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

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 ABSTRACT

 The present invention relates to the combination therapy of specific antibodies which human CSF-1R with specific antibodies which bind human PD-L1.
Fig. 2a

CSF-1 ELISA - Cyno Plasma Batch 1 (0.1 mg/kg anti-CSFIRhMab 2F11-e7)-Animal 1

M-CSF (pg/ml)

Time Point

Pre-Dose

- 2 hr
- 4 hr
- 24 hr
- 48 hr
- 72 hr
- 96 hr
- 168 hr
- d15
- d22

0 2000 4000 8000 12000 16000
Fig. 2c


CSF-1 ELISA - Cyno Plasma Batch 1 (10 mg/kg anti-CSFIR hMab2F11-e7)-Animal 1

M-CSF (pg/ml)

Dose

Time Point

Pre-2 hr 24 hr 48 hr 72 hr 96 hr 168 hr 015 d22

16000 14000 12000 10000 8000 6000 4000 2000 0
Fig. 2d

CSF-1 ELISA - Cyno Plasma Batch 1
(100 mg/kg anti-CSF1R hMab 2F11-e7)-Animal 1

M-CSF (pg/ml)

Time Point

Pre-Dose 2 hr 24 hr 48 hr 72 hr 96 hr 168 hr d15 d22

Dose

16000 14000 12000 10000 M - CSF (pg/ml)

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Fig. 3
Fig. 5

So So Study day 50 so
< mouse CSF1R > < PD-L1 > * * * * 
< PD-L1 > Control Mouse IgG1

Progression > 700 mm
Study day
COMBINATION THERAPY OF ANTIBODIES AGAINST HUMAN CSF-1R AND ANTIBODIES AGAINST HUMAN PD-L1

[0001] 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


[0003] 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 inhibitory tyrosine 969 phosphorilation 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).

[0004] 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, macrophages; 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) (Hum. 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).


[0006] 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, PLCg, and Cbl (Bourette, R. P. and Rohrschneider, L. R., Growth Factors 17 (2000) 155-166).

[0007] 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 (Polland, 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.


PD-L1 and PD-L1 Antibodies


[0010] 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 06: 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.

[0011] 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* 63: 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.

[0012] 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.

[0013] 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**

[0014] 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.

[0015] 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.

[0016] The antibody which binds to human CSF-1 in the combination therapy is characterized in comprising

- a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
- 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
- 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
- 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;

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

- 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
- 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
- c) a heavy chain variable domain VH of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:107.

[0038] In one embodiment the antibody is for use in the treatment of cancer.
In one embodiment the antibody is for use in the prevention or treatment of metastasis.

In one embodiment the antibody is for use in the treatment of bone loss.

In one embodiment the antibody is for use in the treatment of inflammatory diseases.

In one embodiment the antibody is for use in treating or delaying progression of an immune related disease such as tumor immunity.

In one embodiment the antibody is for use in stimulating an immune response or function, such as T cell activity.

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:

1. The inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R expressing tumor cells;
2. The inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
3. The inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages and/or
4. The inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;

wherein the antibody is administered in combination with an antibody which binds to human PD-L1;

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

1. a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
2. a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
3. a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
4. a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
5. a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
6. and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

1. a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
2. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
3. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
4. a heavy chain variable domain VH of SEQ ID NO:95, or
5. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
6. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
7. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
8. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
9. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
10. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
11. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
12. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
13. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
14. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
15. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
16. a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

The invention further comprises 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, wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

1. a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
2. a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or
3. a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or
4. a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or
5. a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;
6. and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

1. a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
2. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
3. a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
4. a heavy chain variable domain VH of SEQ ID NO:95, or
[0080]  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

[0081]  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

[0082]  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

[0083]  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

[0084]  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

[0085]  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

[0086]  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

[0087]  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

[0088]  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

[0089]  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

[0090]  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

[0091]  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

[0092]  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

[0093]  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

[0094]  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

[0095]  p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0096]  In one embodiment the antibodies are of human IgG1 subclass or human IgG4 subclass.

[0097]  The invention further comprises:

[0098]  A) a method for

[0099]  i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;

[0100]  ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;

[0101]  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

[0102]  iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;

[0103]  wherein an antibody which binds to human CSF-1R, is administered in combination with an antibody which binds to human PD-L1,

[0104]  or

[0105]  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,

[0106]  wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0107]  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

[0108]  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

[0109]  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

[0110]  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

[0111]  e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0112]  and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0113]  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

[0114]  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

[0115]  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

[0116]  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

[0117]  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

[0118]  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

[0119]  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

[0120]  h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VH of SEQ ID NO:99, or

[0121]  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
[0122] 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
[0123] 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
[0124] l) a heavy chain variable domain VH pf SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
[0125] 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
[0126] 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
[0127] 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
[0128] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VH of SEQ ID NO:107.

[0129] 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 (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).

[0130] The invention comprises the combination treatment if 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 issue) 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 CSR-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 CSR-1R ligand level, wherein, the increase is at least about 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5, 9.5, 10.5, 15.5, 20.5, 25.5, 30.5, 35.5, 40.5, 45.5, 50.5, 60.5, 70.5, 75.5, 80.5, 90.5, 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.

[0131] 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

[0132] 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 CTo Viability Assay (CellTiterGlo® Pro-mega). Calculation of % cell viability: RLU signals from treated cells divided by RLU signal from untreated control without antibody. (n=4).

[0133] 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 (MFI); 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±SEM; n=5).

[0134] FIG 2a-d CSF-1 levels in Cynomolgus monkey after application of different dosages of anti-CSF-1R antibody hMab 2F11-e7.

[0135] 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-cultures 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 CFSElow dividing cells. One representative experiment out of two is depicted as mean±SEM of triplicate wells.

[0136] 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).

[0137] 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

[0138] 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) 251-257).

[0139] 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 is consistent with published hypothesis 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 in necrotic cells and necrotic tumor areas.

[0140] The subtype and marker expression of different macrophage subpopulations is linked with their functional state. M2 macrophages can support tumorgenesis by:

[0141] a) enhancing angiogenesis via the secretion of angiogenic factors such as VEGF or bFGF,

[0142] 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),

[0143] 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).


[0145] 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 (De Nardo, D., et al., Cancer Discovery 1 (2011) 54-67).

[0146] 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 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-1R dependent macrophage signature by gene expression profiling. In breast cancer and leiomyosarcoma patient tumors this CSF-1 response gene signature predicts poor prognosis (Espinsona, I. et al., Am. J. Pathol. 6 (2009) 2347-2356; Beck, A. et al., Clin. Cancer Res. 3 (2009) 778-787).

[0147] 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-24 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, T. et al., J. Biol. Chem. 286 (2011) 952-960).

[0148] 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, E. 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 (Chambres, S., Future Oncol 5 (2009) 1429-1440).

[0149] Preclinical models provide validation of CSF-1R as an oncology target. Blockade of 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 (DeMardo, D. et al., Cancer Discovery 1 (2011) 54-67).


[0151] 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) 540-552. In that publication, it was shown that CSF-1R has transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 869 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee, P. S., et al., Enbio. J. 18 (1999) 3616-3628).

[0152] 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 (CSF1R-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 extracellular5 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 MGSQPGVILL LLVATAW1GQG (SEQ ID NO: 67). The human CSF-1R fragment D4-D3 (SEQ ID NO: 85) comprises the respective subdomains D4-D3.

[0153] 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).

[0154] 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).

[0155] The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of hematopoietic precursors to the macrophage lineage (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).

[0156] 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 fns-like cytokine receptor (FLT3). In spite of the structural homology among this family of growth factor receptors, they have distinct tissues-specific functions.

[0157] CSF-1R is mainly expressed on cells of the monocyte 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.

[0158] 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 1.0x10^-9 mol/l or lower, in one embodiment of a KD-value of 1.0x10^-10 mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BLAcore®, 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 1.0x10^-8 mol/l or lower (in one embodiment 1.0x10^-9 mol/l or lower, in one embodiment of a KD 1.0x10^-9 mol/l or lower (in one embodiment 1.0x10^-9 mol/l or lower).

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


[0160] 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); Boettiger 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 Δex3, 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 Δex3 variants 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).


PD-1 signaling typically has a greater effect on cytokine production than on cellular proliferation, with significant effects on IFN-gamma, TNF-alpha and IL-2 production. PD-1 mediate 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)].

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 Waldenstrom’s macroglobulinemia was not found to upregulate MCH II or B7 constitutive molecules, such cells did produce greater amount of proinflammatory cytokines, particularly TNF-alpha 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).

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”). Kuiper et al., Eur. J. Immunol. 36: 2472-82 (2006). This sPD-1 inhibited DC activation and increased IL-10 productions, in a manner reversible through administration of anti-PD-1.

Additionally, several studies show a receptor for PD-L1 or PD-2 that is independent of PD-1. B7.1 has already been identified as a binding partner for PD-L-1. 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.

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.

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.

The term “human PD-L1” refers to the human protein PD-L1 (SEQ ID NO: 88, PD-L1 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 1.0x10^-8 mol/l or lower, in one embodiment of a KD-value of 1.0x10^-9 mol/l or lower. The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (BLAcore®, 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 1.0x10^-8 mol/l or lower (in one embodiment 1.0x10^-8 mol/l-1.0x10^-13 mol/l), in one embodiment of a KD 1.0x10^-8 mol/l or lower (in one embodiment 1.0x10^-8 mol/l-1.0x10^-13 mol/l).

[0170] 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-c7
- hMab 2F11-e7
- hMab 2F11-d8
- hMab 2F11-g1.

[0171] These antibodies are described in WO2011/070024 and are characterized in comprising the following VH and VL sequences as described herein:

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-CSF-1R antibody</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>hMab 2F11-c11</td>
</tr>
<tr>
<td>hMab 2F11-d8</td>
</tr>
<tr>
<td>hMab 2F11-c7</td>
</tr>
<tr>
<td>hMab 2F11-e7</td>
</tr>
<tr>
<td>hMab 2F11-f12</td>
</tr>
</tbody>
</table>

[0172] 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:

- 243.55.870
- 243.55.111
- 243.55.112
- 243.55.117
- 243.55.179
- 243.55.180
- 243.55.181
- 243.55.182
- 243.55.183
- 243.55.184

[0173] 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>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-PD-L1 antibody</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>243.55.870</td>
</tr>
<tr>
<td>243.55.111</td>
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<tr>
<td>243.55.112</td>
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<tr>
<td>243.55.117</td>
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<td>243.55.179</td>
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<td>243.55.188</td>
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<tr>
<td>243.55.189</td>
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<tr>
<td>243.55.190</td>
</tr>
</tbody>
</table>

[0176] 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:

- a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40,
- b a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32,
- c a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40,
- d a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48,
- e a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0182] 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,
- b a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93,
- c a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94,
- d a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95,
- e a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96,
- f a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97,
- g a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98,
- h a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99,
- i a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100,
- j a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101,
- k a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102,
- l a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103,
- m a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104,
- n a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105,
(0197) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or

(0198) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

(0199) In one embodiment the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

(0200) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24.

(0201) In one embodiment the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

(0202) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32.

(0203) In one embodiment the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

(0204) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40.

(0205) In one embodiment the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

(0206) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48.

(0207) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0208) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92.

(0209) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0210) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93.

(0211) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0212) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94.

(0213) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0214) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95.

(0215) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0216) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96.

(0217) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0218) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97.

(0219) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0220) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98.

(0221) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0222) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99.

(0223) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0224) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100.

(0225) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0226) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101.

(0227) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0228) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102.

(0229) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0230) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103.

(0231) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0232) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104.

(0233) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0234) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105.

(0235) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0236) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106.

(0237) In one embodiment the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

(0238) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.
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.

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.

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.

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 amino acid domains 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”.

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.

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).

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 into 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, Clq binding and Fc receptor binding. Complement activation (CDC) is initiated by binding of complement factor Clq 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 Clq 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 Clq and C3 binding, whereas IgG4 do not activate the complement system and do not bind Clq and C3.

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 mutation on S228P). In one preferred embodiment the human heavy chain constant regions 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 235A), 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 S228). 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 from the group comprising (consisting of) L234A/L235A, L234A/L235A/P329G, N297A and D265A/N297A.

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

In one preferred embodiment the antibodies 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.

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.

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.

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

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:


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 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.

The second mechanism is based on blocking signaling thorough 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 release by tumor cells and stroma induces the differentiation of hematopoietic myeloid monocyte progenitors to mature osteoclasts in collaboration with the receptor myeloid 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) 257-265). 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 diseases 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 osteoblastic 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 (Choueri, M. B., et al., Cancer Metastasis Rev. 25 (2006) 601-609; Vessella, R. L. and Carey, E., Clin. Cancer Res. 12 (20 Pt 2) (2006) 6285s-6290s).

The third mechanism is based on the recent observation that tumor associated macrophages (TAM) found in solid tumors of the breast, prostate, ovariun 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 TNP 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 MC/7 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).

0260] 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 and progression of chronic diseases 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, HIVX for Kaposi’s sarcoma, endometriosis for ovarian cancer and psoriasis 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 scale are M2 macrophages involved in Type 2 reactions that promote cell proliferation, tune inflammation and adaptive immunity ad promote tissue remodeling, angiogenesis and repair (Mantovanii, A., et al., Trends Immunol. 25 (2004) 677-686). Chronic inflammation resulting in epithelial 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 inflammatory and hemorragheic 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.

0261] Thus, one embodiment of the invention are the CSF-1R antibodies described herein in 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, bronchioalviolar 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, astrocytomias, schwannomas, epemydymas, maleloblastomias, menin- gomas, squamous cell carcinomas, pineal gland 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 cancers 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, psiratic arthritis, osteoarthritis, inflammatory arthritis, and inflammation.


0263] 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.

0264] 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 anti-body 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).

[0265] 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 sequestrone 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.

[0266] 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 effect 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 increase the risk of osteoporosis-related fractures (Stoch, S. A., et al., J. Clin. Endocrinol. Metab. 86 (2001) 2787-2791).

[0267] Targeted inhibition of CSF-1R signaling is likely to be beneficial in other indications as well when targets cell types includes osteoclast and macrophages e.g. treatment of specific complications in response to joint replacement as a consequence of rheumatoid arthritis. Implant failure due to peri-prosthetic 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 peri-prosthetic osteolysis (Drees, P., et al., Natl. Clin. Pract. Rheumatoid. 3 (2007) 165-171).

[0268] Glucocorticoid-induced osteoporosis (GIOP) is another indication on which a CSF-1R inhibitor could prevent bone loss after longterm glucocorticosteroid use that is given as a result of various conditions among those chronic obstructive pulmonary disease, asthma and rheuma-toid arthritis (Guzman-Clark, J. R. et al., Arthritis Rheum. 57 (2007) 140-146; Feldstein, A. C., et al., Osteoporosis. Int. 16 (2005) 2168-2174).

[0269] Rheumatoid arthritis, psoriatic arthritis and inflammatory arthridities 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 (Richlin, C. T., et al., J. Clin. Invest. 111 (2003) 821-8310). 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, J. K., et al., J. Lenkoc. 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 pathogenies 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.


[0271] 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 neuroprotective 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).

[0272] 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.

[0273] Thus another embodiment of the invention are the CSF-1R antibodies being characterized by the above men-
tioned 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 arthritis, and inflammation.

[0274] 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 fragment 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.

[0275] 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.

[0276] 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 fragment for the prevention or treatment of metastasis.

[0277] 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.

[0278] 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.

[0279] 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.

[0280] 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 antibody or alternatively for the manufacture of a medicament for the combination treatment of cancer with an anti-PD-L1 antibody as described herein.

[0281] 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.

[0282] 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 sequence 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.

[0283] 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 disease 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.

[0284] 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 fragment 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.

[0285] The invention comprises the use of an antibody characterized 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 (or use in stimulating an immune response or function, such as T cell activity in combination with an anti-PD-L1 antibody as described herein.

[0286] 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

[0287] a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, and

[0288] the antibody which binds to human PD-L1 used in such combination treatments is characterized in comprising

[0289] a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92.

[0290] 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 \textit{E. coli} cells, and the antibody is recovered from the cells (from the supernatant or after cells lysis).


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. \textit{Current Protocols in Molecular Biology}, Greene Publishing and Wiley Interscience, New York (1987).


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.

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.

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 effects 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.

The monoclonal antibodies are suitable 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.

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 “transform 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.

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.

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.

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.

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 substance is known in the art. In addition to water, the carrier can be, for example, an isotonic buffered saline solution.

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.

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 excre-
tion 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] 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.

[0309] 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.

[0310] 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.

[0311] In addition to the anti-CSF-1R antibody in combination with the anti-PD-L1 antibody also a chemotherapeutic agent can be administered.

[0312] 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™ (temozolomide), ethylenimines/methyleneimine such as thiethylmenelamine (TEM), triethylenemelamine (THAM), hexamethylmethyleneimine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC), antimetabolites including folate acid analogs such as methotrexate and trimetrexate, pyrimidine analogs such as 5-fluorouracil (5FU), fluorodeoxyuridin, gemcitabine, cytosine arabinoside (AraC, cytarbine), 5-azaeadine, 2,2'-difluorodeoxyctydin, purine analogs such as 6-merca.rho. topurine, 6-thioguanine, azathioprine, T-deoxycysteamine (pentostatin), erthrodihydroxyomaleoneladein (EHN), fludara- bine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2-Cda); natural products including antimiotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorebline, taxotere, estramustine, and estramustine phosphate; pipodophytoxins such as etopside and teniposide; antibiotics such as actinomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleom- ycin, 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, anthropoecines such as mitoxantrone, substituted urea such as hydroxyurea, methylhydrazine derivatives including N-methylhydrazine (MIH) and procarbazone, 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, medroxyprogestosterone acetate and mege- strol acetate; estrogen such as diethylstilbestrol and ethyl estradiol equivalents; antiestrogen such as tamoxifen; androgens such as flutamide, gondadotropin-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 (e.g., paclitaxel (Taxol), docetaxel (Taxotere), modified paclitaxel (e.g., Abraxane and Opaxio), doxorubicin, sunitinib (Sutent), sorafenib ( Nexavar), and other multit kinase inhibitors, oxaliplatin, cisplatin and carboplatin, etoposide, gemcitabine, and vinblastine. In one embodiment the chemotherapeutic agent is selected from the group consisting of taxanes (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).

[0313] 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 (Hycantin) 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.

[0314] 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.

[0315] In one embodiment the CSF-1R antibody/PD-L1 antibody combination therapy is no chemotherapeutic agents are administered.

[0316] The invention comprises also a method for the treatment of a patient suffering from such disease.

[0317] 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.

[0318] 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.

[0319] 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.

[0320] 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**

[0321] SEQ ID NO: 1 heavy chain CDR3, hMab 2F11
[0322] SEQ ID NO: 2 heavy chain CDR2, hMab 2F11
[0323] SEQ ID NO: 3 heavy chain CDR1, hMab 2F11
[0324] SEQ ID NO: 4 light chain CDR3, hMab 2F11
[0325] SEQ ID NO: 5 light chain CDR2, hMab 2F11
[0326] SEQ ID NO: 6 light chain CDR1, hMab 2F11
[0327] SEQ ID NO: 7 heavy chain variable domain, hMab 2F11
[0328] SEQ ID NO: 8 light chain variable domain, hMab 2F11
[0329] SEQ ID NO: 9 heavy chain CDR3, hMab 2E10
[0330] SEQ ID NO: 10 heavy chain CDR2, hMab 2E10
[0331] SEQ ID NO: 11 heavy chain CDR1, hMab 2E10
[0332] SEQ ID NO: 12 light chain CDR3, hMab 2E10
[0333] SEQ ID NO: 13 light chain CDR2, hMab 2E10
[0334] SEQ ID NO: 14 light chain CDR1, hMab 2E10
[0335] SEQ ID NO: 15 heavy chain variable domain, hMab 2E10
[0336] SEQ ID NO: 16 light chain variable domain, hMab 2E10
[0337] SEQ ID NO: 17 heavy chain CDR3, hMab 2F11-c11
[0338] SEQ ID NO: 18 heavy chain CDR2, hMab 2F11-c11
[0339] SEQ ID NO: 19 heavy chain CDR1, hMab 2F11-c11
[0340] SEQ ID NO: 20 light chain CDR3, hMab 2F11-c11
[0341] SEQ ID NO: 21 light chain CDR2, hMab 2F11-c11
[0342] SEQ ID NO: 22 light chain CDR1, hMab 2F11-c11
[0343] SEQ ID NO: 23 heavy chain variable domain, hMab 2F11-c11
[0344] SEQ ID NO: 24 light chain variable domain, hMab 2F11-c11
[0345] SEQ ID NO: 25 heavy chain CDR3, hMab 2F11-d8
[0346] SEQ ID NO: 26 heavy chain CDR2, hMab 2F11-d8
[0347] SEQ ID NO: 27 heavy chain CDR1, hMab 2F11-d8
[0348] SEQ ID NO: 28 light chain CDR3, hMab 2F11-d8
[0349] SEQ ID NO: 29 light chain CDR2, hMab 2F11-d8
[0350] SEQ ID NO: 30 light chain CDR1, hMab 2F11-d8
[0351] SEQ ID NO: 31 heavy chain variable domain, hMab 2F11-d8
[0352] SEQ ID NO: 32 light chain variable domain, hMab 2F11-d8
[0353] SEQ ID NO: 33 heavy chain CDR3, hMab 2F11-e7
[0354] SEQ ID NO: 34 heavy chain CDR2, hMab 2F11-e7
[0355] SEQ ID NO: 35 heavy chain CDR1, hMab 2F11-e7
[0356] SEQ ID NO: 36 light chain CDR3, hMab 2F11-e7
[0357] SEQ ID NO: 37 light chain CDR2, hMab 2F11-e7
[0358] SEQ ID NO: 38 light chain CDR1, hMab 2F11-e7
[0359] SEQ ID NO: 39 heavy chain variable domain, hMab 2F11-e7
[0360] SEQ ID NO: 40 light chain variable domain, hMab 2F11-e7
[0361] SEQ ID NO: 41 heavy chain CDR3, hMab 2F11-f12
[0362] SEQ ID NO: 42 heavy chain CDR2, hMab 2F11-f12
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[0363] SEQ ID NO: 43 heavy chain CDR1, hMab 2F11-f12
[0364] SEQ ID NO: 44 light chain CDR3, hMab 2F11-f12
[0365] SEQ ID NO: 45 light chain CDR2, hMab sF11-f12
[0366] SEQ ID NO: 46 light chain CDR1, hMab 2F11-f12
[0367] SEQ ID NO: 47 heavy chain variable domain, hMab 2F11-f12
[0368] SEQ ID NO: 48 light chain variable domain, hMab 2F11-f12
[0369] SEQ ID NO: 49 heavy chain CDR3, hMab 2F11-g1
[0370] SEQ ID NO: 50 heavy chain CDR2, hMab 2F11-g1
[0371] SEQ ID NO: 51 heavy chain CDR1, hMab 2F11-g1
[0372] SEQ ID NO: 52 light chain CDR3, hMab 2F11-g1
[0373] SEQ ID NO: 53 light chain CDR2, hMab 2F11-g1
[0374] SEQ ID NO: 54 light chain CDR1, hMab 2F11-g1
[0375] SEQ ID NO: 55 heavy chain variable domain, hMab 2F11-g1
[0376] SEQ ID NO: 56 light chain variable domain, hMab 2F11-g1
[0377] SEQ ID NO: 57 human kappa light chain constant region
[0378] SEQ ID NO: 58 human heavy chain constant region derived from IgG1
[0379] SEQ ID NO: 59 human heavy chain constant region derived from IgG1 mutated on L234A and L235A
[0380] SEQ ID NO: 60 human heavy chain constant region derived from IgG4
[0381] SEQ ID NO: 61 human heavy chain constant region derived from IgG4 mutated on S228P
[0382] SEQ ID NO: 62 human wildtype CSF-1R (wt CSF-1R) (including signal sequence)
[0383] SEQ ID NO: 63 human mutant CSF-1R L301S Y969F (including signal sequence)
[0384] SEQ ID NO: 64 human CSF-1R Extracellular Domain (domains D1-D5)
[0385] SEQ ID NO: 65 human CSF-1R fragment domains D1-D5
[0386] SEQ ID NO: 66 human CSF-1R fragment domains D1-D3
[0387] SEQ ID NO: 67 signal peptide
[0388] SEQ ID NO: 68 Primer
[0389] SEQ ID NO: 69 heavy chain CDR3, Mab 1G10
[0390] SEQ ID NO: 70 heavy chain CDR3, Mab 1G10
[0391] SEQ ID NO: 71 heavy chain CDR1, Mab 1G10
[0392] SEQ ID NO: 72 light chain CDR3, Mab 1G10
[0393] SEQ ID NO: 73 light chain CDR2, Mab 1G10
[0394] SEQ ID NO: 74 light chain CDR1, Mab 1G10
[0395] SEQ ID NO: 75 heavy chain variable domain, Mab 1G10
[0396] SEQ ID NO: 76 light chain variable domain, Mab 1G10
[0397] SEQ ID NO: 77 heavy chain CDR3, Mab 2H7
[0398] SEQ ID NO: 78 heavy chain CDR2, Mab 2H7
[0399] SEQ ID NO: 79 heavy chain CDR1, Mab 2H7
[0400] SEQ ID NO: 80 light chain CDR3, Mab 2H7
[0401] SEQ ID NO: 81 light chain CDR2, Mab 2H7
[0402] SEQ ID NO: 82 light chain CDR1, Mab 2H7
[0403] SEQ ID NO: 83 heavy chain variable domain, Mab 2H7
[0404] SEQ ID NO: 84 light chain variable domain, Mab 2H7
[0405] SEQ ID NO: 85 human CSF-1R fragment domains D4-D5
[0406] SEQ ID NO: 86 human CSF-1R (including signal sequence)

In the Following Embodiment of the Invention are Described:

[0407] SEQ ID NO: 87 human IL-34 (including signal sequence)
[0408] SEQ ID NO: 88 human PD-L1 (including signal sequence)
[0409] SEQ ID NO: 89 heavy chain variable domain VH variant 1, anti-PD-L1 243.55
[0410] SEQ ID NO: 90 heavy chain variable domain VH variant 2, anti-PD-L1 243.55
[0411] SEQ ID NO: 91 heavy chain variable domain VH variant 3, anti-PD-L1 243.55
[0412] SEQ ID NO: 92 light chain variable domain VL variant 1, anti-PD-L1 243.55
[0413] SEQ ID NO: 93 light chain variable domain VL variant 2, anti-PD-L1 243.55
[0414] SEQ ID NO: 94 light chain variable domain VL variant 3, anti-PD-L1 243.55
[0415] SEQ ID NO: 95 light chain variable domain VL variant 4, anti-PD-L1 243.55
[0416] SEQ ID NO: 96 light chain variable domain VL variant 5, anti-PD-L1 243.55
[0417] SEQ ID NO: 97 light chain variable domain VL variant 6, anti-PD-L1 243.55
[0418] SEQ ID NO: 98 light chain variable domain VL variant 7, anti-PD-L1 243.55
[0419] SEQ ID NO: 99 light chain variable domain VL variant 8, anti-PD-L1 243.55
[0420] SEQ ID NO: 100 light chain variable domain VL variant 9, anti-PD-L1 243.55
[0421] SEQ ID NO: 101 light chain variable domain VL variant 10, anti-PD-L1 243.55
[0422] SEQ ID NO: 102 light chain variable domain VL variant 11, anti-PD-L1 243.55
[0423] SEQ ID NO: 103 light chain variable domain VL variant 12, anti-PD-L1 243.55
[0424] SEQ ID NO: 104 light chain variable domain VL variant 13, anti-PD-L1 243.55
[0425] SEQ ID NO: 105 light chain variable domain VL variant 14, anti-PD-L1 243.55
[0426] SEQ ID NO: 106 light chain variable domain VL variant 15, anti-PD-L1 243.55

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 one 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

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 disease, 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.
cell activity, wherein the antibody is administered in combination with an antibody which binds to human PD-L1;

[0430] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0431] 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

[0432] 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

[0433] c) 1 heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

[0434] a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

[0435] a) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0436] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0437] 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

[0438] 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

[0439] c) a heavy chain variable domain VH of SEQ ID NO:99 and a light chain variable domain VL of SEQ ID NO:97, or

[0440] a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

[0441] e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:91, or

[0442] f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

[0443] g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

[0444] h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

[0445] i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:92, or

[0446] j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

[0447] k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

[0448] 1) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

[0449] 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

[0450] 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

[0451] 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

[0452] p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0453] 2. Use of a combination of

[0454] A) an antibody which binds to human CSF-1R, comprising

[0455] 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

[0456] 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

[0457] 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

[0458] 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

[0459] e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0460] and

[0461] B) an antibody which binds to human PD-L1 comprising

[0462] 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

[0463] 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

[0464] 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

[0465] 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

[0466] 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

[0467] 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

[0468] 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

[0469] 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

[0470] 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

[0471] 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

[0472] 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
[0473] 1) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
[0474]   a) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
[0475]   b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
[0476]   c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
[0477]   d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:107.

[0478] 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.

[0479] 3. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of cancer.


[0481] 5. The antibody or use according to any one of embodiments 1 or 2, for use in the prevention or treatment of metastasis.

[0482] 6. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of bone loss.

[0483] 7. The antibody or use according to any one of embodiments 1 or 2, for use in the treatment of inflammatory diseases.

[0484] 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.

[0485] 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.

[0486] 10. A) An antibody which binds to human CFS-1R wherein the antibody is administered in combination with an antibody which binds to human PD-L1 for use in

[0487]   i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1 expressing tumor cells;
[0488]   ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
[0489]   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
[0490]   iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;

[0491] or

[0492] B) use of an antibody which binds to human CSF-1R for the manufacture of a medicament for use in

[0493]   i) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R expressing tumor cells;
[0494]   ii) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate;
[0495]   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
[0496]   iv) the inhibition of cell differentiation (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages,

[0497] wherein the antibody is administered in combination with an antibody which binds to human PD-L1;

[0498] wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0499]   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
[0500]   b) a heavy chain variable domain VH of SEQ ID NO:32 and a light chain variable domain VL of SEQ ID NO:32, or
[0501]   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
[0502]   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
[0503]   e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0504] and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0505]   a) a heavy chain variable domain VH of SEQ ID NO:89 and light chain variable domain VL of SEQ ID NO:92, or
[0506]   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
[0507]   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
[0508]   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
[0509]   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
[0510]   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
[0511]   g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VH of SEQ ID NO:98, or
[0512]  b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
[0513]  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
[0514]  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
[0515]  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
[0516]  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
[0517]  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
[0518]  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
[0519]  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
[0520]  p) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:107.

[0521]  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, or

[0522]  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,

[0523]  wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0524]  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
[0525]  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
[0526]  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
[0527]  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
[0528]  e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

[0529]  and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0530]  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
[0531]  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
[0532]  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
[0533]  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
[0534]  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
[0535]  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
[0536]  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
[0537]  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
[0538]  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
[0539]  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
[0540]  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
[0541]  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
[0542]  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
[0543]  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
[0544]  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
[0545]  p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

[0546]  12. The antibody or use according any one of the preceding embodiments,

[0547]  wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

[0548]  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
[0549]  and wherein the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

[0550]  a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VH of SEQ ID NO:92.
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.

14. The antibody or use according to any one of the preceding embodiments, characterized in that said antibodies have reduced or minimal effector function.

15. The antibody or use according to any one of the preceding embodiments, wherein the minimal effector function results from an effectorless Fe mutation.

16. The antibody or use according to any one of the preceding embodiments, wherein the effectorless Fe mutation is L254A/L255A or L234A/L235A/P329G or N297A or D265A/N297A.

17. A method for

1) the inhibition of cell proliferation in CSF-1R ligand-dependent and/or CSF-1R ligand-independent CSF-1R expressing tumor cells;

2) the inhibition of cell proliferation of tumors with CSF-1R ligand-dependent and/or CSF-1R, ligand-independent CSF-1R expressing macrophage infiltrate;

3) the inhibition of cell survival (in CSF-1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes and macrophages; and/or

4) the inhibition of cell differentiation (in CSF1R ligand-dependent and/or CSF-1R ligand-independent) CSF-1R expressing monocytes into macrophages;

wherein an antibody which binds to human CSF-1R, is administered in combination with an antibody which binds to human PD-L1.

or

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.

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

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

2) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

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

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

5) 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

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

7) 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

8) 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

9) 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

10) 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

11) 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

12) g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VH of SEQ ID NO:98, or

13) 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

14) 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

15) 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

16) 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

17) 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

18) 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

19) 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

20) 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

21) 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-Induced CSF-1R Phosphorylation in NIH3T3-CSF-1R Recombinant Cells

4.5x10^5 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, 1x nonessential amino acids, 10% FBS (PAA, Cat. No. A15-649) and 100 μg/ml Pen/Strep (Sigma, Cat. No. P4333 [10 mg/ml]) until they reached confluence. Thereafter cells were washed with serum-free DMEM media (PAA Cat. No. E15-011) supplemented with sodium selenite [5 μg/ml] (Sigma, Cat. No. S9133), transferring [10 μg/ml] (Sigma, Cat. No. T8158), BSA [400 μg/ml] (Roche Diagnosis GmbH, Cat. No. 10753078), 4 mM L-glutamine (Sigma,
Cat. No. G7513), 2 mM sodium pyruvate (Gibco, Cat. No. 11360), 1x nonessential amino acids (Gibco, Cat: 11410-035), 2-mercaptoethanol [0.5 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 nm/μl 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 if 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/l protease inhibitor tablet (Roche Diagnostics GmbH Cat. No. 1836 170) per 10 ml buffer/10 μl/ml phosphatase inhibitor cocktail 1 (Sigma Cat. No. P-2850, 100x Stock)/10 μl/ml protease inhibitor 1 (Sigma Cat. No. P-5726, 100x Stock)/10 μl/ml 1 M NaF) was added. After 30 minutes on ice the plates were shaken vigorously on a plate shaker for 3 minutes and then centrifuged 10 minutes at 2200 rpm (Heraeus Megafuge 10).

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 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

<table>
<thead>
<tr>
<th>CSF-1R Mab</th>
<th>Phosphorylation IC50 [μg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mab 2F11</td>
<td>219.4</td>
</tr>
<tr>
<td>Mab 2E10</td>
<td>752.0</td>
</tr>
<tr>
<td>Mab 2H7</td>
<td>703.4</td>
</tr>
<tr>
<td>Mab 2H7</td>
<td>56.6</td>
</tr>
<tr>
<td>SC-2-4A5</td>
<td>1006.6</td>
</tr>
</tbody>
</table>

**Example 3**

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

**Example 2**

**Growth Inhibitors of NIH3T3-CSF-1R**

Recombinant Cells in 3D Culture Under Treatment with anti-CSF-1R Monoclonal Antibodies (CellTiterGlo-Assay)

**Table 4**

<table>
<thead>
<tr>
<th>CSF-1R Mab</th>
<th>wtCSF-1R IC50 [μg/ml]</th>
<th>Mutant CSF-1R IC50 [μg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMab 2F11</td>
<td>4.9</td>
<td>0.54</td>
</tr>
<tr>
<td>1.2-SM</td>
<td>1.19</td>
<td>&gt;20 μg/ml (&gt;19% inhibition at 20 μg/ml)</td>
</tr>
<tr>
<td>CXIIG6</td>
<td>&gt;20 μg/ml (21% inhibition at 20 μg/ml)</td>
<td>&gt;20 μg/ml (36% stimulation)</td>
</tr>
<tr>
<td>ab10676</td>
<td>14.15</td>
<td>&gt;20 μg/ml (0% inhibition at 20 μg/ml)</td>
</tr>
<tr>
<td>SC 2-4A5</td>
<td>16.62</td>
<td>2.56</td>
</tr>
</tbody>
</table>

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

**Example 3**

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 (2x10^3 cells/well) in 100 μl RPMI 1640 (Gibco—Cat. No. 31870) supplemented with 10% FCS (GIBCO—Cat. No. 011-0980014M), 4 mM L-glutamine (GIBCO—Cat. No. 25030 and 1x PenStrep (Roche Cat. No. 1074 440) at 3720 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 to 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 below), survival of monocytes by antibody treatment, an IC₅₀ was calculated (see Table below).

### Table 5

<table>
<thead>
<tr>
<th>CSF-1R Mab</th>
<th>IC₅₀ [µg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mab 2F11</td>
<td>0.08</td>
</tr>
<tr>
<td>Mab 2E10</td>
<td>0.06</td>
</tr>
<tr>
<td>Mab 2H7</td>
<td>0.03</td>
</tr>
<tr>
<td>Mab 1G10</td>
<td>0.06</td>
</tr>
<tr>
<td>SC 2-4A5</td>
<td>0.36</td>
</tr>
</tbody>
</table>

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

**Example 4**

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

**Example 5**

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

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 microtiters-plates (2.5x10⁵ cells/well) in 100 µl RPMI 1640 (Gibco—Cat. No. 31870) supplemented with 10% FCS (GIBCO—Cat. No. 011-090014M), 4 mM L-glutamine (GIBCO—Cat. No. 25030) and 1x PenStrep (Roche Cat. No. 1074 440) at 37°C and 5% CO₂ in a humidified atmosphere. When 100 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 antibody. 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 2F11, e.g. hMab 2F11-c11, hMab 2F11-d8, hMab 2F11-e7, hMab 2F11-f12, showed IC₅₀ values of 0.07 µg/ml (hMab 2F11-c11), 0.07 µg/ml (hMab 2F11-d8), 0.04 µg/ml (hMab 2F11-e7) and 0.09 µg/ml (hMab 2F11-f12).

**Example 6**

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

Serum CSF-1 levels provide a pharmacodynamic markers 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 0 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.

**Example 7**

Administration hMab 2F11-e7 induced a dramatic increase in CSF-1 by ~1000-fold, which depending on the dose administered lasted for 47 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-CSF1R Antibody and a T Cell Engaging Agents

[0597] 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

[0598] 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 by the manufacturer. Finally, TAMs were isolated by adding anti-Ly6G and anti-Ly6C positive selection beads in order to remove granulocytic and monocyteic cells from TAM preparations. Final cell purity was analyzed and was usually ~90%. Subsequently, TAMs 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 Shero 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

[0599] 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 cells, the final titer was adjusted to 1×10^7 cells/ml. Subsequently, 100 μl of this suspension (1×10^7 cells) were inoculated subcutaneously into 7-9 weeks old female C57BL/6N mice (obtained from Charles River, Sulzfeld, Germany), 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., 6xq3d) started after tumors were established and had reached an average size of 100 mm^3.

Tumor volume was measured twice a week and animal weights were monitored in parallel.

[0600] In first experiment monotherapy with <mouse CSF1R> antibody did not inhibit primary tumor growth when compared to control antibody treatment (TGI: 0%, TCR: 107 CI: 0.80-1.43, median time to progression >700mm³: 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).

[0601] 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>
<thead>
<tr>
<th>Group</th>
<th>TGI (day 21)</th>
<th>TCR (day 12)</th>
<th>95% CI</th>
<th>Median time to progression (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Mouse IgG1)</td>
<td>0%</td>
<td>1.07</td>
<td>(1.43-0.80)</td>
<td>21</td>
</tr>
<tr>
<td>&lt;mouse CSF1R&gt;</td>
<td>83%</td>
<td>0.27</td>
<td>(0.49-0.09)</td>
<td>32</td>
</tr>
<tr>
<td>&lt;anti-PD-L1&gt;</td>
<td>83%</td>
<td>0.28</td>
<td>(0.51-0.09)</td>
<td>37</td>
</tr>
</tbody>
</table>

[0602] 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-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>
<thead>
<tr>
<th>Group</th>
<th>TGI (day 21)</th>
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<tr>
<td>&lt;mouse CSF1R&gt;</td>
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<td>0.27</td>
<td>(0.49-0.09)</td>
<td>32</td>
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<tr>
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<td>(0.51-0.09)</td>
<td>37</td>
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</tbody>
</table>

[0603] 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

[0604] 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 1x10^6 cells/ml. Subsequently 100 μl of this suspension (1x10^6 cells) were inoculated subcutaneously into 11-13 weeks old female Balb/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 cross-reactive anti PD-L1 antibody (10 mg/kg i.p. 6x q3d) started after tumors were established and had reached an average size of 150 mm³. While treatment in monotherapy groups started in day 9 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 [0605] 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-CSF-1R>/<anti-PD-L1> antibody combination group.

[0606] 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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Gly Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met
50 55 60
Ser Arg Leu Ser Ile Arg Lys Asp Asn Ser Lys Ser Glu Val Phe Leu
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Lys Met Asn Arg Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Val
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Thr Val Ser Ser
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Gly Gly Ser Thr Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
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Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys

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Asp Pro Arg Leu Tyr Phe Asp

1 5

Val Ile Trp Thr Gly Gly Thr Asn Tyr Asn Ser Gly Phe Met Ser

1 5 10 15

Ser Phe Asp Ile Ser

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35 40 45
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50 55 60
Ser Arg Leu Arg Ile Thr Lys Asn Ser Lys Ser Gin Val Leu Leu
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FEATURE:
OTHER INFORMATION: heavy chain CDR1, hMab 2F11-c11

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FEATURE:
OTHER INFORMATION: light chain CDR1, hMab 2F11-c11

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FEATURE:
OTHER INFORMATION: light chain CDR1, hMab 2F11-c11

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ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: heavy chain variable domain, hMab 2F11-c11

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ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain CDR2, hMab 2F11-c11

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OTHER INFORMATION: heavy chain CDR2, hMab 2F11-c11

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OTHER INFORMATION: light chain CDR3, hMab 2F11-c11

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Arg Asp Glu Arg Leu Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
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Thr Val Ser Ser
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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
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<223> OTHER INFORMATION: heavy chain CDR2, hMab 2F11-d9
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Gly Gln Ser Phe Ser Tyr Pro Thr
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Gly Ala Ser Asn Arg Tyr Thr
1   5

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

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 Glu Glu Leu Glu Trp Met
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Gly Val Ile Trp Thr Asp Gly Ala Asn Tyr Ala Glu Lys Phe Gln
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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 Ala Gln Lys Leu Gln
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Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met
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Glu Leu Arg Ser Leu Arg Ser Asp Thr Ala Val Tyr Tyr Cys Ala
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Thr Val Ser Ser
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Tyr Ala Ala Ser Asn Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
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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 Glu Gin Gin Ser Phe Ser Tyr Pro Thr
85  90  95
Phe Gly Gin Gly Thr Lys Leu Glu Ile Lys
100 105

Amp Gln Arg Leu Tyr Phe Asp Val
1  5

Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met Ser
1  5  10  15
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SEQ ID NO 44
LENGTH: 7
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain CDR2, hMab 2F11-f12

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SEQ ID NO 45
LENGTH: 11
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain CDR1, hMab 2F11-f12

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SEQ ID NO 46
LENGTH: 116
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: heavy chain variable domain, hMab 2F11-f12

Arg Ala Ser Glu Asp Val Asn Thr Tyr Val Ser
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SEQ ID NO 47
LENGTH: 106
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain variable domain, hMab 2F11-f12

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Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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<210> SEQ ID NO 52
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Gly Gln Ser Phe Ser Tyr Pro Thr
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ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain CDR1, hMab 2F11-g1

SEQUENCE: 53

Gly Ala Ser Ser Arg Ala Thr

SEQ ID NO 54
LENGTH: 11
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain CDR1, hMab 2F11-g1

SEQUENCE: 54
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SEQ ID NO 55
LENGTH: 116
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain variable domain, hMab 2F11-g1

SEQUENCE: 55
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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
Asp Ile Ser Trp Ile Arg Gin Pro Pro Gly Lys Gly Leu Glu Trp Ile
Gly Val Ile Trp Thr Asp Gly Gly Thr Asn Tyr Asn Ser Pro Leu Lys
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gin Phe Ser Leu
Lys Leu Ser Ser Val Thr Ala Asp Thr Ala Val Tyr Cys Ala
Arg Asp Gin Arg Leu Tyr Phe Asp Val Trp Gly Gin Gly Thr Thr Val
Thr Val Ser Ser

SEQ ID NO 56
LENGTH: 106
TYPE: PRT
ORGANISM: Artificial
FEATURE:
OTHER INFORMATION: light chain variable domain, hMab 2F11-g1

SEQUENCE: 56
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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gin Ala Pro Arg Leu Leu Ile
Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
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Tyr Pro Arg Glu Ala Lys Val Glu Tyr Val Asp Ala Leu Glu
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50 55 60
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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Gly Val His Thr Phe Pro Ala Leu Val Gin Ser Gly Leu Tyr Ser
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Leu Ser Ser Val Val Thr Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80
Tyr Ile Cys Asn Val Asn His 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
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Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro
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<233> OTHER INFORMATION: human heavy chain constant region derived from IgG1 mutated on L234A and L235A

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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser 30 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 Pro Ser Ser Leu Gly Thr Glu 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 Pro Ser Val Phe Leu Phe Pro Pro 110 115 120 125
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys 130 135 140
Val Val Val Asp 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 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 Gin Pro Glu Asn
260 265 270
Asn Tyr Lys Thr Thr 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 Gin Gln Gly Asn
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<210> SEQ ID NO 60
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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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 Leu Gin Ser Ser Gly Lys Leu Tyr Ser
50  55  60
Leu 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 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 Gin Glu Asp Pro Glu Val Gin Phe Asn Trp Tyr Val Asp
145 150 155 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gin Phe
165 170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gin Asp
180 185 190
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-Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu 196 200 205
-Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Glu Pro Arg 210 215 220
-Glu Pro Glu Val Tyr Thr Leu Pro Ser Pro Ser Glu Glu Met Thr Lys 225 230 235 240
-Amn Glu 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 Glu Pro Glu Asn Asn Tyr Lys 260 265 270
-Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser 275 280 285
-Arg Leu Thr Val Asp Ser Arg Trp Gln Glu Gly Asn Val Phe Ser 290 295 300
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-Gly Val His Thr Phe Pro Ala Val Leu Glu Ser Gly Leu Tyr Ser 50 55 60
-Leu Ser Ser Val Val Val Pro Ser Ser Leu Lys Gly Thr Thr 65 70 75 80
-Tyr Thr Cys Asn Val Asp His 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 Pro Lys Pro Lys 115 120 125
-Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val 130 135 140
-Asp Val Ser Glu Asp Pro Glu Val Glu 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
-Amn 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
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<213> ORGANISM: Homo sapiens

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Glu Trp Asp Gly Pro Pro Ser Pro His Trp Thr Tyr Ser Asp Gly 50 55 60
Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gin 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
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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 Gin Ser Gin Asp Tyr Gin 165 170 175
Cys Ser Ala Leu Met Gly Gin Arg Lys Val Met Ser Ile Ser Ile Arg 180 185 190
Leu Lys Val Gin 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 Gin Ile Val Cys 210 215 220
Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Glu His Asn
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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 Leu Pro Cys Leu Leu Thr Asp 100 105 110
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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: signal peptide

<400> SEQUENCE: 67

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<212> TYPE: DNA
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<400> SEQUENCE: 68

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<210> SEQ ID NO 69
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<213> ORGANISM: Mus musculus

<400> SEQUENCE: 69

Asp Leu Arg Leu Tyr Phe Asp Val
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<210> SEQ ID NO 70
<211> LENGTH: 16
<212> TYPE: PRT
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Val Ile Trp Ser Gly Gly Gly Thr Asn Tyr Asn Ser Pro Phe Met Ser
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<210> SEQ ID NO 71
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<212> TYPE: PRT
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<400> SEQUENCE: 71

Gly Phe Ser Leu Thr Ser Tyr Asp Ile Ser
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<210> SEQ ID NO 72
<211> LENGTH: 8
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<400> SEQUENCE: 72

Gly Glu Ser Phe Thr Tyr Pro Thr
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<210> SEQ ID NO 73
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<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 73

Gly Ser Ser Asn Arg Tyr Thr
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<210> SEQ ID NO 74
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Lys Ala Ser Glu Asp Val Gly Thr Tyr Val Ser
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Arg Val Gln Leu Lys Gly Ser Gly Pro Gly Leu Val Ala Pro Ser Gin
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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 Thr Asn Tyr Asn Ser Pro Phe Met
50   55    60
Ser Arg Leu Arg Ile Ser Lys Asp Asp Ser Arg Ser Gin Val Phe Leu
65   70    75    80
Lys Val Asn Arg Leu Gln Thr Asp Thr Ala Ile Tyr Tyr Cys Val
95   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

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 Gin Asp Val Gly Thr Tyr
20   25    30
Val Ser Trp Tyr Gln Gln Lys Pro Glu Gin 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 Gin Ala
65   70    75    80
Glu Asp Leu Ala Asp Tyr Ser Cys Gly Gin Ser Phe Thr Tyr Pro Thr
85   90    95
Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys
100  105

Asp Pro Arg Leu Tyr Phe Asp Val
1    5
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  1  5 10 15

Gly Ser Ser Leu Asp Ser Phe Asp Ile Ser
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  <213> ORGANISM: Mus musculus
  <400> SEQUENCE: 79

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  <213> ORGANISM: Mus musculus
  <400> SEQUENCE: 80

Gly Ala Ser Asn Arg Tyr Thr
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Lys Ala Ser Glu Asp Val Val Thr Tyr Val Ser
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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 Gln Leu Glu Trp Leu
  35 40 45

Gly Val Ile Trp Thr 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
  65 70 75 80

Lys Met Ser Ser Leu Gln Ser Asp Thr Ala Ile Tyr Tyr Cys Val
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Arg Asp Pro Arg Leu Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val

Thr Val Ser Ser

100 105 110

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<400> SEQUENCE: 84

Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly

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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

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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

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<400> SEQUENCE: 85

Val Val Glu Ser Ala Tyr Leu Asn Leu Ser Ser Glu Gln Asn Leu Ile

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Gln Glu Val Thr Val Gly Gln Gly Leu Asn Leu Lys Val Met Val Glu

20 25 30

Ala Tyr Pro Gly Leu Gln Gly Phe Asn Thr Tyr Leu Gly Pro Phe

35 40 45

Ser Asp His Gln Pro Glu Pro Gly 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 Gln Gln 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 Glu Pro Asn Val Thr Trp Leu Gln Cys Ser Gly His Thr

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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
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<213> ORGANISM: homo sapiens
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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  Gln  Thr  Ser  Cys  Gln
50   55   60
Ile   Thr  Phe  Glu  Phe  Val  Asp  Gln  Glu  Glu  Leu  Lys  Asp  Pro  Val  Cys
65   70   75   80
Tyr   Leu  Lys  Lys  Ala  Phe  Leu  Val  Gln  Asp  Ile  Met  Gln  Asp  Thr
85   90   95
Met   Arg  Phe  Arg  Asp  Asn  Thr  Pro  Asn  Ala  Ile  Ala  Ile  Val  Glu  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  Asn  Val  Phe  Asn  Glu  Thr  Lys  Asn  Leu  Leu
145  150  155  160
Asp   Lys  Asp  Trp  Asn  Ile  Phe  Ser  Lys  Asn  Asn  Ser  Phe  Ala
165  170  175
Glu   Cys  Ser  Ser  Gln  Asp  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  Glu  Arg  Pro  Pro  Arg  Ser
245  250  255
Thr   Cys  Gln  Ser  Phe  Glu  Pro  Pro  Glu  Thr  Pro  Val  Lys  Asp  Ser
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<210> SEQ ID NO 87  
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<212> TYPE: PRT  
<213> ORGANISM: homo sapiens  
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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  
Gln Arg Ala Gln 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 Trp Ser Ser Pro Ser Ser Pro Pro
 210 215 220
His Ser Thr Gly Ser Val Arg Pro Val Arg Ala Gln Gly Gly Glu 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 Phe Met Thr Tyr Trp His Leu Leu
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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 Phe Pro Val Glu Lys Gln Leu
 35  40  45
Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Asn 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 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 Ala Gly Glu 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 Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
180 185 190
Val Thr Ser Thr Leu Arg Ile Asn 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: 99  
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 Ser Thr Tyr Thr 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 Gln Thr Ala 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: 99  
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 Ser Thr Tyr Thr 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 Gln Thr Ala 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  
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Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 110
Leu Val Thr Val Ser Ala
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<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 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 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
95 90 95
Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105
Leu Val Thr Val Ser Ala
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<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

Amp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Amp 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
95 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 93
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURES: 
<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 Gln 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
95 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> FEATURES: 
<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 Gln 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
95 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> FEATURES: 
<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
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
**SEQ ID NO 96**

**LENGTH:** 108

**TYPE:** PRT

**ORGANISM:** Artificial sequence

**FEATURE:**

**OTHER INFORMATION:** sequence is synthesized

**SEQUENCE:**

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

**SEQ ID NO 97**

**LENGTH:** 108

**TYPE:** PRT

**ORGANISM:** Artificial sequence

**FEATURE:**

**OTHER INFORMATION:** sequence is synthesized

**SEQUENCE:**

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

**SEQ ID NO 98**

**LENGTH:** 108

**TYPE:** PRT

**ORGANISM:** Artificial sequence

**FEATURE:**

**OTHER INFORMATION:** sequence is synthesized

**SEQUENCE:**

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

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 Gly Lys 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
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Tyr Thr Pro Pro

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

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

<400> SEQUENCE: 101

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Phe Tyr Thr Pro Pro

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

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

<400> SEQUENCE: 102

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

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**SEQ ID NO:** 106  
**LENGTH:** 108  
**ORGANISM:** Artificial sequence  
**FEATURE:**  
OTHER INFORMATION: sequence is synthesized
1. A method for treating colon cancer, 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) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
   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
   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
   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.

2-8. (canceled)

9. A method of:
   i) inhibiting cell proliferation in CSF-1R ligand-dependent and/or CSF-1 ligand-independent CSF-1R expressing tumor cells; or
   ii) the inhibition of inhibiting cell proliferation of tumors with CSF-1R ligand dependent and/or CSF-1R ligand-independent CSF-1R expressing macrophage infiltrate, 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) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
   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
   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
   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.

10. A method of inhibiting a CSF-1R-expressing tumor or inhibiting a tumor with CSF-1R-expressing macrophage infiltrate in a patient suffering from cancer, 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) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or
   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
   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
   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 said 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 said antibody which binds to human PD-L1 have reduced effector function.

13. The method of claim 12, wherein the reduced 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, wherein the numbering is according to EU numbering convention, and wherein the Fc is a human IgG Fc.

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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