antagonist disclosing as antagonist anti-CSF-1-antibodies only. WO 2005/046657 relates to the treatment of inflammatory bowel disease by anti-CSF-1-antibodies. US 2002/0141994 relates to inhibitors of colony stimulating factors. WO 2006/096489 relates to the treatment of rheumatoid arthritis by anti-CSF-1-antibodies. WO 2009/026303 and WO 2009/112245 relate to certain anti-CSF-1R antibodies binding to CSF-1R within the first three subdomains (D1 to D3) of the Extracellular Domain (CSF-1R-ECD).

Summary ~~of the Invention~~

The disclosure~~invention~~ comprises an antibody binding to human CSF-1R, characterized in that the antibody binds to human CSF-1R fragment delD4 (SEQ ID NO: 65) and to human CSF-1R Extracellular Domain (SEQ ID NO: 64) with a ratio of 1:50 or lower.

The disclosure~~invention~~ further comprises an antibody according to the disclosure~~invention~~ characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,
b) the heavy chain variable domain is SEQ ID NO:15 and the light chain variable domain is SEQ ID NO:16;
c) the heavy chain variable domain is SEQ ID NO:75 and the light chain variable domain is SEQ ID NO:76;
d) the heavy chain variable domain is SEQ ID NO:83 and the light chain variable domain is SEQ ID NO:84;

or a humanized version thereof.

The disclosure~~invention~~ further comprises an antibody according to the disclosure~~invention~~ characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,
b) the heavy chain variable domain is SEQ ID NO:15 and the light chain variable domain is SEQ ID NO:16;

or a humanized version thereof.

In one aspect, there is provided an antibody binding to human CSF-1R, characterized in that a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8, or b) a humanized version thereof.

In another aspect, there is provided an~~one embodiment the~~ antibody binding to human CSF-1R, ~~according to the invention is~~ characterized in that

a) the heavy chain variable domain is SEQ ID NO:23 and the light chain variable domain is SEQ ID NO:24, or

b) the heavy chain variable domain is SEQ ID NO:31 and the light chain variable domain is SEQ ID NO:32, or

c) the heavy chain variable domain is SEQ ID NO:39 and the light chain variable domain is SEQ ID NO:40, or

d) the heavy chain variable domain is SEQ ID NO:47 and the light chain variable domain is SEQ ID NO:48, or

e) the heavy chain variable domain is SEQ ID NO:55 and the light chain variable domain is SEQ ID NO:56.

The disclosure~~invention~~ further comprises an antibody according to the disclosure~~invention~~, characterized in that

a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6, or

b) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 9, a CDR2 region of SEQ ID NO: 10, and a CDR1 region of SEQ ID NO: 11, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:12, a CDR2 region of SEQ ID NO: 13, and a CDR1 region of SEQ ID NO: 14, or

c) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 17, a CDR2 region of SEQ ID NO: 18, and a CDR1 region of SEQ ID NO:19, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 20, a CDR2 region of SEQ ID NO:21, and a CDR1 region of SEQ ID NO:22, or

d) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 25, a CDR2 region of SEQ ID NO: 26, and a CDR1 region of SEQ ID NO: 27, and the light chain variable domain comprises a CDR3 region of

SEQ ID NO:28, a CDR2 region of SEQ ID NO: 29, and a CDR1 region of SEQ ID NO: 30, or

e) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 33, a CDR2 region of SEQ ID NO: 34, and a CDR1 region of SEQ ID NO: 35, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:36, a CDR2 region of SEQ ID NO: 37, and a CDR1 region of SEQ ID NO: 38, or

f) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:41, a CDR2 region of SEQ ID NO: 42, and a CDR1 region of SEQ ID NO:43, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 44, a CDR2 region of SEQ ID NO:45, and a CDR1 region of SEQ ID NO:46, or

g) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:52, a CDR2 region of SEQ ID NO: 53, and a CDR1 region of SEQ ID NO: 54; or

h) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:69, a CDR2 region of SEQ ID NO: 70, and a CDR1 region of SEQ ID NO:71, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 72, a CDR2 region of SEQ ID NO:73, and a CDR1 region of SEQ ID NO:74, or

i) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 77, a CDR2 region of SEQ ID NO: 78, and a CDR1 region of SEQ ID NO: 79, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:80, a CDR2 region of SEQ ID NO: 81, and a CDR1 region of SEQ ID NO: 82.

In another aspect, there is provided an antibody binding to human CSF-1R, characterized in that

a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 4, a CDR2 region of SEQ ID NO:5, and a CDR1 region of SEQ ID NO:6, or

b) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 17, a CDR2 region of SEQ ID NO: 18, and a CDR1 region of SEQ ID NO:19, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 20, a CDR2 region of SEQ ID NO:21, and a CDR1 region of SEQ ID NO:22, or

c) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 25, a CDR2 region of SEQ ID NO: 26, and a CDR1 region of SEQ ID NO: 27, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:28, a CDR2 region of SEQ ID NO: 29, and a CDR1 region of SEQ ID NO: 30, or

d) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 33, a CDR2 region of SEQ ID NO: 34, and a CDR1 region of SEQ ID NO: 35, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:36, a CDR2 region of SEQ ID NO: 37, and a CDR1 region of SEQ ID NO: 38, or

e) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:41, a CDR2 region of SEQ ID NO: 42, and a CDR1 region of SEQ ID NO:43, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 44, a CDR2 region of SEQ ID NO:45, and a CDR1 region of SEQ ID NO:46, or

f) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 51, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:52, a CDR2 region of SEQ ID NO: 53, and a CDR1 region of SEQ ID NO: 54.

Preferably the antibody according to the disclosure~~invention~~ is of human IgG1 subclass or of human IgG4 subclass.

Another aspect~~A further embodiment~~ of the disclosure~~invention~~ is a pharmaceutical composition comprising an antibody according to the disclosure~~invention~~.

The disclosureinvention further comprises the use an of an antibody according to the disclosureinvention for the manufacture of a medicament for treatment of a CSF-1R mediated disease.

In another aspect, there is providedThe invention further comprises the use an of an antibody according to the disclosureinvention for the manufacture of a medicament for treatment of cancer.

In another aspect, there is providedThe invention further comprises the use an of an antibody according to the disclosureinvention for the manufacture of a medicament for treatment of bone loss.

In another aspect, there is providedThe invention further comprises the use an of an antibody according to the disclosureinvention for the manufacture of a medicament for treatment of metastasis.

In another aspect, there is providedThe invention further comprises the use an of an antibody according to the disclosureinvention for the manufacture of a medicament for treatment of inflammatory diseases.

The disclosureinvention further comprises an antibody according to the disclosureinvention for treatment of a CSF-1R mediated disease.

The disclosureinvention further comprises an antibody according to the disclosureinvention for treatment of cancer.

The disclosureinvention further comprises an antibody according to the disclosureinvention for treatment of bone loss.

The disclosureinvention further comprises an antibody according to the disclosureinvention for treatment of metastasis.

The disclosureinvention further comprises an antibody according to the disclosureinvention for treatment of inflammatory diseases.

In another aspect, there is provided the antibody as defined above for use in the treatment of cancer.

In another aspect, there is provided the antibody as defined above for use in the treatment of bone loss.

In another aspect, there is provided the antibody as defined above for use in the prevention or treatment of metastasis.

In another aspect, there is provided the antibody as defined above for use in the treatment of inflammatory diseases.

In another aspect, there is provided a nucleic acid encoding an antibody as defined above.

A further embodiment of the disclosure~~invention~~ is a nucleic acid encoding an antibody according to the disclosure~~invention~~ characterized in that

a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, a CDR2 region of SEQ ID NO: 2, and a CDR1 region of SEQ ID NO:3, and the light chain variable domain comprises a CDR3 region of SEQ ID

SEQ ID NO:52, a CDR2 region of SEQ ID NO: 53, and a CDR1 region of SEQ ID NO: 54, or

h) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO:69, a CDR2 region of SEQ ID NO: 70, and a CDR1 region of SEQ ID NO:71, and the light chain variable domain comprises a CDR3 region of SEQ ID NO: 72, a CDR2 region of SEQ ID NO:73, and a CDR1 region of SEQ ID NO:74, or

i) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 77, a CDR2 region of SEQ ID NO: 78, and a CDR1 region of SEQ ID NO: 79, and the light chain variable domain comprises a CDR3 region of SEQ ID NO:80, a CDR2 region of SEQ ID NO: 81, and a CDR1 region of SEQ ID NO: 82.

A further embodiment of the disclosure~~invention~~ is a nucleic acid encoding an antibody according to the disclosure~~invention~~ characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,
b) the heavy chain variable domain is SEQ ID NO:15 and the light chain variable domain is SEQ ID NO:16;
c) the heavy chain variable domain is SEQ ID NO:75 and the light chain variable domain is SEQ ID NO:76;
d) the heavy chain variable domain is SEQ ID NO:83 and the light chain variable domain is SEQ ID NO:84;

or a humanized version thereof.

A further embodiment of the disclosure~~invention~~ is a nucleic acid encoding an antibody according to the disclosure~~invention~~ characterized in that

a) the heavy chain variable domain is SEQ ID NO:23 and the light chain variable domain is SEQ ID NO:24, or
b) the heavy chain variable domain is SEQ ID NO:31 and the light chain variable domain is SEQ ID NO:32, or
c) the heavy chain variable domain is SEQ ID NO:39 and the light chain variable domain is SEQ ID NO:40, or

d) the heavy chain variable domain is SEQ ID NO:47 and the light chain variable domain is SEQ ID NO:48, or

e) the heavy chain variable domain is SEQ ID NO:55 and the light chain variable domain is SEQ ID NO:56.

The disclosure~~invention~~ further provides expression vectors containing nucleic acid according to the disclosure~~invention~~ capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell, and host cells containing such vectors for the recombinant production of an antibody according to the disclosure~~invention~~. In another aspect, there is provided an expression vector characterized in comprising a nucleic acid as defined above for the expression of the antibody as defined above in a prokaryotic or eukaryotic host cell.

In another aspect, there is provided~~The invention further comprises~~ a prokaryotic or eukaryotic host cell comprising a vector according to the disclosure~~invention~~.

The disclosure~~invention~~ further comprises a method for the production of a recombinant human or humanized antibody according to the disclosure~~invention~~, characterized by expressing a nucleic acid according to the disclosure~~invention~~ in a prokaryotic or eukaryotic host cell and recovering said antibody from said cell or the cell culture supernatant. In another aspect, there is provided a method for the production of a recombinant antibody as defined above, characterized by expressing a nucleic acid as defined above in a prokaryotic or eukaryotic host cell and recovering said antibody from said cell or the cell culture supernatant. The disclosure~~invention~~ further comprises the antibody obtained by such a recombinant method.

Antibodies according to the disclosure~~invention~~ show benefits for patients in need of a CSF-1R targeting therapy. The antibodies according to the disclosure~~invention~~ show efficient antiproliferative activity against ligand–independent and ligand-dependant proliferation and are therefore especially useful in the treatment of cancer and metastasis.

The disclosure~~invention~~ further provides a method for treating a patient suffering from cancer, comprising administering to a patient diagnosed as having such a disease (and therefore being in need of such a therapy) an effective amount of an antibody according to the disclosure~~invention~~. The antibody is administered preferably in a pharmaceutical composition.

A further embodiment of the disclosure~~invention~~ is a method for the treatment of a patient suffering from cancer characterized by administering to the patient an antibody according to the disclosure~~invention~~.

Surprisingly it has been found that, using a human CSF-1R fragment delD4 in which the D4 subdomain of human CSF-1R-ECD was deleted (SEQ ID NO:65),

the new anti-CSF-1R antibodies according to the disclosure~~invention~~ could be selected. These antibodies show valuable properties like excellent ligand-dependant cell growth inhibition and at the same time ligand independent cell growth inhibition of NIH 3T3 cell, retrovirally infected with either an expression vector for full-length wildtype CSF-1R (SEQ ID NO:62) or mutant CSF-1R L301S Y969F (SEQ ID NO:63) whereby mutant CSF-1R recombinant cells are able to form spheroids independent of the CSF-1 ligand. Furthermore the antibodies according to the disclosure~~invention~~ inhibit (both) human and cynomolgous macrophage differentiation, as they inhibit survival of human and cynomolgous monocytes.

Detailed Description of the Invention

The invention comprises an antibody binding to human CSF-1R, characterized in that the antibody binds to human CSF-1R fragment delD4 (comprising the extracellular subdomains D1 –D3 and D5) (SEQ ID NO: 65) and to human CSF-1R Extracellular Domain (CSF-1R-ECD) (comprising the extracellular subdomains D1 –D5) (SEQ ID NO: 64) with a ratio of 1:50 or lower.

The invention further comprises an antibody according to the invention characterized in comprising as heavy chain variable domain CDR3 region a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47 or SEQ ID NO:55.

The invention further comprises an antibody according to the invention characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,
b) the heavy chain variable domain is SEQ ID NO:15 and the light chain variable domain is SEQ ID NO:16;
or a humanized version thereof.

The invention further comprises an antibody according to the invention characterized in that

a) the heavy chain variable domain is SEQ ID NO:7 and the light chain variable domain is SEQ ID NO:8,