been associated with breast cancer xenograft growth as well as poor prognosis in breast cancer patients. Two point mutations were seen in CSF-1R in about 10-20% of acute myelocytic leukemia, chronic myelocytic leukemia and myelodysplasia patients tested in one study, and one of the mutations was found to disrupt receptor turnover (Ridge, S. A., et al., *Proc. Natl. Acad. Sci USA* 87 (1990) 1377-1380). However the incidence of the mutations could not be confirmed in later studies (Abu-Duhier, F. M., et al., *Br. J.*

Haematol. 120 (2003) 464-470). Mutations were also found in some cases of hepatocellular cancer (Yang, D. H., et al., *Hepatobiliary Pancreat. Dis. Int.* 3 (2004) 86-89) and idiopathic myelofibrosis (Abu-Duhier, F. M., et al., *Br. J. Haematol.* 120 (2003) 464-470). Recently, in the GDM-1 cell line derived from a patient with myelomonoblastic leukemia the Y571D mutation in CSF-1R was identified (Chase, A., et al., *Leukemia* 23 (2009) 358-364).

[0238] Pigmented villonodular synovitis (PVNS) and Tenosynovial Giant cell tumors (TGCT) can occur as a result of a translocation that fuses the M-CSF gene to a 15 collagen gene COL6A3 and results in overexpression of M-CSF (West, R. B., et al., *Proc. Natl. Acad. Sci. USA* 103 (2006) 690-695). A landscape effect is proposed to be responsible for the resulting tumor mass that consists of monocytic cells attracted by cells that express M-CSF. TGCTs are smaller tumors that can be relatively easily removed from fingers where they mostly occur. PVNS is more aggressive as it can recur in large joints and is not as easily controlled surgically.

[0239] The second mechanism is based on blocking signaling through M-CSF/CSF-1R at metastatic sites in bone which induces osteoclastogenesis, bone resorption and osteolytic bone lesions. Breast, multiple myeloma and lung cancers are examples of cancers that have been found to metastasize to the bone and cause osteolytic bone disease resulting in skeletal complications. M-CSF released by tumor cells and stroma induces the differentiation of hematopoietic myeloid monocyte progenitors to mature osteoclasts in collaboration with the receptor activator of nuclear factor kappa-B ligand-RANKL. During this process, M-CSF acts as a permissive factor by giving the survival signal to osteoclasts (Tanaka, S., et al., *J. Clin. Invest.* 91 (1993) 257-263). Inhibition of CSF-1R activity during osteoclast differentiation and maturation with an anti-CSF-1R antibody is likely to prevent unbalanced activity of osteoclasts that cause osteolytic disease and the associated skeletal related events in metastatic disease. Whereas breast, lung cancer and multiple myeloma typically result in osteolytic lesions, metastasis to the bone in prostate cancer initially has an osteoblastic appearance in which increased bone forming activity results in 'woven bone' which is different from typical lamellar structure of normal bone. During disease progression bone lesions display a significant osteolytic component as well as high serum levels of bone resorption and suggests that anti-resorptive therapy may be useful. Bisphosphonates have been shown to inhibit the formation of osteolytic lesions and reduced the number of skeletal-related events only in men with hormone-refractory metastatic prostate cancer but at this point their effect on osteoblastic lesions is controversial and bisphosphonates have not been beneficial in preventing bone metastasis or hormone responsive prostate cancer to date. The effect of anti-resorptive agents in mixed osteolytic/osteoblastic prostate cancer is still being studied in the clinic (Choueiri, M. B., et al., *Cancer Metastasis Rev.* 25 (2006) 601-609; Vessella, R. L. and Corey, E., *Clin. Cancer Res.* 12 (20 Pt 2) (2006) 6285s-6290s).

[0240] The third mechanism is based on the recent observation that tumor associated macrophages (TAM) found in solid tumors of the breast, prostate, ovarian and cervical cancers correlated with poor prognosis (Bingle, L., et al., *J. Pathol.* 196 (2002) 254-265; Pollard, J. W., *Nat. Rev. Cancer* 4 (2004) 71-78). Macrophages are recruited to the tumor by M-CSF and other chemokines. The macrophages can then

contribute to tumor progression through the secretion of angiogenic factors, proteases and other growth factors and cytokines and may be blocked by inhibition of CSF-1R signaling. Recently it was shown by Zins et al (Zins, K., et al., Cancer Res. 67 (2007) 1038-1045) that expression of siRNA of Tumor necrosis factor alpha (TNF alpha), M-CSF or the combination of both would reduce tumor growth in a mouse xenograft model between 34% and 50% after intratumoral injection of the respective siRNA. siRNA targeting the TNF alpha secreted by the human SW620 cells reduced mouse M-CSF levels and led to reduction of macrophages in the tumor. In addition treatment of MCF7 tumor xenografts with an antigen binding fragment directed against M-CSF did result in 40% tumor growth inhibition, reversed the resistance to chemotherapeutics and improved survival of the mice when given in combination with chemotherapeutics (Paulus, P., et al., Cancer Res. 66 (2006) 4349-4356).

[0241] TAMs are only one example of an emerging link between chronic inflammation and cancer. There is additional evidence for a link between inflammation and cancer as many chronic diseases are associated with an increased risk of cancer, cancers arise at sites of chronic inflammation, chemical mediators of inflammation are found in many cancers; deletion of the cellular or chemical mediators of inflammation inhibits development of experimental cancers and long-term use of anti-inflammatory agents reduce the risk of some cancers. A link to cancer exists for a number of inflammatory conditions among those *H. pylori* induced gastritis for gastric cancer, Schistosomiasis for bladder cancer, HHVX for Kaposi's sarcoma, endometriosis for ovarian cancer and prostatitis for prostate cancer (Balkwill, F., et al., Cancer Cell 7 (2005) 211-217). Macrophages are key cells in chronic inflammation and respond differentially to their microenvironment. There are two types of macrophages that are considered extremes in a continuum of functional states: M1 macrophages are involved in Type 1 reactions. These reactions involve the activation by microbial products and consequent killing of pathogenic microorganisms that result in reactive oxygen intermediates. On the other end of the extreme are M2 macrophages involved in Type 2 reactions that promote cell proliferation, tune inflammation and adaptive immunity and promote tissue remodeling, angiogenesis and repair (Mantovani, A., et al., Trends Immunol. 25 (2004) 677-686). Chronic inflammation resulting in established neoplasia is usually associated with M2 macrophages. A pivotal cytokine that mediates inflammatory reactions is TNF alpha that true to its name can stimulate anti-tumor immunity and hemorrhagic necrosis at high doses but has also recently been found to be expressed by tumor cells and acting as a tumor promoter (Zins, K., et al., Cancer Res. 67 (2007) 1038-1045; Balkwill, F., Cancer Metastasis Rev. 25 (2006) 409-416). The specific role of macrophages with respect to the tumor still needs to be better understood including the potential spatial and temporal dependence on their function and the relevance to specific tumor types.

[0242] Thus one embodiment of the invention are the CSF-1R antibodies described herein for use in the treatment of cancer in combination with an anti-PD-L1 antibody as described herein. The term "cancer" as used herein may be, for example, lung cancer, non small cell lung (NSCL) cancer, bronchioloalveolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach

cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwannomas, ependymomas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. In one preferred embodiment such cancer is a breast cancer, colorectal cancer, melanoma, head and neck cancer, lung cancer or prostate cancer. In one preferred embodiment such cancer is a breast cancer, ovarian cancer, cervical cancer, lung cancer or prostate cancer. In another preferred embodiment such cancer is breast cancer, lung cancer, colon cancer, ovarian cancer, melanoma cancer, bladder cancer, renal cancer, kidney cancer, liver cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric carcinoma cancer, esophageal cancer, mesothelioma, prostate cancer, leukemia, lymphoma, myelomas. In one preferred embodiment such cancers are further characterized by CSF-1 or CSF-1R expression or overexpression. One further embodiment the invention are the CSF-1R antibodies of the present invention for use in the simultaneous treatment of primary tumors and new metastases. Thus another embodiment of the invention are the CSF-1R antibodies of the present invention for use in the treatment of periodontitis, histiocytosis X, osteoporosis, Paget's disease of bone (PDB), bone loss due to cancer therapy, periprosthetic osteolysis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, inflammatory arthritides, and inflammation.

[0243] Rabello, D., et al., Biochem. Biophys. Res. Commun. 347 (2006) 791-796 has demonstrated that SNPs in the CSF1 gene exhibited a positive association with aggressive periodontitis: an inflammatory disease of the periodontal tissues that causes tooth loss due to resorption of the alveolar bone.

[0244] Histiocytosis X (also called Langerhans cell histiocytosis, LCH) is a proliferative disease of Langerhans dendritic cells that appear to differentiate into osteoclasts in bone and extra osseous LCH lesions. Langerhans cells are derived from circulating monocytes. Increased levels of M-CSF that have been measured in sera and lesions where found to correlate with disease severity (da Costa, C. E., et al., J. Exp. Med. 201 (2005) 687-693). The disease occurs primarily in a pediatric patient population and has to be treated with chemotherapy when the disease becomes systemic or is recurrent.

[0245] The pathophysiology of osteoporosis is mediated by loss of bone forming osteoblasts and increased osteoclast dependent bone resorption. Supporting data has been described by Cenci et al showing that an anti-M-CSF antibody injection preserves bone density and inhibits bone resorption in ovariectomized mice (Cenci, S., et al., J. Clin. Invest. 105 (2000) 1279-1287). Recently a potential link

between postmenopausal bone loss due to estrogen deficiency was identified and found that the presence of TNF alpha producing T-cell affected bone metabolism (Roggia, C., et al., *Minerva Med.* 95 (2004) 125-132). A possible mechanism could be the induction of M-CSF by TNF alpha in vivo. An important role for M-CSF in TNF-alpha-induced osteoclastogenesis was confirmed by the effect of an antibody directed against M-CSF that blocked the TNF alpha induced osteolysis in mice and thereby making inhibitors of CSF-1R signaling potential targets for inflammatory arthritis (Kitaura, H., et al., *J. Clin. Invest.* 115 (2005) 3418-3427).

[0246] Paget's disease of bone (PDB) is the second most common bone metabolism disorder after osteoporosis in which focal abnormalities of increased bone turnover lead to complications such as bone pain, deformity, pathological fractures and deafness. Mutations in four genes have been identified that regulate normal osteoclast function and predispose individuals to PDB and related disorders: insertion mutations in TNFRSF11A, which encodes receptor activator of nuclear factor (NF) kappaB (RANK)—a critical regulator of osteoclast function, inactivating mutations of TNFRSF11B which encodes osteoprotegerin (a decoy receptor for RANK ligand), mutations of the sequestosome 1 gene (SQSTM1), which encodes an important scaffold protein in the NFkappaB pathway and mutations in the valosin-containing protein (VCP) gene. This gene encodes VCP, which has a role in targeting the inhibitor of NFkappaB for degradation by the proteasome (Daroszewska, A. and Ralston, S. H., *Nat. Clin. Pract. Rheumatol.* 2 (2006) 270-277). Targeted CSF-1R inhibitors provide an opportunity to block the deregulation of the RANKL signaling indirectly and add an additional treatment option to the currently used bisphosphonates.

[0247] Cancer therapy induced bone loss especially in breast and prostate cancer patients is an additional indication where a targeted CSF-1R inhibitor could prevent bone loss (Lester, J. E., et al., *Br. J. Cancer* 94 (2006) 30-35). With the improved prognosis for early breast cancer the long-term consequences of the adjuvant therapies become more important as some of the therapies including chemotherapy, irradiation, aromatase inhibitors and ovary ablation affect bone metabolism by decreasing the bone mineral density, resulting in increased risk for osteoporosis and associated fractures (Lester, J. E., et al., *Br. J. Cancer* 94 (2006) 30-35). The equivalent to adjuvant aromatase inhibitor therapy in breast cancer is androgen ablation therapy in prostate cancer which leads to loss of bone mineral density and significantly increases the risk of osteoporosis-related fractures (Stoch, S. A., et al., *J. Clin. Endocrinol. Metab.* 86 (2001) 2787-2791).

[0248] Targeted inhibition of CSF-1R signaling is likely to be beneficial in other indications as well when targeted cell types include osteoclasts and macrophages e.g. treatment of specific complications in response to joint replacement as a consequence of rheumatoid arthritis. Implant failure due to periprosthetic bone loss and consequent loosening of prostheses is a major complication of joint replacement and requires repeated surgery with high socioeconomic burdens for the individual patient and the health-care system. To date, there is no approved drug therapy to prevent or inhibit periprosthetic osteolysis (Drees, P., et al., *Nat. Clin. Pract. Rheumatol.* 3 (2007) 165-171).

[0249] Glucocorticoid-induced osteoporosis (GIOP) is another indication in which a CSF-1R inhibitor could prevent bone loss after long-term glucocorticosteroid use that is

given as a result of various conditions among those chronic obstructive pulmonary disease, asthma and rheumatoid arthritis (Guzman-Clark, J. R., et al., *Arthritis Rheum.* 57 (2007) 140-146; Feldstein, A. C., et al., *Osteoporos. Int.* 16 (2005) 2168-2174).

[0250] Rheumatoid arthritis, psoriatic arthritis and inflammatory arthritides are in itself potential indications for CSF-1R signaling inhibitors in that they consist of a macrophage component and to a varying degree bone destruction (Ritchlin, C. T., et al., *J. Clin. Invest.* 111 (2003) 821-831). Osteoarthritis and rheumatoid arthritis are inflammatory autoimmune disease caused by the accumulation of macrophages in the connective tissue and infiltration of macrophages into the synovial fluid, which is at least partially mediated by M-CSF. Campbell, I., K., et al., *J. Leukoc. Biol.* 68 (2000) 144-150, demonstrated that M-CSF is produced by human-joint tissue cells (chondrocytes, synovial fibroblasts) in vitro and is found in synovial fluid of patients with rheumatoid arthritis, suggesting that it contributes to the synovial tissue proliferation and macrophage infiltration which is associated with the pathogenesis of the disease. Inhibition of CSF-1R signaling is likely to control the number of macrophages in the joint and alleviate the pain from the associated bone destruction. In order to minimize adverse effects and to further understand the impact of the CSF-1R signaling in these indications, one method is to specifically inhibit CSF-1R without targeting a myriad other kinases, such as Raf kinase.

[0251] Recent literature reports correlate increased circulating M-CSF with poor prognosis and atherosclerotic progression in chronic coronary artery disease (Saitoh, T., et al., *J. Am. Coll. Cardiol.* 35 (2000) 655-665; Ikonomidis, I., et al., *Eur. Heart. J.* 26 (2005) p. 1618-1624); M-CSF influences the atherosclerotic process by aiding the formation of foam cells (macrophages with ingested oxidized LDL) that express CSF-1R and represent the initial plaque (Murayama, T., et al., *Circulation* 99 (1999) 1740-1746).

[0252] Expression and signaling of M-CSF and CSF-1R is found in activated microglia. Microglia, which are resident macrophages of the central nervous system, can be activated by various insults, including infection and traumatic injury. M-CSF is considered a key regulator of inflammatory responses in the brain and M-CSF levels increase in HIV-1, encephalitis, Alzheimer's disease (AD) and brain tumors. Microgliosis as a consequence of autocrine signaling by M-CSF/CSF-1R results in induction of inflammatory cytokines and nitric oxides being released as demonstrated by e.g. using an experimental neuronal damage model (Hao, A. J., et al., *Neuroscience* 112 (2002) 889-900; Murphy, G. M., Jr., et al., *J. Biol. Chem.* 273 (1998) 20967-20971). Microglia that have increased expression of CSF-1R are found to surround plaques in AD and in the amyloid precursor protein V717F transgenic mouse model of AD (Murphy, G. M., Jr., et al., *Am. J. Pathol.* 157 (2000) 895-904). On the other hand op/op mice with fewer microglia in the brain resulted in fibrillar deposition of A-beta and neuronal loss compared to normal control suggesting that microglia do have a neuro-protective function in the development of AD lacking in the op/op mice (Kaku, M., et al., *Brain Res. Brain Res. Protoc.* 12 (2003) 104-108).

[0253] Expression and signaling of M-CSF and CSF-1R is associated with inflammatory bowel disease (IBD) (WO 2005/046657). The term "inflammatory bowel disease" refers to serious, chronic disorders of the intestinal tract

characterized by chronic inflammation at various sites in the gastrointestinal tract, and specifically includes ulcerative colitis (UC) and Crohn's disease.

[0254] Thus another embodiment of the invention are the CSF-1R antibodies being characterized by the above mentioned amino acid sequences and amino acid sequence in combination with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence for use in the treatment of periodontitis, histiocytosis X, osteoporosis, Paget's disease of bone (PDB), bone loss due to cancer therapy, periprosthetic osteolysis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, inflammatory arthritides, and inflammation.

[0255] The invention comprises the combination therapy with an antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the treatment of cancer.

[0256] The invention comprises the combination therapy with an antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the treatment of bone loss.

[0257] The invention comprises the combination therapy with an antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the prevention or treatment of metastasis.

[0258] The invention comprises the combination therapy of antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for treatment of inflammatory diseases.

[0259] The invention comprises the combination therapy of antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for use in treating or delaying progression of an immune related disease such as tumor immunity.

[0260] The invention comprises the combination therapy of antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments with an anti-PD-L1 antibody being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for use in stimulating an immune response or function, such as T cell activity.

[0261] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the combination treatment of cancer with an anti-PD-L1 anti-

body or alternatively for the manufacture of a medicament for the combination treatment of cancer with an anti-PD-L1 antibody as described herein.

[0262] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the combination treatment of bone loss with an anti-PD-L1 antibody as described herein or alternatively for the manufacture of a medicament for the combination treatment of bone loss with an anti-PD-L1 antibody as described herein.

[0263] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for the prevention or treatment of metastasis in the combination with an anti-PD-L1 antibody as described herein or alternatively for the manufacture of a medicament for the prevention or treatment of metastasis in the combination with an anti-PD-L1 antibody as described herein.

[0264] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for combination treatment of inflammatory diseases with an anti-PD-L1 antibody as described herein or alternatively for the manufacture of a medicament for the combination treatment of inflammatory diseases with an anti-PD-L1 antibody as described herein.

[0265] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for use in treating or delaying progression of an immune related disease such as tumor immunity in combination with an anti-PD-L1 antibody as described herein or alternatively for the manufacture of a medicament for use in treating or delaying progression of an immune related disease such as tumor immunity in combination with an anti-PD-L1 antibody as described herein.

[0266] The invention comprises the use of an antibody characterized in comprising the antibody binding to human CSF-1R being characterized by the above mentioned amino acid sequences and amino acid sequence fragments for use in stimulating an immune response or function, such as T cell activity in combination with an anti-PD-L1 antibody as described herein or alternatively for the manufacture of a medicament for use in stimulating an immune response or function, such as T cell activity in combination with an anti-PD-L1 antibody as described herein.

[0267] In one preferred embodiment of the invention the antibody which binds to human CSF-1R used in the above described combination treatments and medical uses of different diseases is characterized in comprising a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, and the antibody which binds to human PD-L1 used in such combination treatments is characterized in comprising a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92.

[0268] The antibodies described herein are preferably produced by recombinant means. Such methods are widely known in the state of the art and comprise protein expression in prokaryotic and eukaryotic cells with subsequent isolation

of the antibody polypeptide and usually purification to a pharmaceutically acceptable purity. For the protein expression nucleic acids encoding light and heavy chains or fragments thereof are inserted into expression vectors by standard methods. Expression is performed in appropriate prokaryotic or eukaryotic host cells, such as CHO cells, NSO cells, SP2/0 cells, HEK293 cells, COS cells, yeast, or *E. coli* cells, and the antibody is recovered from the cells (from the supernatant or after cells lysis).

[0269] Recombinant production of antibodies is well-known in the state of the art and described, for example, in the review articles of Makrides, S. C., *Protein Expr. Purif* 17 (1999) 183-202; Geisse, S., et al., *Protein Expr. Purif* 8 (1996) 271-282; Kaufman, R. J., *Mol. Biotechnol.* 16 (2000) 151-161; Werner, R. G., *Drug Res.* 48 (1998) 870-880.

[0270] The antibodies may be present in whole cells, in a cell lysate, or in a partially purified, or substantially pure form. Purification is performed in order to eliminate other cellular components or other contaminants, e.g. other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis, and others well known in the art. See Ausubel, F., et al., ed. *Current Protocols in Molecular Biology*, Greene Publishing and Wiley Interscience, New York (1987).

[0271] Expression in NSO cells is described by, e.g., Barnes, L. M., et al., *Cytotechnology* 32 (2000) 109-123; Barnes, L. M., et al., *Biotech. Bioeng.* 73 (2001) 261-270. Transient expression is described by, e.g., Durocher, Y., et al., *Nucl. Acids. Res.* 30 (2002) E9. Cloning of variable domains is described by Orlandi, R., et al., *Proc. Natl. Acad. Sci. USA* 86 (1989) 3833-3837; Carter, P., et al., *Proc. Natl. Acad. Sci. USA* 89 (1992) 4285-4289; Norderhaug, L., et al., *J. Immunol. Methods* 204 (1997) 77-87. A preferred transient expression system (HEK 293) is described by Schlaeger, E.-J. and Christensen, K., in *Cytotechnology* 30 (1999) 71-83, and by Schlaeger, E.-J., in *J. Immunol. Methods* 194 (1996) 191-199.

[0272] The heavy and light chain variable domains according to the invention are combined with sequences of promoter, translation initiation, constant region, 3' untranslated region, polyadenylation, and transcription termination to form expression vector constructs. The heavy and light chain expression constructs can be combined into a single vector, co-transfected, serially transfected, or separately transfected into host cells which are then fused to form a single host cell expressing both chains.

[0273] The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, enhancers and polyadenylation signals.

[0274] Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However,

enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[0275] The monoclonal antibodies are suitably separated from the culture medium by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. DNA and RNA encoding the monoclonal antibodies are readily isolated and sequenced using conventional procedures. The hybridoma cells can serve as a source of such DNA and RNA. Once isolated, the DNA may be inserted into expression vectors, which are then transfected into host cells such as HEK 293 cells, CHO cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of recombinant monoclonal antibodies in the host cells.

[0276] As used herein, the expressions "cell", "cell line", and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Variant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

[0277] In another aspect, the present invention provides a composition, e.g. a pharmaceutical composition, containing one or a combination of monoclonal antibodies, or the antigen-binding portion thereof, of the present invention, formulated together with a pharmaceutically acceptable carrier.

[0278] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption/resorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for injection or infusion.

[0279] A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

[0280] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. In addition to water, the carrier can be, for example, an isotonic buffered saline solution.

[0281] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

[0282] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient (effective amount). The selected dosage level will depend upon a

variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0283] The term “a method of treating” or its equivalent, when applied to, for example, cancer refers to a procedure or course of action that is designed to reduce or eliminate the number of cancer cells in a patient, or to alleviate the symptoms of a cancer. “A method of treating” cancer or another proliferative disorder does not necessarily mean that the cancer cells or other disorder will, in fact, be eliminated, that the number of cells or disorder will, in fact, be reduced, or that the symptoms of a cancer or other disorder will, in fact, be alleviated. Often, a method of treating cancer will be performed even with a low likelihood of success, but which, given the medical history and estimated survival expectancy of a patient, is nevertheless deemed to induce an overall beneficial course of action.

[0284] The terms “administered in combination with” or “co-administration”, “co-administering”, “combination therapy” or “combination treatment” refer to the administration of the anti-CSF-1R as described herein, and the anti-PD-L1 antibody as described herein e.g. as separate formulations/applications (or as one single formulation/application). The co-administration can be simultaneous or sequential in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Said antibody and said further agent are co-administered either simultaneously or sequentially (e.g. intravenous (i.v.) through a continuous infusion. When both therapeutic agents are co-administered sequentially the dose is administered either on the same day in two separate administrations, or one of the agents is administered on day 1 and the second is co-administered on day 2 to day 7, preferably on day 2 to 4. Thus in one embodiment the term “sequentially” means within 7 days after the dose of the first component, preferably within 4 days after the dose of the first component; and the term “simultaneously” means at the same time. The terms “co-administration” with respect to the maintenance doses of anti-CSF-1R antibody and/or anti-PD-L1 antibody mean that the maintenance doses can be either co-administered simultaneously, if the treatment cycle is appropriate for both drugs, e.g. every week. Or the further agent is e.g. administered e.g. every first to third day and said antibody is administered every week. Or the maintenance doses are co-administered sequentially, either within one or within several days.

[0285] It is self-evident that the antibodies are administered to the patient in a “therapeutically effective amount” (or simply “effective amount”) which is the amount of the respective compound or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0286] The amount of co-administration and the timing of co-administration will depend on the type (species, gender, age, weight, etc.) and condition of the patient being treated and the severity of the disease or condition being treated.

Said anti-CSF-1R antibody and further agent are suitably co-administered to the patient at one time or over a series of treatments e.g. on the same day or on the day after.

[0287] Depending on the type and severity of the disease, about 0.1 mg/kg to 50 mg/kg (e.g. 0.1-20 mg/kg) of said anti-CSF-1R antibody and/or anti-PD-L1 antibody; is an initial candidate dosage for co-administration of both drugs to the patient. The invention comprises the use of the antibodies according to the invention for the treatment of a patient suffering from cancer, especially from colon, lung or pancreas cancer.

[0288] Depending on the type and severity of the disease, about 0.1 mg/kg to 50 mg/kg (e.g. 0.1-20 mg/kg) of said anti-CSF-1R antibody and/or anti-PD-L1 antibody; is an initial candidate dosage for co-administration of both drugs to the patient. The invention comprises the use of the antibodies according to the invention for the treatment of a patient suffering from cancer, especially from colon, lung or pancreas cancer.

[0289] In addition to the anti-CSF-1R antibody in combination with the anti-PD-L1 antibody also a chemotherapeutic agent can be administered.

[0290] In one embodiment such additional chemotherapeutic agents, which may be administered with anti-CSF-1R antibody as described herein and the anti-PD-L1 antibody as described herein, include, but are not limited to, anti-neoplastic agents including alkylating agents including: nitrogen mustards, such as mechlorethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas, such as carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU); Temodal™ (temozolamide), ethylenimines/methylmelamine such as triethylenemelamine (TEM), triethylene, thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC); antimetabolites including folic acid analogs such as methotrexate and trimetrexate, pyrimidine analogs such as 5-fluorouracil (5FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'-difluorodeoxycytidine, purine analogs such as 6-mercaptopurine, 6-thioguanine, azathioprine, T-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2-CdA); natural products including antimitotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorelbine, taxotere, estramustine, and estramustine phosphate; pipodophylotoxins such as etoposide and teniposide; antibiotics such as actinomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycin C, and actinomycin; enzymes such as L-asparaginase; biological response modifiers such as interferon-alpha, IL-2, G-CSF and GM-CSF; miscellaneous agents including platinum coordination complexes such as oxaliplatin, cisplatin and carboplatin, anthracenediones such as mitoxantrone, substituted urea such as hydroxyurea, methylhydrazine derivatives including N-methylhydrazine (MIH) and procarbazine, adrenocortical suppressants such as mitotane (o, p-DDD) and aminoglutethimide; hormones and antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide; Gemzar™ (gemcitabine), progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate; estrogen such as diethylstil-

bestrol and ethinyl estradiol equivalents; anticestrogen such as tamoxifen; androgens including testosterone propionate and fluoxymesterone/equivalents; antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide; and non-steroidal antiandrogens such as flutamide. Therapies targeting epigenetic mechanism including, but not limited to, histone deacetylase inhibitors, demethylating agents (e.g., Vidaza) and release of transcriptional repression (ATRA) therapies can also be combined with the antigen binding proteins. In one embodiment the chemotherapeutic agent is selected from the group consisting of taxanes (like e.g. paclitaxel (Taxol), docetaxel (Taxotere), modified paclitaxel (e.g., Abraxane and Opaxio), doxorubicin, sunitinib (Sutent), sorafenib (Nexavar), and other multikinase inhibitors, oxaliplatin, cisplatin and carboplatin, etoposide, gemcitabine, and vinblastine. In one embodiment the chemotherapeutic agent is selected from the group consisting of taxanes (like e.g. taxol (paclitaxel), docetaxel (Taxotere), modified paclitaxel (e.g. Abraxane and Opaxio). In one embodiment, the additional chemotherapeutic agent is selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, or oxaliplatin. In one embodiment the chemotherapeutic agent is 5-fluorouracil, leucovorin and irinotecan (FOLFIRI). In one embodiment the chemotherapeutic agent is 5-fluorouracil, and oxaliplatin (FOLFOX).

[0291] Specific examples of combination therapies with additional chemotherapeutic agents include, for instance, therapies taxanes (e.g., docetaxel or paclitaxel) or a modified paclitaxel (e.g., Abraxane or Opaxio), doxorubicin, capecitabine and/or bevacizumab (Avastin) for the treatment of breast cancer; therapies with carboplatin, oxaliplatin, cisplatin, paclitaxel, doxorubicin (or modified doxorubicin (Caelyx or Doxil)), or topotecan (Hycamtin) for ovarian cancer; the therapies with a multi-kinase inhibitor, MKI, (Sutent, Nexavar, or 706) and/or doxorubicin for treatment of kidney cancer; therapies with oxaliplatin, cisplatin and/or radiation for the treatment of squamous cell carcinoma; therapies with taxol and/or carboplatin for the treatment of lung cancer.

[0292] Therefore, in one embodiment the additional chemotherapeutic agent is selected from the group of taxanes (docetaxel or paclitaxel or a modified paclitaxel (Abraxane or Opaxio), doxorubicin, capecitabine and/or bevacizumab for the treatment of breast cancer.

[0293] In one embodiment the CSF-1R antibody/PD-L1 antibody combination therapy is no chemotherapeutic agents are administered.

[0294] The invention comprises also a method for the treatment of a patient suffering from such disease.

[0295] The invention further provides a method for the manufacture of a pharmaceutical composition comprising an effective amount of an antibody according to the invention together with a pharmaceutically acceptable carrier and the use of the antibody according to the invention for such a method.

[0296] The invention further provides the use of an antibody according to the invention in an effective amount for the manufacture of a pharmaceutical agent, preferably together with a pharmaceutically acceptable carrier, for the treatment of a patient suffering from cancer.

[0297] The invention also provides the use of an antibody according to the invention in an effective amount for the manufacture of a pharmaceutical agent, preferably together with a pharmaceutically acceptable carrier, for the treatment of a patient suffering from cancer.

[0298] The following examples, sequence listing and figures are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Description of the Sequences

[0299] SEQ ID NO: 1 heavy chain CDR3, Mab 2F11
 [0300] SEQ ID NO: 2 heavy chain CDR2, Mab 2F11
 [0301] SEQ ID NO: 3 heavy chain CDR1, Mab 2F11
 [0302] SEQ ID NO: 4 light chain CDR3, Mab 2F11
 [0303] SEQ ID NO: 5 light chain CDR2, Mab 2F11
 [0304] SEQ ID NO: 6 light chain CDR1, Mab 2F11
 [0305] SEQ ID NO: 7 heavy chain variable domain, Mab 2F11
 [0306] SEQ ID NO: 8 light chain variable domain, Mab 2F11
 [0307] SEQ ID NO: 9 heavy chain CDR3, Mab 2E10
 [0308] SEQ ID NO: 10 heavy chain CDR2, Mab 2E10
 [0309] SEQ ID NO: 11 heavy chain CDR1, Mab 2E10
 [0310] SEQ ID NO: 12 light chain CDR3, Mab 2E10
 [0311] SEQ ID NO: 13 light chain CDR2, Mab 2E10
 [0312] SEQ ID NO: 14 light chain CDR1, Mab 2E10
 [0313] SEQ ID NO: 15 heavy chain variable domain, Mab 2E10
 [0314] SEQ ID NO: 16 light chain variable domain, Mab 2E10
 [0315] SEQ ID NO: 17 heavy chain CDR3, hMab 2F11-c11
 [0316] SEQ ID NO: 18 heavy chain CDR2, hMab 2F11-c11
 [0317] SEQ ID NO: 19 heavy chain CDR1, hMab 2F11-c11
 [0318] SEQ ID NO: 20 light chain CDR3, hMab 2F11-c11
 [0319] SEQ ID NO: 21 light chain CDR2, hMab 2F11-c11
 [0320] SEQ ID NO: 22 light chain CDR1, hMab 2F11-c11
 [0321] SEQ ID NO: 23 heavy chain variable domain, hMab 2F11-c11
 [0322] SEQ ID NO: 24 light chain variable domain, hMab 2F11-c11
 [0323] SEQ ID NO: 25 heavy chain CDR3, hMab 2F11-d8
 [0324] SEQ ID NO: 26 heavy chain CDR2, hMab 2F11-d8
 [0325] SEQ ID NO: 27 heavy chain CDR1, hMab 2F11-d8
 [0326] SEQ ID NO: 28 light chain CDR3, hMab 2F11-d8
 [0327] SEQ ID NO: 29 light chain CDR2, hMab 2F11-d8
 [0328] SEQ ID NO: 30 light chain CDR1, hMab 2F11-d8
 [0329] SEQ ID NO: 31 heavy chain variable domain, hMab 2F11-d8
 [0330] SEQ ID NO: 32 light chain variable domain, hMab 2F11-d8
 [0331] SEQ ID NO: 33 heavy chain CDR3, hMab 2F11-e7
 [0332] SEQ ID NO: 34 heavy chain CDR2, hMab 2F11-e7
 [0333] SEQ ID NO: 35 heavy chain CDR1, hMab 2F11-e7
 [0334] SEQ ID NO: 36 light chain CDR3, hMab 2F11-e7
 [0335] SEQ ID NO: 37 light chain CDR2, hMab 2F11-e7
 [0336] SEQ ID NO: 38 light chain CDR1, hMab 2F11-e7
 [0337] SEQ ID NO: 39 heavy chain variable domain, hMab 2F11-e7
 [0338] SEQ ID NO: 40 light chain variable domain, hMab 2F11-e7
 [0339] SEQ ID NO: 41 heavy chain CDR3, hMab 2F11-f12

[0340] SEQ ID NO: 42 heavy chain CDR2, hMab 2F11-fl2
 [0341] SEQ ID NO: 43 heavy chain CDR1, hMab 2F11-fl2
 [0342] SEQ ID NO: 44 light chain CDR3, hMab 2F11412
 [0343] SEQ ID NO: 45 light chain CDR2, hMab 2F11412
 [0344] SEQ ID NO: 46 light chain CDR1, hMab 2F11412
 [0345] SEQ ID NO: 47 heavy chain variable domain, hMab 2F11-fl2
 [0346] SEQ ID NO: 48 light chain variable domain, hMab 2F11-fl2
 [0347] SEQ ID NO: 49 heavy chain CDR3, hMab 2F11-g1
 [0348] SEQ ID NO: 50 heavy chain CDR2, hMab 2F11-g1
 [0349] SEQ ID NO: 51 heavy chain CDR1, hMab 2F11-g1
 [0350] SEQ ID NO: 52 light chain CDR3, hMab 2F11-g1
 [0351] SEQ ID NO: 53 light chain CDR2, hMab 2F11-g1
 [0352] SEQ ID NO: 54 light chain CDR1, hMab 2F11-g1
 [0353] SEQ ID NO: 55 heavy chain variable domain, hMab 2F11-g1
 [0354] SEQ ID NO: 56 light chain variable domain, hMab 2F11-g1
 [0355] SEQ ID NO: 57 human kappa light chain constant region
 [0356] SEQ ID NO: 58 human heavy chain constant region derived from IgG1
 [0357] SEQ ID NO: 59 human heavy chain constant region derived from IgG1 mutated on L234A and L235A
 [0358] SEQ ID NO: 60 human heavy chain constant region derived from IgG4
 [0359] SEQ ID NO: 61 human heavy chain constant region derived from IgG4 mutated on S228P
 [0360] SEQ ID NO: 62 human wildtype CSF-1R (wt CSF-1R) (including signal sequence)
 [0361] SEQ ID NO: 63 human mutant CSF-1R L301S Y969F (including signal sequence)
 [0362] SEQ ID NO: 64 human CSF-1R Extracellular Domain (domains D1-D5)
 [0363] SEQ ID NO: 65 human CSF-1R fragment delD4
 [0364] SEQ ID NO: 66 human CSF-1R fragment domains D1-D3
 [0365] SEQ ID NO: 67 signal peptide
 [0366] SEQ ID NO: 68 Primer
 [0367] SEQ ID NO: 69 heavy chain CDR3, Mab 1G10
 [0368] SEQ ID NO: 70 heavy chain CDR2, Mab 1G10
 [0369] SEQ ID NO: 71 heavy chain CDR1, Mab 1G10
 [0370] SEQ ID NO: 72 light chain CDR3, Mab 1G10
 [0371] SEQ ID NO: 73 light chain CDR2, Mab 1G10
 [0372] SEQ ID NO: 74 light chain CDR1, Mab 1G10
 [0373] SEQ ID NO: 75 heavy chain variable domain, Mab 1G10
 [0374] SEQ ID NO: 76 light chain variable domain, Mab 1G10
 [0375] SEQ ID NO: 77 heavy chain CDR3, Mab 2H7
 [0376] SEQ ID NO: 78 heavy chain CDR2, Mab 2H7
 [0377] SEQ ID NO: 79 heavy chain CDR1, Mab 2H7
 [0378] SEQ ID NO: 80 light chain CDR3, Mab 2H7
 [0379] SEQ ID NO: 81 light chain CDR2, Mab 2H7
 [0380] SEQ ID NO: 82 light chain CDR1, Mab 2H7
 [0381] SEQ ID NO: 83 heavy chain variable domain, Mab 2H7
 [0382] SEQ ID NO: 84 light chain variable domain, Mab 2H7
 [0383] SEQ ID NO: 85 human CSF-1R fragment domains D4-D5

[0384] SEQ ID NO: 86 human CSF-1 (including signal sequence)
 [0385] SEQ ID NO: 87 human IL-34 (including signal sequence)
 [0386] SEQ ID NO: 88 human PD-L1 (including signal sequence)
 [0387] SEQ ID NO: 89 heavy chain variable domain VH variant 1, anti-PD-L1 243.55
 [0388] SEQ ID NO: 90 heavy chain variable domain VH variant 2, anti-PD-L1 243.55
 [0389] SEQ ID NO: 91 heavy chain variable domain VH variant 3, anti-PD-L1 243.55
 [0390] SEQ ID NO: 92 light chain variable domain VL variant 1, anti-PD-L1 243.55
 [0391] SEQ ID NO: 93 light chain variable domain VL variant 2, anti-PD-L1 243.55
 [0392] SEQ ID NO: 94 light chain variable domain VL variant 3, anti-PD-L1 243.55
 [0393] SEQ ID NO: 95 light chain variable domain VL variant 4, anti-PD-L1 243.55
 [0394] SEQ ID NO: 96 light chain variable domain VL variant 5, anti-PD-L1 243.55
 [0395] SEQ ID NO: 97 light chain variable domain VL variant 6, anti-PD-L1 243.55
 [0396] SEQ ID NO: 98 light chain variable domain VL variant 7, anti-PD-L1 243.55
 [0397] SEQ ID NO: 99 light chain variable domain VL variant 8, anti-PD-L1 243.55
 [0398] SEQ ID NO: 100 light chain variable domain VL variant 9, anti-PD-L1 243.55
 [0399] SEQ ID NO: 101 light chain variable domain VL variant 10, anti-PD-L1 243.55
 [0400] SEQ ID NO: 102 light chain variable domain VL variant anti-PD-L1 243.55
 [0401] SEQ ID NO: 103 light chain variable domain VL variant 12, anti-PD-L1 243.55
 [0402] SEQ ID NO: 104 light chain variable domain VL variant 13, anti-PD-L1 243.55
 [0403] SEQ ID NO: 105 light chain variable domain VL variant 14, anti-PD-L1 243.55
 [0404] SEQ ID NO: 106 light chain variable domain VL variant anti-PD-L1 15, 243.55
 [0405] SEQ ID NO: 107 light chain variable domain VL variant 16, anti-PD-L1 243.55

In the Following Embodiment of the Invention are Described

[0406] 1. A) An antibody which binds to human CSF-1R wherein the antibody is administered in combination with an antibody which binds to human PD-L1 for use in the treatment of cancer, for use in the prevention or treatment of metastasis, for use in the treatment inflammatory diseases, for use in the treatment of bone loss, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity; or
 [0407] B) the use of an antibody which binds to human CSF-1R for the manufacture of a medicament for use in the treatment of cancer, for use in the prevention or treatment of metastasis, for use in the treatment inflammatory diseases, for use in the treatment of bone loss, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for

use in stimulating an immune response or function, such as T cell activity, wherein the antibody is administered in combination with an antibody which binds to human PD-L1;

[0408] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0409] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

[0410] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

[0411] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

[0412] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

[0413] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0414] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0415] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or

[0416] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

[0417] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0418] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0419] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0420] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

[0421] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or

[0422] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or

[0423] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

[0424] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

[0425] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

[0426] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or

[0427] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or

[0428] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

[0429] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or

[0430] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0431] 2. Use of a combination of

[0432] A) an antibody which binds to human CSF-1R, comprising

[0433] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

[0434] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

[0435] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

[0436] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

[0437] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0438] and

[0439] B) an antibody which binds to human PD-L1 comprising

[0440] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or

[0441] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

[0442] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0443] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0444] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0445] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

[0446] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or

[0447] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or

[0448] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

[0449] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

[0450] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- [0451] 1) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0452] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0453] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0454] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0455] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0456] for the manufacture of a medicament for use in the treatment of cancer, for use in the prevention or treatment of metastasis, for use in the treatment of inflammatory diseases, for use in the treatment of bone loss, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity, wherein the antibody is administered in combination with an antibody which binds to human PD-L1
- [0457] 3. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of cancer.
- [0458] 4. The antibody or use according to embodiment 3, for use in the treatment of breast cancer, lung cancer, colon cancer, ovarian cancer, melanoma cancer, bladder cancer, renal cancer, kidney cancer, liver cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric carcinoma cancer, esophageal cancer, mesothelioma, prostate cancer, leukemia, lymphomas, myelomas.
- [0459] 5. The antibody or use according to any one of embodiments 1 or 2, for use in the prevention or treatment of metastasis.
- [0460] 6. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of bone loss.
- [0461] 7. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of inflammatory diseases.
- [0462] 8. The antibody or use according to any one of embodiments 1 or 2, for use in treating or delaying progression of an immune related disease such as tumor immunity.
- [0463] 9. The antibody or use according to any one of embodiments 1 or 2 for use in stimulating an immune response or function, such as T cell activity.
- [0464] 10. A) An antibody which binds to human CSF-1R wherein the antibody is administered in combination with an antibody which binds to human PD-L1 for use in
- [0465] i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;
- [0466] ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
- [0467] iii) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or
- [0468] iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;
- [0469] or
- [0470] B) use of an antibody which binds to human CSF-1R for the manufacture of a medicament for use in
- [0471] i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;
- [0472] ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
- [0473] iii) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or
- [0474] iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages,
- [0475] wherein the antibody is administered in combination with an antibody which binds to human PD-L1;
- [0476] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0477] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0478] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0479] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0480] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0481] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0482] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0483] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0484] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0485] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- [0486] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- [0487] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- [0488] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

- [0489] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- [0490] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- [0491] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- [0492] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- [0493] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- [0494] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0495] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0496] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0497] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0498] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0499] 11. A) An antibody which binds to human CSF-1R, for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand and wherein the anti-CSF-1R antibody is administered in combination with an antibody which binds to human PD-L1,
- [0500] or
- [0501] B) use of an antibody which binds to human CSF-1R, for the manufacture of a medicament for use in the treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand and wherein the anti-CSF-1R antibody is administered in combination with an antibody which binds to human PD-L1,
- [0502] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0503] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0504] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0505] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0506] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0507] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0508] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0509] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0510] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0511] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- [0512] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- [0513] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- [0514] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- [0515] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- [0516] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- [0517] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- [0518] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- [0519] 5 k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- [0520] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0521] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0522] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0523] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0524] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
- [0525] 12. The antibody or use according any one of the preceding embodiments,
- [0526] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0527] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

- [0528] and wherein the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0529] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92.
- [0530] 13. The antibody or use according any one of the preceding embodiments, characterized in that said antibodies are of human IgG1 subclass or human IgG4 subclass.
- [0531] 14. The antibody or use according to any one of the preceding embodiments, characterized in that said antibodies have reduced or minimal effector function.
- [0532] 15. The antibody or use according to any one of the preceding embodiments, wherein the minimal effector function results from an effectorless Fc mutation.
- [0533] 16. The antibody or use according to any one of the preceding embodiments, wherein the effectorless Fc mutation is L234A/L235A or L234A/L235A/P329G or N297A or D265A/N297A.
- [0534] 17. A) A method for
- [0535] i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;
- [0536] ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
- [0537] iii) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or
- [0538] iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;
- [0539] wherein an antibody which binds to human CSF-1R, is administered in combination with an antibody which binds to human PD-L1,
- [0540] or
- [0541] B) a method of treatment of a patient having a CSF-1R expressing tumor or having a tumor with CSF-1R expressing macrophage infiltrate, wherein the tumor is characterized by an increase of CSF-1R ligand and wherein an antibody which binds to human CSF-1R is administered in combination with an antibody which binds to human PD-L1,
- [0542] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising
- [0543] a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- [0544] b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- [0545] c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- [0546] d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- [0547] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
- [0548] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising
- [0549] a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- [0550] b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- [0551] c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- [0552] d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- [0553] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- [0554] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- [0555] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- [0556] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- [0557] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- [0558] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- [0559] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- [0560] l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- [0561] m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- [0562] n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- [0563] o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- [0564] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

EXAMPLES

Example 1

Inhibition of CSF-1-Induced CSF-1R Phosphorylation in NIH3T3-CSF-1R Recombinant Cells

[0565] 4.5×10^3 NIH 3T3 cells, retrovirally infected with an expression vector for full-length CSF-1R, were cultured in DMEM (PAA Cat. No. E15-011), 2 mM L-glutamine (Sigma, Cat. No. G7513, 2 mM Sodium pyruvate, 1× nonessential amino acids, 10% FKS (PAA, Cat. No. A15-

649) and 100 µg/ml PenStrep (Sigma, Cat. No. P4333 [10 mg/ml]) until they reached con-fluency. Thereafter cells were washed with serum-free DMEM media (PAA Cat. No.E15-011) supplemented with sodium selenite [5 ng/ml] (Sigma, Cat. No. S9133), transferrin [10 µg/ml] (Sigma, Cat. No. T8158), BSA [400 iug/ml] (Roche Diagnostics GmbH, Cat. No. 10735078), 4 mM L-glutamine (Sigma, Cat. No. G7513), 2 mM sodium pyruvate (Gibco, Cat. No. 11360), 1× nonessential amino acids (Gibco, Cat: 11140-035), 2-mercaptoethanol [0.05 mM] (Merck, Cat. No. M7522), 100 µg/ml and PenStrep (Sigma, Cat. No. P4333) and incubated in 30 µl of the same medium for 16 hours to allow for receptor up-regulation. 10 µl of diluted anti-CSF-1R antibodies were added to the cells for 1.5 h. Then cells were stimulated with 10 µl of 100 ng/ml hu CSF-1 (active 149 aa fragment of human CSF-1 (aa 33-181 of SEQ ID NO: 86); Biomol, DE, Cat. No. 60530) for 5 min. After the incubation, supernatant was removed, cells were washed twice with 80 µl of ice-cold PBS and 50 µl of freshly prepared ice-cold lysis buffer (150 mM NaCl/20 mM Tris pH 7.5/1 mM EDTA/1 mM EGTA/1% Triton X-100/1 protease inhibitor tablet (Roche Diagnostics GmbH Cat. No. 1 836 170) per 10 ml buffer/10 µl/ml phosphatase inhibitor cocktail 1 (Sigma Cat. No. P-2850, 100× Stock)/10 µl/ml protease inhibitor 1 (Sigma Cat. No. P-5726, 100× Stock)/10 µl/ml 1 M NaF) was added. After 30 minutes on ice the plates were shaken vigorously on a plateshaker for 3 minutes and then centrifuged 10 minutes at 2200 rpm (Heraeus Megafuge 10).

[0566] The presence of phosphorylated and total CSF-1 receptor in the cell lysate was analyzed with Elisa. For detection of the phosphorylated receptor the kit from R&D Systems (Cat. No. DYC3268-2) was used according to the instructions of the supplier. For detection of total CSF-1R 10 µl of the lysate was immobilized on plate by use of the capture antibody contained in the kit. Thereafter 1:750 diluted biotinylated anti CSF-1R antibody BAF329 (R&D Systems) and 1:1000 diluted streptavidin-HRP conjugate was added. After 60 minutes plates were developed 25 with freshly prepared ABTS® solution and the absorbance was detected. Data were calculated as % of positive control without antibody and the ratio value phospho/total receptor expressed. The negative control was defined without addition of M-CSF-1. Anti CSF-1R SC 2-4A5 (Santa Cruz Biotechnology, US, see also Sherr, C. J. et al., Blood 73 (1989) 1786-1793), which inhibits the ligand-receptor interaction, was used as reference control.

TABLE 3

Calculated IC50 values for the inhibition of CSF-1 receptor phosphorylation.	
CSF-1R Mab	IC50 CSF-1R Phosphorylation [ng/ml]
Mab 2F11	219.4
Mab 2E10	752.0
Mab 2H7	703.4
Mab 1G10	56.6
SC-2-4A5	1006.6

Example 2

Growth Inhibition of NIH3T3-CSF-1R Recombinant Cells in 3D Culture Under Treatment with Anti-CSF-1R Monoclonal Antibodies (CellTiterGlo®-Assay)

[0567] NIH 3T3 cells, retrovirally infected with either an expression vector for full-length wildtype CSF-1R (SEQ ID NO: 62) or mutant CSF-1R L301S Y969F (SEQ ID NO: 63), were cultured in DMEM high glucose media (PAA, Pasching, Austria) supplemented with 2 mM L-glutamine, 2 mM sodium pyruvate and non-essential amino acids and 10% fetal bovine serum (Sigma, Taufkirchen, Germany) on poly-HEMA (poly(2-hydroxyethylmethacrylate)) (Polysciences, Warrington, Pa., USA)) coated dishes to prevent adherence to the plastic surface. Cells are seeded in medium replacing serum with 5 ng/ml sodium selenite, 10 mg/ml transferrin, 400 µg/ml BSA and 0.05 mM 2-mercaptoethanol. When treated with 100 ng/ml hu CSF-1 (active 149 aa fragment of human CSF-1 (aa 33-181 of SEQ ID NO: 86); Biomol, DE, Cat. No. 60530) wtCSF-1R (expressing cells form dense spheroids that grow three dimensionally, a property that is called anchorage independence. These spheroids resemble closely the three dimensional architecture and organization of solid tumors in situ. Mutant CSF-1R recombinant cells are able to form spheroids independent of the CSF-1 ligand. The anti-CSF-1R antibody according to the invention hMab 2F11-e7 and the anti-CSF-1R antibodies 1.2.SM (ligand displacing CSF-1R antibody described in WO 2009/026303), CXIIG6 (ligand displacing CSF-1R antibody described in WO 2009/112245), the goat polyclonal anti-CSF-1R antibody ab10676 (abcam), and SC 2-4A5 (Santa Cruz Biotechnology, US—see also Sherr, C. J. et al., Blood 73 (1989) 1786-1793) and Mab R&D-Systems 3291 were investigated. Reference control Mab R&D-Systems 3291 did not show inhibition of mutant CSF-1R recombinant cell proliferation. Spheroid cultures were incubated for 3 days in the presence of different concentrations of antibody in order to determine an IC30 (concentration with 30 percent inhibition of cell viability). Maximum concentration was 20 µg/ml The CellTiterGlo® Assay was used to detect cell viability by measuring the ATP-content of the cells.

TABLE 4

CSF-1R Mab	wtCSF-1R IC30 [µg/ml]	Mutant CSF-1R IC30 [µg/ml]
hMab 2F11-e7	4.91	0.54
1.2.SM	1.19	>20 µg/ml (−19% inhibition at 20 µg/ml = 19% stimulation)
CSIIG6	>20 µg/ml (21% inhibition at 20 µg/ml)	>20 µg/ml (−36% inhibition at 20 µg/ml = 36% stimulation)
ab 10676	14.15	>20 µg/ml (0% inhibition at 20 µg/ml)
SC 2-4A5	16.62	2.56

Example 3

Inhibition of Human Macrophage Differentiation Under Treatment with Anti-CSF-1R Monoclonal Antibodies (CellTiterGlo®-Assay)

[0568] Human monocytes were isolated from peripheral blood using the RosetteSep™ Human Monocyte Enrich-

ment Cocktail (StemCell Tech.—Cat. No. 15028). Enriched monocyte populations were seeded into 96 well microtiter-plates (2.5×10^4 cells/well) in 100 μ l RPMI 1640 (Gibco—Cat. No. 31870) supplemented with 10% FCS (GIBCO—Cat. No. 011-090014M), 4 mM L-glutamine (GIBCO—Cat. No. 25030) and 1 $\times$ PenStrep (Roche Cat. No. 1 074 440) at 37° C. and 5% CO₂ in a humidified atmosphere. When 150 ng/ml huCSF-1 was added to the medium, a clear differentiation into adherent macrophages could be observed. This differentiation could be inhibited by addition of anti-CSF-1R antibodies. Furthermore, the monocyte survival is affected and could be analyzed by CellTiterGlo® (CTG) analysis. From the concentration dependent inhibition of the survival of monocytes by antibody treatment, an IC₅₀ was calculated (see Table below).

TABLE 5

CSF-1R Mab	IC ₅₀ [μ g/ml]
Mab 2F11	0.08
Mab 2E10	0.06
Mab 2H7	0.03
Mab 1G10	0.06
SC 2-4A5	0.36

[0569] In a separate test series humanized versions of Mab 2 F11, e.g. hMab 2F11-c11, hMab 2F11-d8, hMab 2F11-e7, hMab 2F11-f12, showed IC50 values of 0.07 μ g/ml (hMab 2F11-c11), 0.07 μ g/ml (hMab 2F11-d8), 0.04 μ g/ml (hMab 2F11-e7) and 0.09 μ g/ml (hMab 2F11-f12).

Example 4

Inhibition of Human Macrophage Differentiation
Under Treatment with Anti-CSF-1R monoclonal
antibodies (CellTiterGlo®-Assay)

[0570] Human monocytes were isolated from peripheral blood using the RosetteSep™ Human Monocyte Enrichment Cocktail (StemCell Tech.—Cat. No. 15028). Enriched monocyte populations were seeded into 96 well microtiter-plates (2.5×10^4 15 cells/well) in 100 μ l RPMI 1640 (Gibco—Cat. No. 31870) supplemented with 10% FCS (GIBCO—Cat. No. 011-090014M), 4 mM L-glutamine (GIBCO—Cat. No. 25030) and 1 $\times$ PenStrep (Roche Cat. No. 1 074 440) at 37° C. and 5% CO₂ in a humidified atmosphere. When 150 ng/ml huCSF-1 was added to the medium, a clear differentiation into adherent macrophages could be observed. This differentiation could be inhibited by addition of anti-CSF-1R antibodies.

[0571] Furthermore, the monocyte survival is affected and could be analyzed by CellTiterGlo® (CTG) analysis. From the concentration dependent inhibition of the survival of monocytes by antibody treatment, an IC₅₀ was calculated. Humanized versions of Mab 2 F11, e.g. hMab 2F11-c11, hMab 2F11-d8, hMab 2F11-e7, hMab 2F11-f12, showed IC50 values of 0.07 μ g/ml (hMab 2F11-c11), 0.07 μ g/ml (hMab 2F11-d8), 0.04 μ g/ml (hMab 2F11-e7) and 0.09 μ g/ml (hMab 2F11-f12).

Example 5

Inhibition of Human M1 and M2 Macrophage
Differentiation Under Treatment with Anti-CSF-1R
Monoclonal Antibodies (CellTiterGlo®-Assay)

[0572] Human monocytes were isolated from peripheral blood using the RosetteSep™ Human Monocyte Enrich-

ment Cocktail (StemCell Tech.—Cat. No. 15028). Enriched monocyte populations were seeded into 96 well microtiter-plates (2.5×10^4 cells/well) in 100 μ l RPMI 1640 (Gibco—Cat. No. 31870) supplemented with 10% FCS (GIBCO—Cat. No. 011-090014M), 4 mM L-glutamine (GIBCO—Cat. No. 25030) and 1 $\times$ PenStrep (Roche Cat. No. 1 074 440) at 37° C. and 5% CO₂ in a humidified atmosphere. When 100 ng/ml huCSF-1 was added for 6 days to the medium, a clear differentiation into adherent, M2 macrophages with elongated morphology could be observed. When 100 ng/ml huGM-CSF was added to the medium for 6 days, a clear differentiation into adherent, M1 macrophages with round morphology could be observed. This differentiation was associated with the expression of certain markers such as CD163 for M2 macrophages and CD80 or high MHC class II for M1 macrophages as assessed by flow cytometry. Cells were washed with PBS and, if adherent, detached using a 5 mM EDTA solution in PBS (20 min at 37° C.). Cells were then well resuspended, washed with staining buffer (5% FCS in PBS) and centrifuged at 300 $\times$ g for 5 min. Pellets were resuspended in 1 ml staining buffer and cells counted in a Neubauer chamber. Approximately 1×10^5 cells were transferred in each FACS tube, centrifuged at 300 $\times$ g for 5 min and resuspended in staining buffer. Fey receptors were blocked by incubation with 1 μ g human IgG/2.5 $\times 10^4$ cells (JIR Cat. No. 009-000-003) in staining buffer for 20 min on ice. Cells were then mixed with 1.5 μ l antibody/2.5 $\times 10^4$ cells for CD80 and CD163 detection whereas 5 μ l antibody/2.5 $\times 10^4$ cells for MHC class II detection was used: PE labeled mouse anti human CD163 (BD Bioscience Cat. No. 556018), PE labeled mouse anti human CD80 (BD Bioscience Cat. No. 557227) and Alexa 647 labeled mouse anti human MHC class II (Dako-Cat. No. M0775). The Alexa 647 label was conjugated to the antibody by using the Zenon Alexa 647 mouse IgG labeling kit (Invitrogen Cat. No. Z25008) After a 1-hour incubation on ice cells were washed twice with staining buffer, resuspended and measured at a FACS Canto II.

[0573] Exclusively M2 macrophage differentiation which is characterized by the expression of CD163, absence of CD80 and low MHC class II expression could be inhibited by addition of humanized anti-CSF-1R antibody hMab 2F11-e7. Furthermore, the M2 but not M1 macrophage survival is affected and could be analyzed by CellTiterGlo® (CTG) analysis. Concentration dependent inhibition of the survival of macrophages by antibody treatment for 7 days is depicted in FIG. 1a. Expression of M1 and M2 macrophage markers assessed by flow cytometry is shown in FIG. 1b.

Example 6

CSF-1 Level Increase During CSF-1R Inhibition in
Cynomolgus Monkey

[0574] Serum CSF-1 levels provide a pharmacodynamic marker of CSF-1R neutralizing activity of anti-human CSF-1R dimerization inhibitor hMab 2F11-e7. One male and one female cynomolgus monkey per dosage group (1 and 10 mg/kg) were intravenously administered anti-CSF1R antibody hMab 2F11-e7. Blood samples for analysis of CSF-1 levels were collected 1 week before treatment (pre-dose), 2, 24, 48, 72, 96, 168 hours post-dose and weekly for two additional weeks. CSF-1 levels were determined using a commercially available ELISA kit (Quantikine® human M-CSF) according to the manufacturer's instructions (R&D

Systems, UK). Monkey CSF-1 level were determined by comparison with CSF-1 standard curve samples provided in the kit.

[0575] Administration of hMab 2F11-e7 induced a dramatic increase in CSF-1 by ~1000-fold, which depending on the dose administered lasted for 48 hr (1 mg/kg) or 15 days (10 mg/kg). Hence, a dimerization inhibitor for CSF-1R offers the advantage to not directly compete with the dramatically upregulated ligand for binding to the receptor in contrast to a ligand displacing antibody. (Results are shown in FIG. 2)

Example 7

Relationship Between M2 Subtype Tumor Associated Macrophages (TAMs) and T Cells—Rationale for Combining Anti-CSF-R1 Antibody and a T Cell Engaging Agents

[0576] To investigate the functional relationship between TAMs and T cells we isolated TAMs from the MC38 tumor and cocultured them with CD8+ T cells.

TAM Suppression Assay

[0577] TAMs were enriched from single cell suspensions of MC38 tumors after enzymatic digest using a two-step protocol: Single cells were stained with CD11b-FITC (clone M1/70) and positively enriched over MACS columns by anti-FITC beads (Miltenyi). Upon removal from the column, anti-FITC beads were detached using release buffer protocol as provided the manufacturer. Finally, TAM were isolated by adding anti-Ly6G and anti-Ly6C positive selection beads in order to remove granulocytic and monocytic cells from TAM preparations. Final cell purity was analyzed and was usually >90%. Subsequently, TAM were titrated in the indicated ratios to total CD3+ T cells labeled with CFSE in U-bottom plates coated with anti-CD3 and soluble anti-CD28 was added. Cell proliferation was determined from CFSElow cells using blank Sphero beads as previously described after 3 days of incubation (Hoves, S. et al. Monocyte-derived human macrophages mediate anergy in allogeneic T cells and induce regulatory T cells. J. Immunol. 177, 2691-2698 (2006)). In the presence of TAMs, T cell expansion induced by activation of CD3 and CD28 was suppressed. (see FIG. 3).

Example 8

Inhibition of Tumor Growth Under Treatment with Anti-CSF-1R Monoclonal Antibody in Combination with PD-L1 Antibody in Subcutaneous Syngeneic MC38 Colon Carcinoma Model

[0578] Cells of the murine colorectal adenocarcinoma cell line MC38 (obtained from Beckman Research Institute of the City of Hope, Calif., USA) were cultured in Dulbecco's Modified Eagle Medium (DMEM, PAN Biotech) supplemented with 10% FCS and 2 mM L-glutamine at 37° C. in a water saturated atmosphere at 5% CO2. At the day of inoculation, MC38 tumor cells were harvested with PBS from culture flasks and transferred into culture medium, centrifuged, washed once and re-suspended in PBS. For injection of cel31s, the final titer was adjusted to 1×10⁷ cells/ml. Subsequently 100 µl of this suspension (1×10⁶ cells) were inoculated subcutaneously into 7-9 weeks old

female C57BL/6N mice (obtained from Charles River, Sulzfeld, Germany). Treatment with control antibody (MOPC-21; Bio X Cell, West Lebanon), anti-murine CSF-1R mAb <mouse CSF1R> antibody at a weekly dose of 30 mg/kg i.p. alone or in combination with a mouse crossreactive anti PD-L1 antibody (10 mg/kg i.p., 6×q3d) started after tumors were established and had reached an average size of 100 mm³. Tumor volume was measured twice a week and animal weights were monitored in parallel.

[0579] In first experiment monotherapy with <mouse CSF1R> antibody did not inhibit primary tumor growth when compared to control antibody treatment (TGI: 0%, TCR: 1.07 CI: 0.80-1.43, median time to progression >700 mm³: 21 days). Anti-PD-L1 monotherapy had an effect on MC38 primary tumor growth (TGI: 83%, TCR: 0.27 CI: 0.09-0.49, median time to progression >700 mm³: 32 days).

[0580] Addition of <mouse CSF1R> antibody to anti-PD-L1 therapy led to a slightly improved anti-tumor efficacy compared to anti-PD-L1 treatment alone (TGI: 83%, TCR: 0.28 CI: 0.09-0.51 median time to progression >700 mm³: 37 days) (see table below).

TABLE 6

Anti tumor Efficacy of <mouse anti-CSF1R> antibody/<anti-PD-L1> antibody combination in the MC38 mouse CRC in vivo model				
Group	TGI (day 21)	TCR (day 12)	95% CI vs. group 1	Median time to progression TV >700 mm ³
Control (Mouse IgG1)	—	—	—	21
<mouse CSF1R>	83%	1.07	(1.43-0.80)	21
<anit-PD-L1>	83%	0.27	(0.49-0.09)	32
<mouse CSF1R>/<anti-PD-L1>	83%	0.28	(0.51-0.09)	37

[0581] Median time of progression >700 mm³ was 21 days for control (mouse IgG1) treated animals. Monotherapy with <mouse CSF1R> antibody did not inhibit primary tumor growth when compared to control antibody treatment (median time to progression >700 mm³: 21 days). Anti-PD-L1 monotherapy had an effect on MC38 primary tumor growth (median time to progression >700 mm³: 32 days). Addition of <mouse CSF1R> antibody to anti-PD-L1 therapy led to a slightly improved anti-tumor efficacy compared to PD-L1 treatment alone (median time to progression >700 mm³: 37 days) (see table below and FIG. 4).

TABLE 7

Anti tumor Efficacy of <mouse anti-CSF1R> antibody/<anti-PD-L1> antibody combination in the MC38 mouse CRC in vivo model (Median time to progression >700 mm3)	
Group	Median time to progression TV >700 mm ³
Control (Mouse IgG1)	21
<mouse CSF1R>	21
<anti-PD-L1>	32
<mouse CSF1R>/<anti-PD-L1>	37

[0582] In analogous experiments, but starting treatment at different tumor sizes (e.g. starting treatment when the tumor

has reached a volume above and below 100 mm³ (different groups are evaluated) and in a further experiment also using different anti PD-L1 antibodies described in table 2, the inhibition of tumor growth under treatment with anti-CSF-1R monoclonal antibody in combination with anti-PD-L1 antibody in subcutaneous syngeneic MC38 colon carcinoma model is evaluated.

Example 9

Inhibition of Tumor Growth Under Treatment with Anti-CSF-1R Monoclonal Antibody in Combination with PD-L1 Antibody in Subcutaneous Syngeneic CT26.WT Colon Carcinoma Model

[0583] Cells of the murine colorectal adenocarcinoma cell line CT26.WT tumor cells (obtained from ATCC) were cultured in Dulbecco's Modified Eagle Medium (DMEM, PAN Biotech) supplemented with 10% FCS and 2 mM L-glutamine at 37° C. in a water saturated atmosphere at 5% CO₂. At the day of inoculation, CT26.WT tumor cells were harvested with PBS from culture flasks and transferred into culture medium, centrifuged, washed once and re-suspended in PBS. For injection of cells, the final titer was adjusted to 1×10⁷ cells/ml. Subsequently 100 of this suspension (1×10⁶ cells) were inoculated subcutaneously into 11-13 weeks old

female Balb/c mice (obtained from Charles River, Sulzfeld, Germany). Treatment with control antibody (MOPC-21; Bio×Cell, West Lebanon), anti-murine CSF-1R mAb <mouse CSF1R> antibody at a weekly dose of 30 mg/kg i.p. alone or in combination with a mouse crossreactive anti PD-L1 antibody (10 mg/kg i.p., 6×q3d) started after tumors were established and had reached an average size of 150 mm³. While treatment in monotherapy groups started on day 9 10 after tumor cell inoculation, treatment in combination group was sequential (day 9: start of treatment with anti-murine CSF-1R mAb; day 11: start of treatment with anti PD-L1 antibody). Tumor volume was measured twice a week and animal weights were monitored in parallel. Results are shown in Figure

[0584] Median time to progression ≥700 mm³ was 17 days for IgG control treatment group, 16 days for <mouse anti-CSF1R> antibody monotherapy group, 18 days for <anti-PD-L1> antibody monotherapy group and 18 days for <mouse anti-CSF1R>/<anti-PD-L1> antibody combination group.

[0585] While all animals in control or monotherapy groups needed to be terminated due to progressive tumor burden one animal of the <mouse anti-CSF1R>/<anti-PD-L1> antibody combination group experienced tumor shrinkage and remained tumor-free until study termination on day 79 after tumor inoculation.

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Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Glu	Asp	Val	Asn	Thr	Tyr
			20					25					30		
Val	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40					45			
Tyr	Gly	Ala	Ser	Asn	Arg	Tyr	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gly	Gln	Ser	Phe	Ser	Tyr	Pro	Thr
				85					90					95	
Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
			100					105							

<210> SEQ ID NO 33
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR3, hMab 2F11-e7

<400> SEQUENCE: 33

Asp	Gln	Arg	Leu	Tyr	Phe	Asp	Val
1					5		

<210> SEQ ID NO 34
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2, hMab 2F11-e7

<400> SEQUENCE: 34

Val	Ile	Trp	Thr	Asp	Gly	Gly	Thr	Asn	Tyr	Ala	Gln	Lys	Leu	Gln	Gly
1				5				10						15	

<210> SEQ ID NO 35
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR1, hMab 2F11-e7

-continued

<400> SEQUENCE: 35

Ser Tyr Asp Ile Ser
1 5

<210> SEQ ID NO 36

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: light chain CDR3, hMab 2F11-e7

<400> SEQUENCE: 36

Gln Gln Ser Phe Ser Tyr Pro Thr
1 5

<210> SEQ ID NO 37

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: light chain CDR2, hMab 2F11-e7

<400> SEQUENCE: 37

Ala Ala Ser Asn Arg Tyr Thr
1 5

<210> SEQ ID NO 38

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: light chain CDR1, hMab 2F11-e7

<400> SEQUENCE: 38

Arg Ala Ser Glu Asp Val Asn Thr Tyr Val Ser
1 5 10

<210> SEQ ID NO 39

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: heavy chain variable domain, hMab 2F11-e7

<400> SEQUENCE: 39

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45Gly Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Ala Gln Lys Leu Gln
50 55 60Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met
65 70 75 80Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95Arg Asp Gln Arg Leu Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110

-continued

Thr Val Ser Ser
115

<210> SEQ ID NO 40
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain variable domain, hMab 2F11-e7

<400> SEQUENCE: 40

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asp Val Asn Thr Tyr
20 25 30
Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Tyr Pro Thr
85 90 95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 41
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR3, hMab 2F11-f12

<400> SEQUENCE: 41

Asp Gln Arg Leu Tyr Phe Asp Val
1 5

<210> SEQ ID NO 42
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2, hMab 2F11-f12

<400> SEQUENCE: 42

Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met Ser
1 5 10 15

<210> SEQ ID NO 43
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR1, hMab 2F11-f12

<400> SEQUENCE: 43

Thr Tyr Asp Ile Ser
1 5

<210> SEQ ID NO 44
<211> LENGTH: 8

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR3, hMab 2F11-f12

<400> SEQUENCE: 44

Gly Gln Ser Phe Ser Tyr Pro Thr
1 5

<210> SEQ ID NO 45
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR2, hMab 2F11-f12

<400> SEQUENCE: 45

Gly Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 46
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR1, hMab 2F11-f12

<400> SEQUENCE: 46

Arg Ala Ser Glu Asp Val Asn Thr Tyr Val Ser
1 5 10

<210> SEQ ID NO 47
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain variable domain, hMab 2F11-f12

<400> SEQUENCE: 47

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 Phe Ser Leu Thr Thr Tyr
20 25 30

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

Gly Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met
50 55 60

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

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

Arg Asp Gln Arg Leu Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 48
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:

-continued

<223> OTHER INFORMATION: light chain variable domain, hMab 2F11-f12

<400> SEQUENCE: 48

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

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

Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 49

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: heavy chain CDR3, hMab 2F11-g1

<400> SEQUENCE: 49

Asp Gln Arg Leu Tyr Phe Asp Val
1 5

<210> SEQ ID NO 50

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: heavy chain CDR2, hMab 2F11-g1

<400> SEQUENCE: 50

Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 51

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: heavy chain CDR1, hMab 2F11-g1

<400> SEQUENCE: 51

Thr Tyr Asp Ile Ser
1 5

<210> SEQ ID NO 52

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: light chain CDR3, hMab 2F11-g1

<400> SEQUENCE: 52

Gly Gln Ser Phe Ser Tyr Pro Thr
1 5

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<210> SEQ ID NO 53
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR2, hMab 2F11-g1

<400> SEQUENCE: 53

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> SEQ ID NO 54
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR1, hMab 2F11-g1

<400> SEQUENCE: 54

Arg Ala Ser Glu Asp Val Asn Thr Tyr Leu Ala
1 5 10

<210> SEQ ID NO 55
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain variable domain, hMab 2F11-g1

<400> SEQUENCE: 55

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
20 25 30
Asp Ile Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Asp Gln Arg Leu Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110
Thr Val Ser Ser
115

<210> SEQ ID NO 56
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: light chain variable domain, hMab 2F11-g1

<400> SEQUENCE: 56

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asp Val Asn Thr Tyr
20 25 30

```
<210> SEQ ID NO 57
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

Arg 1	Thr	Val	Ala	Ala 5	Pro	Ser	Val	Phe	Ile 10	Phe	Pro	Pro	Ser	Asp 15	Glu
Gln	Leu	Lys	Ser 20	Gly	Thr	Ala	Ser	Val 25	Val	Cys	Leu	Leu	Asn 30	Asn	Phe
Tyr	Pro	Arg 35	Glu	Ala	Lys	Val	Gln 40	Trp	Lys	Val	Asp 45	Asn	Ala	Leu	Gln
Ser 50	Gly	Asn	Ser	Gln	Glu	Ser 55	Val	Thr	Glu	Gln	Asp 60	Ser	Lys	Asp	Ser
Thr 65	Tyr	Ser	Leu	Ser 70	Ser	Thr	Leu	Thr	Leu	Ser 75	Lys	Ala	Asp	Tyr	Glu 80
Lys	His	Lys	Val 85	Tyr	Ala	Cys	Glu	Val	Thr 90	His	Gln	Gly	Leu	Ser 95	Ser
Pro	Val	Thr 100	Lys	Ser	Phe	Asn	Arg	Gly 105	Glu	Cys					

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<210> SEQ ID NO 58
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys
1				5					10					15	
Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70				75						80
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
			115				120					125			

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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

<210> SEQ ID NO 59

<211> LENGTH: 330

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

 <223> OTHER INFORMATION: human heavy chain constant region derived from
 IgG1 mutated on L234A and L235A

<400> SEQUENCE: 59

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

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130	135	140
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp		
145	150	155 160
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu		
	165	170 175
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu		
	180	185 190
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn		
	195	200 205
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly		
	210	215 220
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu		
	225	230 235 240
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr		
	245	250 255
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn		
	260	265 270
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe		
	275	280 285
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn		
	290	295 300
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr		
	305	310 315 320
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
	325	330

<210> SEQ ID NO 60

<211> LENGTH: 327

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg		
1	5	10 15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		
	20	25 30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser		
	35	40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
	50	55 60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
	65	70 75 80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
	85	90 95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser 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

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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
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
Leu	Ser	Leu	Ser	Leu	Gly	Lys										325		

<210> SEQ ID NO 61

<211> LENGTH: 327

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: human heavy chain constant region derived from IgG4 mutated onS228P

<400> SEQUENCE: 61

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	1	5	10	15
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	20	25	30	
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	35	40	45	
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	50	55	60	
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	65	70	75	80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	85	90	95	
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	100	105	110	
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	115	120	125	
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	130	135	140	
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	145	150	155	160
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	165	170	175	

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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

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<210> SEQ ID NO 62

<211> LENGTH: 972

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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

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

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

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

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

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

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

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

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

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

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

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

Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val

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195					200					205					
Pro	Ala	Glu	Leu	Val	Arg	Ile	Arg	Gly	Glu	Ala	Ala	Gln	Ile	Val	Cys
210						215					220				
Ser	Ala	Ser	Ser	Val	Asp	Val	Asn	Phe	Asp	Val	Phe	Leu	Gln	His	Asn
225					230					235					240
Asn	Thr	Lys	Leu	Ala	Ile	Pro	Gln	Gln	Ser	Asp	Phe	His	Asn	Asn	Arg
				245						250				255	
Tyr	Gln	Lys	Val	Leu	Thr	Leu	Asn	Leu	Asp	Gln	Val	Asp	Phe	Gln	His
			260						265				270		
Ala	Gly	Asn	Tyr	Ser	Cys	Val	Ala	Ser	Asn	Val	Gln	Gly	Lys	His	Ser
		275					280					285			
Thr	Ser	Met	Phe	Phe	Arg	Val	Val	Glu	Ser	Ala	Tyr	Leu	Asn	Leu	Ser
	290					295					300				
Ser	Glu	Gln	Asn	Leu	Ile	Gln	Glu	Val	Thr	Val	Gly	Glu	Gly	Leu	Asn
305					310						315				320
Leu	Lys	Val	Met	Val	Glu	Ala	Tyr	Pro	Gly	Leu	Gln	Gly	Phe	Asn	Trp
			325						330					335	
Thr	Tyr	Leu	Gly	Pro	Phe	Ser	Asp	His	Gln	Pro	Glu	Pro	Lys	Leu	Ala
			340					345					350		
Asn	Ala	Thr	Thr	Lys	Asp	Thr	Tyr	Arg	His	Thr	Phe	Thr	Leu	Ser	Leu
		355					360					365			
Pro	Arg	Leu	Lys	Pro	Ser	Glu	Ala	Gly	Arg	Tyr	Ser	Phe	Leu	Ala	Arg
	370					375					380				
Asn	Pro	Gly	Gly	Trp	Arg	Ala	Leu	Thr	Phe	Glu	Leu	Thr	Leu	Arg	Tyr
385					390					395					400
Pro	Pro	Glu	Val	Ser	Val	Ile	Trp	Thr	Phe	Ile	Asn	Gly	Ser	Gly	Thr
			405						410					415	
Leu	Leu	Cys	Ala	Ala	Ser	Gly	Tyr	Pro	Gln	Pro	Asn	Val	Thr	Trp	Leu
		420						425					430		
Gln	Cys	Ser	Gly	His	Thr	Asp	Arg	Cys	Asp	Glu	Ala	Gln	Val	Leu	Gln
		435					440					445			
Val	Trp	Asp	Asp	Pro	Tyr	Pro	Glu	Val	Leu	Ser	Gln	Glu	Pro	Phe	His
	450					455					460				
Lys	Val	Thr	Val	Gln	Ser	Leu	Leu	Thr	Val	Glu	Thr	Leu	Glu	His	Asn
465					470					475					480
Gln	Thr	Tyr	Glu	Cys	Arg	Ala	His	Asn	Ser	Val	Gly	Ser	Gly	Ser	Trp
			485						490					495	
Ala	Phe	Ile	Pro	Ile	Ser	Ala	Gly	Ala	His	Thr	His	Pro	Pro	Asp	Glu
		500						505					510		
Phe	Leu	Phe	Thr	Pro	Val	Val	Val	Ala	Cys	Met	Ser	Ile	Met	Ala	Leu
		515						520				525			
Leu	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Tyr	Lys	Tyr	Lys	Gln	Lys	Pro
	530						535				540				
Lys	Tyr	Gln	Val	Arg	Trp	Lys	Ile	Ile	Glu	Ser	Tyr	Glu	Gly	Asn	Ser
545					550					555					560
Tyr	Thr	Phe	Ile	Asp	Pro	Thr	Gln	Leu	Pro	Tyr	Asn	Glu	Lys	Trp	Glu
			565						570					575	
Phe	Pro	Arg	Asn	Asn	Leu	Gln	Phe	Gly	Lys	Thr	Leu	Gly	Ala	Gly	Ala
			580					585					590		
Phe	Gly	Lys	Val	Val	Glu	Ala	Thr	Ala	Phe	Gly	Leu	Gly	Lys	Glu	Asp
	595						600					605			

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Ala	Val	Leu	Lys	Val	Ala	Val	Lys	Met	Leu	Lys	Ser	Thr	Ala	His	Ala	
610						615					620					
Asp	Glu	Lys	Glu	Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Met	Ser	His	Leu	
625					630					635					640	
Gly	Gln	His	Glu	Asn	Ile	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	His	Gly	
				645					650					655		
Gly	Pro	Val	Leu	Val	Ile	Thr	Glu	Tyr	Cys	Cys	Tyr	Gly	Asp	Leu	Leu	
		660						665					670			
Asn	Phe	Leu	Arg	Arg	Lys	Ala	Glu	Ala	Met	Leu	Gly	Pro	Ser	Leu	Ser	
	675						680					685				
Pro	Gly	Gln	Asp	Pro	Glu	Gly	Gly	Val	Asp	Tyr	Lys	Asn	Ile	His	Leu	
690						695					700					
Glu	Lys	Lys	Tyr	Val	Arg	Arg	Asp	Ser	Gly	Phe	Ser	Ser	Gln	Gly	Val	
705					710					715					720	
Asp	Thr	Tyr	Val	Glu	Met	Arg	Pro	Val	Ser	Thr	Ser	Ser	Asn	Asp	Ser	
			725						730					735		
Phe	Ser	Glu	Gln	Asp	Leu	Asp	Lys	Glu	Asp	Gly	Arg	Pro	Leu	Glu	Leu	
		740						745					750			
Arg	Asp	Leu	Leu	His	Phe	Ser	Ser	Gln	Val	Ala	Gln	Gly	Met	Ala	Phe	
	755						760					765				
Leu	Ala	Ser	Lys	Asn	Cys	Ile	His	Arg	Asp	Val	Ala	Ala	Arg	Asn	Val	
770					775					780						
Leu	Leu	Thr	Asn	Gly	His	Val	Ala	Lys	Ile	Gly	Asp	Phe	Gly	Leu	Ala	
785				790						795					800	
Arg	Asp	Ile	Met	Asn	Asp	Ser	Asn	Tyr	Ile	Val	Lys	Gly	Asn	Ala	Arg	
			805					810					815			
Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ser	Ile	Phe	Asp	Cys	Val	Tyr	
		820						825					830			
Thr	Val	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Leu	Leu	Trp	Glu	Ile	
	835					840					845					
Phe	Ser	Leu	Gly	Leu	Asn	Pro	Tyr	Pro	Gly	Ile	Leu	Val	Asn	Ser	Lys	
850					855					860						
Phe	Tyr	Lys	Leu	Val	Lys	Asp	Gly	Tyr	Gln	Met	Ala	Gln	Pro	Ala	Phe	
865				870					875					880		
Ala	Pro	Lys	Asn	Ile	Tyr	Ser	Ile	Met	Gln	Ala	Cys	Trp	Ala	Leu	Glu	
			885					890					895			
Pro	Thr	His	Arg	Pro	Thr	Phe	Gln	Gln	Ile	Cys	Ser	Phe	Leu	Gln	Glu	
		900						905					910			
Gln	Ala	Gln	Glu	Asp	Arg	Arg	Glu	Arg	Asp	Tyr	Thr	Asn	Leu	Pro	Ser	
	915						920					925				
Ser	Ser	Arg	Ser	Gly	Gly	Ser	Gly	Ser	Ser	Ser	Ser	Glu	Leu	Glu	Glu	
930					935						940					
Glu	Ser	Ser	Ser	Glu	His	Leu	Thr	Cys	Cys	Glu	Gln	Gly	Asp	Ile	Ala	
945				950						955				960		
Gln	Pro	Leu	Leu	Gln	Pro	Asn	Asn	Tyr	Gln	Phe	Cys					
			965					970								

<210> SEQ ID NO 63

<211> LENGTH: 972

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

-continued

<223> OTHER INFORMATION: mutant CSF-1R L301S Y969F

<400> SEQUENCE: 63

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Ser 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

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Asn	Pro	Gly	Gly	Trp	Arg	Ala	Leu	Thr	Phe	Glu	Leu	Thr	Leu	Arg	Tyr	385	390	395	400
Pro	Pro	Glu	Val	Ser	Val	Ile	Trp	Thr	Phe	Ile	Asn	Gly	Ser	Gly	Thr	405	410	415	
Leu	Leu	Cys	Ala	Ala	Ser	Gly	Tyr	Pro	Gln	Pro	Asn	Val	Thr	Trp	Leu	420	425	430	
Gln	Cys	Ser	Gly	His	Thr	Asp	Arg	Cys	Asp	Glu	Ala	Gln	Val	Leu	Gln	435	440	445	
Val	Trp	Asp	Asp	Pro	Tyr	Pro	Glu	Val	Leu	Ser	Gln	Glu	Pro	Phe	His	450	455	460	
Lys	Val	Thr	Val	Gln	Ser	Leu	Leu	Thr	Val	Glu	Thr	Leu	Glu	His	Asn	465	470	475	480
Gln	Thr	Tyr	Glu	Cys	Arg	Ala	His	Asn	Ser	Val	Gly	Ser	Gly	Ser	Trp	485	490	495	
Ala	Phe	Ile	Pro	Ile	Ser	Ala	Gly	Ala	His	Thr	His	Pro	Pro	Asp	Glu	500	505	510	
Phe	Leu	Phe	Thr	Pro	Val	Val	Val	Ala	Cys	Met	Ser	Ile	Met	Ala	Leu	515	520	525	
Leu	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Tyr	Lys	Tyr	Lys	Gln	Lys	Pro	530	535	540	
Lys	Tyr	Gln	Val	Arg	Trp	Lys	Ile	Ile	Glu	Ser	Tyr	Glu	Gly	Asn	Ser	545	550	555	560
Tyr	Thr	Phe	Ile	Asp	Pro	Thr	Gln	Leu	Pro	Tyr	Asn	Glu	Lys	Trp	Glu	565	570	575	
Phe	Pro	Arg	Asn	Asn	Leu	Gln	Phe	Gly	Lys	Thr	Leu	Gly	Ala	Gly	Ala	580	585	590	
Phe	Gly	Lys	Val	Val	Glu	Ala	Thr	Ala	Phe	Gly	Leu	Gly	Lys	Glu	Asp	595	600	605	
Ala	Val	Leu	Lys	Val	Ala	Val	Lys	Met	Leu	Lys	Ser	Thr	Ala	His	Ala	610	615	620	
Asp	Glu	Lys	Glu	Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Met	Ser	His	Leu	625	630	635	640
Gly	Gln	His	Glu	Asn	Ile	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	His	Gly	645	650	655	
Gly	Pro	Val	Leu	Val	Ile	Thr	Glu	Tyr	Cys	Cys	Tyr	Gly	Asp	Leu	Leu	660	665	670	
Asn	Phe	Leu	Arg	Arg	Lys	Ala	Glu	Ala	Met	Leu	Gly	Pro	Ser	Leu	Ser	675	680	685	
Pro	Gly	Gln	Asp	Pro	Glu	Gly	Gly	Val	Asp	Tyr	Lys	Asn	Ile	His	Leu	690	695	700	
Glu	Lys	Lys	Tyr	Val	Arg	Arg	Asp	Ser	Gly	Phe	Ser	Ser	Gln	Gly	Val	705	710	715	720
Asp	Thr	Tyr	Val	Glu	Met	Arg	Pro	Val	Ser	Thr	Ser	Ser	Asn	Asp	Ser	725	730	735	
Phe	Ser	Glu	Gln	Asp	Leu	Asp	Lys	Glu	Asp	Gly	Arg	Pro	Leu	Glu	Leu	740	745	750	
Arg	Asp	Leu	Leu	His	Phe	Ser	Ser	Gln	Val	Ala	Gln	Gly	Met	Ala	Phe	755	760	765	
Leu	Ala	Ser	Lys	Asn	Cys	Ile	His	Arg	Asp	Val	Ala	Ala	Arg	Asn	Val	770	775	780	
Leu	Leu	Thr	Asn	Gly	His	Val	Ala	Lys	Ile	Gly	Asp	Phe	Gly	Leu	Ala				

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

<210> SEQ ID NO 64

<211> LENGTH: 493

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: human CSF-1R Extracellular Domain

<400> SEQUENCE: 64

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				

-continued

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			
			485					490							

<210> SEQ ID NO 65

<211> LENGTH: 388

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: human CSF-1R fragment delD4

<400> SEQUENCE: 65

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

-continued

20					25					30					
Gly	Pro	Pro	Ser	Pro	His	Trp	Thr	Leu	Tyr	Ser	Asp	Gly	Ser	Ser	Ser
	35						40					45			
Ile	Leu	Ser	Thr	Asn	Asn	Ala	Thr	Phe	Gln	Asn	Thr	Gly	Thr	Tyr	Arg
	50					55					60				
Cys	Thr	Glu	Pro	Gly	Asp	Pro	Leu	Gly	Gly	Ser	Ala	Ala	Ile	His	Leu
	65					70					75				80
Tyr	Val	Lys	Asp	Pro	Ala	Arg	Pro	Trp	Asn	Val	Leu	Ala	Gln	Glu	Val
						85			90					95	
Val	Val	Phe	Glu	Asp	Gln	Asp	Ala	Leu	Leu	Pro	Cys	Leu	Leu	Thr	Asp
			100					105					110		
Pro	Val	Leu	Glu	Ala	Gly	Val	Ser	Leu	Val	Arg	Val	Arg	Gly	Arg	Pro
			115					120					125		
Leu	Met	Arg	His	Thr	Asn	Tyr	Ser	Phe	Ser	Pro	Trp	His	Gly	Phe	Thr
	130					135					140				
Ile	His	Arg	Ala	Lys	Phe	Ile	Gln	Ser	Gln	Asp	Tyr	Gln	Cys	Ser	Ala
	145					150					155				160
Leu	Met	Gly	Gly	Arg	Lys	Val	Met	Ser	Ile	Ser	Ile	Arg	Leu	Lys	Val
						165			170					175	
Gln	Lys	Val	Ile	Pro	Gly	Pro	Pro	Ala	Leu	Thr	Leu	Val	Pro	Ala	Glu
			180					185					190		
Leu	Val	Arg	Ile	Arg	Gly	Glu	Ala	Ala	Gln	Ile	Val	Cys	Ser	Ala	Ser
			195					200					205		
Ser	Val	Asp	Val	Asn	Phe	Asp	Val	Phe	Leu	Gln	His	Asn	Asn	Thr	Lys
	210					215					220				
Leu	Ala	Ile	Pro	Gln	Gln	Ser	Asp	Phe	His	Asn	Asn	Arg	Tyr	Gln	Lys
	225					230					235				240
Val	Leu	Thr	Leu	Asn	Leu	Asp	Gln	Val	Asp	Phe	Gln	His	Ala	Gly	Asn
						245			250					255	
Tyr	Ser	Cys	Val	Ala	Ser	Asn	Val	Gln	Gly	Lys	His	Ser	Thr	Ser	Met
			260					265					270		
Phe	Phe	Arg	Tyr	Pro	Pro	Glu	Val	Ser	Val	Ile	Trp	Thr	Phe	Ile	Asn
			275					280					285		
Gly	Ser	Gly	Thr	Leu	Leu	Cys	Ala	Ala	Ser	Gly	Tyr	Pro	Gln	Pro	Asn
	290					295					300				
Val	Thr	Trp	Leu	Gln	Cys	Ser	Gly	His	Thr	Asp	Arg	Cys	Asp	Glu	Ala
	305					310					315				320
Gln	Val	Leu	Gln	Val	Trp	Asp	Asp	Pro	Tyr	Pro	Glu	Val	Leu	Ser	Gln
						325			330				335		
Glu	Pro	Phe	His	Lys	Val	Thr	Val	Gln	Ser	Leu	Leu	Thr	Val	Glu	Thr
			340					345					350		
Leu	Glu	His	Asn	Gln	Thr	Tyr	Glu	Cys	Arg	Ala	His	Asn	Ser	Val	Gly
			355					360					365		
Ser	Gly	Ser	Trp	Ala	Phe	Ile	Pro	Ile	Ser	Ala	Gly	Ala	His	Thr	His
	370					375					380				
Pro	Pro	Asp	Glu												
	385														

<210> SEQ ID NO 66

<211> LENGTH: 292

<212> TYPE: PRT

<213> ORGANISM: Artificial

-continued

<220> FEATURE:

<223> OTHER INFORMATION: human CSF-1R fragment D1-D3

<400> SEQUENCE: 66

Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val Lys Pro Gly
1 5 10 15
Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val Glu Trp Asp
20 25 30
Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly Ser Ser Ser
35 40 45
Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly Thr Tyr Arg
50 55 60
Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala Ile His Leu
65 70 75 80
Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala Gln Glu Val
85 90 95
Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu Leu Thr Asp
100 105 110
Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg Gly Arg Pro
115 120 125
Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His Gly Phe Thr
130 135 140
Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln Cys Ser Ala
145 150 155 160
Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg Leu Lys Val
165 170 175
Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val Pro Ala Glu
180 185 190
Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys Ser Ala Ser
195 200 205
Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn Asn Thr Lys
210 215 220
Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg Tyr Gln Lys
225 230 235 240
Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His Ala Gly Asn
245 250 255
Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser Thr Ser Met
260 265 270
Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln
275 280 285
Asn Leu Ile Gln
290

<210> SEQ ID NO 67

<211> LENGTH: 21

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: signal peptide

<400> SEQUENCE: 67

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

-continued

20

<210> SEQ ID NO 68
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 68

cacctccatg ttcttcggt acccccaga ggtaag 36

<210> SEQ ID NO 69
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 69

Asp Leu Arg Leu Tyr Phe Asp Val
1 5

<210> SEQ ID NO 70
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 70

Val Ile Trp Ser Gly Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met Ser
1 5 10 15

<210> SEQ ID NO 71
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 71

Gly Phe Ser Leu Thr Ser Tyr Asp Ile Ser
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 72

Gly Gln Ser Phe Thr Tyr Pro Thr
1 5

<210> SEQ ID NO 73
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 73

Gly Ser Ser Asn Arg Tyr Thr
1 5

<210> SEQ ID NO 74
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 74

-continued

Lys Ala Ser Glu Asp Val Gly Thr Tyr Val Ser
1 5 10

<210> SEQ ID NO 75
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 75

Arg Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30
Asp Ile Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ser Gly Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met
50 55 60
Ser Arg Leu Arg Ile Ser Lys Asp Asp Ser Arg Ser Gln Val Phe Leu
65 70 75 80
Lys Val Asn Arg Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Val
85 90 95
Arg Asp Leu Arg Leu Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val
100 105 110
Thr Val Ser Ser
115

<210> SEQ ID NO 76
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 76

Lys Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Val Ser Val Gly
1 5 10 15
Glu Arg Val Ser Leu Ser Cys Lys Ala Ser Glu Asp Val Gly Thr Tyr
20 25 30
Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ser Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60
Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80
Glu Asp Leu Ala Asp Tyr Ser Cys Gly Gln Ser Phe Thr Tyr Pro Thr
85 90 95
Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 77
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 77

Asp Pro Arg Leu Tyr Phe Asp Val
1 5

-continued

<210> SEQ ID NO 78
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 78

Val Ile Trp Thr Gly Gly Gly Thr Asn Tyr Asn Ser Gly Phe Met Ser
1 5 10 15

<210> SEQ ID NO 79
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 79

Gly Ser Ser Leu Asp Ser Phe Asp Ile Ser
1 5 10

<210> SEQ ID NO 80
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 80

Gly Gln Thr Phe Ser Tyr Pro Thr
1 5

<210> SEQ ID NO 81
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 81

Gly Ala Ser Asn Arg Tyr Thr
1 5

<210> SEQ ID NO 82
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 82

Lys Ala Ser Glu Asp Val Val Thr Tyr Val Ser
1 5 10

<210> SEQ ID NO 83
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 83

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Ser Ser Leu Asp Ser Phe
20 25 30

Asp Ile Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Thr Gly Gly Gly Thr Asn Tyr Asn Ser Gly Phe Met
50 55 60

Ser Arg Leu Arg Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu

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65	70	75	80
Lys Met Ser Ser Leu Gln Ser Asp Asp Thr Ala Ile Tyr Tyr Cys Val	85	90	95
Arg Asp Pro Arg Leu Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val	100	105	110
Thr Val Ser Ser	115		

<210> SEQ ID NO 84
 <211> LENGTH: 106
 <212> TYPE: PRT
 <213> ORGANISM: Mus musculus

<400> SEQUENCE: 84

Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly	1	5	10	15
Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asp Val Val Thr Tyr	20	25	30	
Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Lys Leu Leu Ile	35	40	45	
Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly	50	55	60	
Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Ile Gln Ala	65	70	75	80
Glu Asp Leu Ala Asp Tyr Tyr Cys Gly Gln Thr Phe Ser Tyr Pro Thr	85	90	95	
Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys	100	105		

<210> SEQ ID NO 85
 <211> LENGTH: 218
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: human CSF-1R fragment domains D4-D5

<400> SEQUENCE: 85

Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln Asn Leu Ile	1	5	10	15
Gln Glu Val Thr Val Gly Glu Gly Leu Asn Leu Lys Val Met Val Glu	20	25	30	
Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp Thr Tyr Leu Gly Pro Phe	35	40	45	
Ser Asp His Gln Pro Glu Pro Lys Leu Ala Asn Ala Thr Thr Lys Asp	50	55	60	
Thr Tyr Arg His Thr Phe Thr Leu Ser Leu Pro Arg Leu Lys Pro Ser	65	70	75	80
Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg Asn Pro Gly Gly Trp Arg	85	90	95	
Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr Pro Pro Glu Val Ser Val	100	105	110	
Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr Leu Leu Cys Ala Ala Ser	115	120	125	
Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu Gln Cys Ser Gly His Thr	130	135	140	

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Asp Arg Cys Asp Glu Ala Gln Val Leu Gln Val Trp Asp Asp Pro Tyr
145          150          155          160

Pro Glu Val Leu Ser Gln Glu Pro Phe His Lys Val Thr Val Gln Ser
          165          170          175

Leu Leu Thr Val Glu Thr Leu Glu His Asn Gln Thr Tyr Glu Cys Arg
          180          185          190

Ala His Asn Ser Val Gly Ser Gly Ser Trp Ala Phe Ile Pro Ile Ser
          195          200          205

Ala Gly Ala His Thr His Pro Pro Asp Glu
210          215

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<210> SEQ ID NO 86

<211> LENGTH: 554

<212> TYPE: PRT

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 86

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Met Thr Ala Pro Gly Ala Ala Gly Arg Cys Pro Pro Thr Thr Trp Leu
1          5          10          15

Gly Ser Leu Leu Leu Val Cys Leu Leu Ala Ser Arg Ser Ile Thr
          20          25          30

Glu Glu Val Ser Glu Tyr Cys Ser His Met Ile Gly Ser Gly His Leu
          35          40          45

Gln Ser Leu Gln Arg Leu Ile Asp Ser Gln Met Glu Thr Ser Cys Gln
          50          55          60

Ile Thr Phe Glu Phe Val Asp Gln Glu Gln Leu Lys Asp Pro Val Cys
          65          70          75          80

Tyr Leu Lys Lys Ala Phe Leu Leu Val Gln Asp Ile Met Glu Asp Thr
          85          90          95

Met Arg Phe Arg Asp Asn Thr Pro Asn Ala Ile Ala Ile Val Gln Leu
          100          105          110

Gln Glu Leu Ser Leu Arg Leu Lys Ser Cys Phe Thr Lys Asp Tyr Glu
          115          120          125

Glu His Asp Lys Ala Cys Val Arg Thr Phe Tyr Glu Thr Pro Leu Gln
          130          135          140

Leu Leu Glu Lys Val Lys Asn Val Phe Asn Glu Thr Lys Asn Leu Leu
          145          150          155          160

Asp Lys Asp Trp Asn Ile Phe Ser Lys Asn Cys Asn Asn Ser Phe Ala
          165          170          175

Glu Cys Ser Ser Gln Asp Val Val Thr Lys Pro Asp Cys Asn Cys Leu
          180          185          190

Tyr Pro Lys Ala Ile Pro Ser Ser Asp Pro Ala Ser Val Ser Pro His
          195          200          205

Gln Pro Leu Ala Pro Ser Met Ala Pro Val Ala Gly Leu Thr Trp Glu
          210          215          220

Asp Ser Glu Gly Thr Glu Gly Ser Ser Leu Leu Pro Gly Glu Gln Pro
          225          230          235          240

Leu His Thr Val Asp Pro Gly Ser Ala Lys Gln Arg Pro Pro Arg Ser
          245          250          255

Thr Cys Gln Ser Phe Glu Pro Pro Glu Thr Pro Val Val Lys Asp Ser
          260          265          270

Thr Ile Gly Gly Ser Pro Gln Pro Arg Pro Ser Val Gly Ala Phe Asn

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275					280					285					
Pro	Gly	Met	Glu	Asp	Ile	Leu	Asp	Ser	Ala	Met	Gly	Thr	Asn	Trp	Val
290						295					300				
Pro	Glu	Glu	Ala	Ser	Gly	Glu	Ala	Ser	Glu	Ile	Pro	Val	Pro	Gln	Gly
305					310					315					320
Thr	Glu	Leu	Ser	Pro	Ser	Arg	Pro	Gly	Gly	Gly	Ser	Met	Gln	Thr	Glu
				325					330					335	
Pro	Ala	Arg	Pro	Ser	Asn	Phe	Leu	Ser	Ala	Ser	Ser	Pro	Leu	Pro	Ala
			340					345					350		
Ser	Ala	Lys	Gly	Gln	Gln	Pro	Ala	Asp	Val	Thr	Gly	Thr	Ala	Leu	Pro
		355					360					365			
Arg	Val	Gly	Pro	Val	Arg	Pro	Thr	Gly	Gln	Asp	Trp	Asn	His	Thr	Pro
	370					375					380				
Gln	Lys	Thr	Asp	His	Pro	Ser	Ala	Leu	Leu	Arg	Asp	Pro	Pro	Glu	Pro
385					390					395					400
Gly	Ser	Pro	Arg	Ile	Ser	Ser	Leu	Arg	Pro	Gln	Gly	Leu	Ser	Asn	Pro
				405					410					415	
Ser	Thr	Leu	Ser	Ala	Gln	Pro	Gln	Leu	Ser	Arg	Ser	His	Ser	Ser	Gly
		420						425					430		
Ser	Val	Leu	Pro	Leu	Gly	Glu	Leu	Glu	Gly	Arg	Arg	Ser	Thr	Arg	Asp
		435					440					445			
Arg	Arg	Ser	Pro	Ala	Glu	Pro	Glu	Gly	Gly	Pro	Ala	Ser	Glu	Gly	Ala
	450					455					460				
Ala	Arg	Pro	Leu	Pro	Arg	Phe	Asn	Ser	Val	Pro	Leu	Thr	Asp	Thr	Gly
465					470					475					480
His	Glu	Arg	Gln	Ser	Glu	Gly	Ser	Phe	Ser	Pro	Gln	Leu	Gln	Glu	Ser
				485					490					495	
Val	Phe	His	Leu	Leu	Val	Pro	Ser	Val	Ile	Leu	Val	Leu	Leu	Ala	Val
			500					505					510		
Gly	Gly	Leu	Leu	Phe	Tyr	Arg	Trp	Arg	Arg	Arg	Ser	His	Gln	Glu	Pro
		515					520					525			
Gln	Arg	Ala	Asp	Ser	Pro	Leu	Glu	Gln	Pro	Glu	Gly	Ser	Pro	Leu	Thr
	530					535					540				
Gln	Asp	Asp	Arg	Gln	Val	Glu	Leu	Pro	Val						
545					550										
<210> SEQ ID NO 87															
<211> LENGTH: 242															
<212> TYPE: PRT															
<213> ORGANISM: homo sapiens															
<400> SEQUENCE: 87															
Met	Pro	Arg	Gly	Phe	Thr	Trp	Leu	Arg	Tyr	Leu	Gly	Ile	Phe	Leu	Gly
1				5					10					15	
Val	Ala	Leu	Gly	Asn	Glu	Pro	Leu	Glu	Met	Trp	Pro	Leu	Thr	Gln	Asn
			20					25					30		
Glu	Glu	Cys	Thr	Val	Thr	Gly	Phe	Leu	Arg	Asp	Lys	Leu	Gln	Tyr	Arg
		35					40					45			
Ser	Arg	Leu	Gln	Tyr	Met	Lys	His	Tyr	Phe	Pro	Ile	Asn	Tyr	Lys	Ile
	50					55					60				
Ser	Val	Pro	Tyr	Glu	Gly	Val	Phe	Arg	Ile	Ala	Asn	Val	Thr	Arg	Leu
65					70				75						80

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Gln	Arg	Ala	Gln	Val	Ser	Glu	Arg	Glu	Leu	Arg	Tyr	Leu	Trp	Val	Leu
			85						90					95	
Val	Ser	Leu	Ser	Ala	Thr	Glu	Ser	Val	Gln	Asp	Val	Leu	Leu	Glu	Gly
		100						105				110			
His	Pro	Ser	Trp	Lys	Tyr	Leu	Gln	Glu	Val	Glu	Thr	Leu	Leu	Leu	Asn
	115					120						125			
Val	Gln	Gln	Gly	Leu	Thr	Asp	Val	Glu	Val	Ser	Pro	Lys	Val	Glu	Ser
	130					135					140				
Val	Leu	Ser	Leu	Leu	Asn	Ala	Pro	Gly	Pro	Asn	Leu	Lys	Leu	Val	Arg
145					150					155					160
Pro	Lys	Ala	Leu	Leu	Asp	Asn	Cys	Phe	Arg	Val	Met	Glu	Leu	Leu	Tyr
			165						170					175	
Cys	Ser	Cys	Cys	Lys	Gln	Ser	Ser	Val	Leu	Asn	Trp	Gln	Asp	Cys	Glu
		180						185					190		
Val	Pro	Ser	Pro	Gln	Ser	Cys	Ser	Pro	Glu	Pro	Ser	Leu	Gln	Tyr	Ala
	195					200						205			
Ala	Thr	Gln	Leu	Tyr	Pro	Pro	Pro	Pro	Trp	Ser	Pro	Ser	Ser	Pro	Pro
	210				215						220				
His	Ser	Thr	Gly	Ser	Val	Arg	Pro	Val	Arg	Ala	Gln	Gly	Glu	Gly	Leu
225					230					235					240
Leu	Pro														

<210> SEQ ID NO 88

<211> LENGTH: 290

<212> TYPE: PRT

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 88

Met	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Met	Thr	Tyr	Trp	His	Leu	Leu
1				5					10					15	
Asn	Ala	Phe	Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr
		20						25					30		
Gly	Ser	Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu
		35				40						45			
Asp	Leu	Ala	Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile
	50					55					60				
Ile	Gln	Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Ser
65					70				75					80	
Tyr	Arg	Gln	Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn
			85					90					95		
Ala	Ala	Leu	Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr
		100						105					110		
Arg	Cys	Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val
	115					120						125			
Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val
	130					135					140				
Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr
145					150					155					160
Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser
			165					170						175	
Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn
		180						185					190		

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Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr
		195					200					205			
Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu
	210					215					220				
Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His
225					230					235					240
Leu	Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr
			245						250					255	
Phe	Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys
		260						265					270		
Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu
		275					280					285			
Glu	Thr														
	290														

<210> SEQ ID NO 89
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 89

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ser
		20						25					30		
Trp	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40						45			
Ala	Trp	Ile	Ser	Pro	Tyr	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr
65				70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90				95		
Ala	Arg	Arg	His	Trp	Pro	Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ala										
	115														

<210> SEQ ID NO 90
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 90

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ser
		20						25					30		
Trp	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40						45			
Ala	Trp	Ile	Ser	Pro	Tyr	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				

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

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

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> SEQ ID NO 91
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 91

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Ser
20 25 30

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

Ala Trp Ile Leu Pro Tyr Gly Gly Ser Ser Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> SEQ ID NO 92
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 92

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

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

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

-continued

100	105
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<210> SEQ ID NO 93
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 93

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

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

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 94
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 94

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

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

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ala Pro Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 95
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 95

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

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
      20                      25                      30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35                      40                      45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
      50                      55                      60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65                      70                      75                      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Thr Val Pro Trp
      85                      90                      95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100                      105

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<210> SEQ ID NO 96
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

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<400> SEQUENCE: 96

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1       5              10              15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Asn Thr Phe
      20                      25                      30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35                      40                      45
Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
      50                      55                      60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65                      70                      75                      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Thr Val Pro Arg
      85                      90                      95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100                      105

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<210> SEQ ID NO 97
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

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<400> SEQUENCE: 97

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1       5              10              15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
      20                      25                      30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35                      40                      45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
      50                      55                      60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65                      70                      75                      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Gly Val Pro Arg

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85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg		
100	105	
<210> SEQ ID NO 98		
<211> LENGTH: 108		
<212> TYPE: PRT		
<213> ORGANISM: Artificial sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: sequence is synthesized		
<400> SEQUENCE: 98		
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
1	5	10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala		
20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
35	40	45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Phe Thr Pro Pro		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg		
100	105	
<210> SEQ ID NO 99		
<211> LENGTH: 108		
<212> TYPE: PRT		
<213> ORGANISM: Artificial sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: sequence is synthesized		
<400> SEQUENCE: 99		
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
1	5	10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala		
20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
35	40	45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Phe Ile Thr Pro Thr		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg		
100	105	
<210> SEQ ID NO 100		
<211> LENGTH: 108		
<212> TYPE: PRT		
<213> ORGANISM: Artificial sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: sequence is synthesized		
<400> SEQUENCE: 100		

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
           20           25           30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
           35           40           45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
           50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Tyr Thr Pro Pro
           85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
           100           105

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<210> SEQ ID NO 101
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

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<400> SEQUENCE: 101

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
           20           25           30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
           35           40           45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
           50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Phe Tyr Thr Pro Pro
           85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
           100           105

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<210> SEQ ID NO 102
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: sequence is synthesized

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<400> SEQUENCE: 102

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
           20           25           30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
           35           40           45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
           50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

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65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Leu Phe Thr Pro Pro			
	85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg			
	100	105	

<210> SEQ ID NO 103
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 103

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala			
	20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
	35	40	45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly			
	50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Leu Tyr Thr Pro Pro			
	85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg			
	100	105	

<210> SEQ ID NO 104
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 104

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala			
	20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
	35	40	45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly			
	50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Trp Tyr His Pro Pro			
	85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg			
	100	105	

<210> SEQ ID NO 105
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:

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<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 105

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Phe Tyr Ile Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 106

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 106

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Tyr Thr Pro Thr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 107

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: sequence is synthesized

<400> SEQUENCE: 107

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

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50					55					60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Phe	Ile	Pro	Pro
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg				
			100					105							

1. A method for treating cancer, preventing or for treating metastasis, for treating inflammatory diseases, for treating bone loss, for treating or delaying progression of an immune related disease, or for stimulating an immune response or function, the method comprising administering to a patient in need thereof an effective amount of an antibody which binds to human colony stimulating factor 1 receptor (CSF-1R), and an antibody which binds to human programmed death-ligand 1 (PD-L1),

wherein the antibody which binds to human CSF-1R comprises:

- a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56.

2. The method of claim 1, wherein the patient is in need of treatment of cancer.

3. The method of claim 2, wherein the cancer is breast cancer, lung cancer, colon cancer, ovarian cancer, melanoma cancer, bladder cancer, renal cancer, kidney cancer, liver cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric carcinoma cancer, esophageal cancer, mesothelioma, prostate cancer, leukemia, lymphoma, or myeloma.

4. The method of claim 1, wherein the patient is in need of prevention or treatment of metastasis.

5. The method of claim 1, wherein the patient is in need of treatment of bone loss.

6. The antibody according to claim 1, wherein the patient is in need of treatment of inflammatory diseases.

7. The method of claim 1, wherein the patient is in need of treating or delaying progression of an immune related disease.

8. The method of claim 1, wherein the patient is in need of stimulating an immune response or function.

9. A method of:

- inhibiting cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R-expressing tumor cells; or

- inhibiting cell proliferation of tumors with CSF-1R ligand dependent and/or CSF-1R ligand-independent CSF-1R-expressing macrophage infiltrate; or

- inhibiting cell survival in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R-expressing monocytes and macrophages; or

- inhibiting cell differentiation CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R-expressing monocytes into macrophages,

the method comprising administering to a patient in need thereof an effective amount of an antibody which binds to human colony stimulating factor 1 receptor (CSF-1R), and an antibody which binds to human programmed death-ligand 1 (PD-L1),

wherein the antibody which binds to human CSF-1R comprises:

- a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
- a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
- a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56.

10. A method of treating a patient having a CSF-1R-expressing tumor or having a tumor with CSF-1R-expressing macrophage infiltrate, wherein the tumor expresses increased levels of CSF-1R ligand, the method comprising administering to the patient an effective amount of an antibody which binds to human colony stimulating factor 1 receptor (CSF-1R), and an antibody which binds to human programmed death-ligand 1 (PD-L1),

wherein the antibody which binds to human CSF-1R comprises:

- a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
- a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56.

11. The method of claim 1, wherein said antibody which binds to human CSF-1R and antibody which binds to human PD-L1 are human IgG1 subclass or human IgG4 subclass.

12. The method of claim 1, wherein said antibody which binds to human CSF-1R and antibody which binds to human PD-L1 have reduced or minimal effector function.

13. The method of claim 12, wherein the minimal effector function results from an effectorless Fc mutation.

14. The method of claim 13, wherein the effectorless Fc mutation is L234A/L235A or L234A/L235A/P329G or N297A or D265A/N297A.

15. The method of claim 1, wherein the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, and wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

16. The method of claim 1, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40.

17. The method of claim 1, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40; and the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

18. The method of claim 9, wherein the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, and wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain

variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

19. The method of claim 9, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40.

20. The method of claim 9, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40; and the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

21. The method of claim 10, wherein the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, and wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

22. The method of claim 10, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40.

23. The method of claim 10, wherein the antibody which binds to human CSF-1R comprises a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40; and the antibody which binds to human PD-L1 comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the three complementarity determining regions (CDRs) of the heavy chain variable domain VH of SEQ ID NO:89 and the light chain variable domain comprises the three complementarity determining regions (CDRs) of the light chain variable domain VL of SEQ ID NO:92.

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