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VAN DOR HORST E H ET AL: "Discovery of fully human anti-MET monoclonal antibodies with antitumor activity against jhik enk mum hi ml hi colon cancer tumor models in vivo", NEOPLASIA, NEOPLASIA PRESS, ANN ARBOR, MI, US, vol. 11, no. 4, 1 April 2009 (2009-04-01), pages 355-364, XP008118189, ISSN: 1522-8002

DESCRIPTION

[0001] The present invention relates to antibodies that bind c-Met and their use in treating conditions and disorders in which pathogenesis is mediated by this receptor.

[0002] c-Met, a member of the tyrosine kinase superfamily, is the receptor for Hepatocyte Growth Factor (HGF). Binding of HGF to c-Met leads to receptor dimerization or multimerization, phosphorylation of multiple tyrosine residues in the intracellular region, catalytic activation, and downstream signaling. c-Met is also activated via ligand-independent mechanisms, including receptor over-expression, amplification, and mutation. c-Met activation enhances cellular proliferation, migration, morphogenesis, survival (including protection from apoptosis), and protease synthesis, characteristics that are associated with invasive cell phenotype and poor clinical outcomes and drug resistance in cancer patients. The c-Met signaling pathway is one of the most frequently dysregulated pathways in human cancers, and occurs in virtually all types of solid tumors.

[0003] PCT International Publication WO 09/007427 discloses murine and CDR-grafted, humanized c-Met antibodies. Murine antibody 224G11 disclosed therein did not bind the c-Met Sema domain. Further functional properties of the humanized IgG1 derivative of this murine antibody, denoted h224G11 Mab, are reported in Abstracts nos. 835 (*in vitro* data) and 2792 (*in vivo* data) and their accompanying posters presented at the meeting of the American Association for Cancer Research (Denver, CO) in April, 2009. These abstracts and posters disclose that bivalent h224G11 Mab is devoid of intrinsic agonistic properties, behaves as a full antagonist of c-Met, and potentially decreases c-Met dimerization. Murine 224G11 is reported to down-regulate c-Met and block c-Met phosphorylation *in vivo*. In the case of other receptors, dimerization is a prerequisite for receptor internalization and degradation. These abstracts and posters disclose no data relating to c-Met internalization. Furthermore, the epitope to which the humanized antibody binds within c-Met is not identified.

[0004] PCT International Publication WO 05/016382 also discloses c-Met antibodies but does not identify the epitope(s) to which the antibodies bind. An epitope mapping example is provided, however, the reported results merely indicate that six c-Met antibodies bind to a common epitope while a seventh c-Met antibody binds a distinct epitope. The particular epitopes to which these c-Met antibodies bind is not provided.

[0005] There exists a need for antagonist antibodies to human c-Met, binding of which to the α -chain of human c-Met facilitates internalization of the receptor from the cell surface, in the presence and/or absence of HGF. There is also a need for antagonist antibodies to human c-Met, which binding to the α -chain of human c-Met facilitates internalization of the receptor from the cell surface in cells comprising c-Met variants containing gain of function mutations. There is also a need for antagonist antibodies to human c-Met which induce c-Met degradation and reduction of phosphorylated c-Met. Such antagonist activities could decrease the number of available binding sites for HGF on tumor cell surfaces, and terminate the pathway activation caused by overexpression, amplification, or mutation of c-Met. At the same time, such antagonist antibodies should inhibit HGF binding to c-Met and HGF-induced c-Met activation, and induce little or no agonist activity themselves.

[0006] Antibody compounds of the present invention meet these needs. They bind to epitopes in the α -chain of the human c-Met Sema domain, inhibiting HGF-binding to c-Met and receptor activation, while inducing little or no agonist activity. The antibodies of the present invention also induce internalization of the receptor in the presence or absence of HGF and also in cells comprising c-Met variants containing gain of function mutations. They induce degradation of c-Met and induce reduction of phosphorylated human c-Met, and inhibit HGF-dependent and HGF-independent proliferation of tumor cells that express this receptor. In view of these properties, these antibody compounds should be therapeutically useful in treating cancers mediated by c-Met via a variety of different mechanisms.

[0007] In addition, the present antibody compounds possess a number of other desirable properties. They exhibit high affinity (K_D) to c-Met, block HGF-mediated c-Met phosphorylation and downstream signaling, cellular proliferation, and cellular migration; and induce only weak phosphorylation of c-Met while inducing little or no HGF-like biological agonist activities such as induction of tumor cell proliferation, motility, invasion, tubulogenesis, angiogenesis, or anti-apoptotic effects. They inhibit both ligand (HGF)-dependent and ligand-independent c-Met pathway activation. Additionally, antibody compounds of the present invention preferentially bind human c-Met extracellular domain (ECD) compared to the ECDs of the closely related receptors RON and PlexinA2, and do not cause "shedding" of the c-Met ECD.

[0008] According to the present invention there is provided a c-Met monoclonal antibody, or antigen-binding fragment thereof, comprising three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs), wherein LCDR1 comprises the amino acid sequence SVSSSVSSYLH (SEQ ID NO: 53), LCDR2 comprises the amino acid sequence STSNLAS (SEQ ID NO: 54), LCDR3 comprises the amino acid sequence QVYSGYPLT (SEQ ID NO: 56),

HCDR1 comprises the amino acid sequence GYTFTDYMH (SEQ ID NO: 65), HCDR2 comprises the amino acid sequence RVNPNRRGTTYNQKFEG (SEQ ID NO: 68), and HCDR3 comprises the amino acid sequence ANWLDY (SEQ ID NO: 69).

[0009] Preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention binds an epitope within the α -chain of human c-Met and induces internalization of cell surface human c-Met.

[0010] More preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention induces hepatocyte-growth factor (HGF)- independent internalization of cell surface human c-Met.

[0011] Even more preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention, binds within an amino acid sequence selected from:

1. a) $_{121}$ VDTYYDDQL $_{130}$ (SEQ ID NO:77),
2. b) $_{131}$ ISCGSVNRGTCQRHVFPNHTADIQS $_{156}$ (SEQ ID NO:78),
3. c) $_{179}$ ALGAKVLSSVKDRFINF $_{195}$ (SEQ ID NO:79), and
4. d) $_{216}$ VRRLKETKDGFM $_{227}$ (SEQ ID NO:80).

[0012] It is preferred that the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention, binds within an amino acid sequence selected from:

1. a. $_{123}$ DTYYDD $_{128}$ (SEQ ID NO:81),
2. b. $_{144}$ HVFPNHTADIQS $_{156}$ (SEQ ID NO: 82),
3. c. $_{192}$ FINF $_{195}$ (SEQ ID NO:83), and
4. d. $_{220}$ KETKDGFM $_{227}$ (SEQ ID NO:84).

[0013] Even more preferred is a monoclonal antibody, or antigen binding fragment thereof, according to the present invention which binds an amino acid sequence within the conformational epitope characterized by $_{123}$ DTYYDD $_{128}$ (SEQ ID NO:81), $_{144}$ HVFPNHTADIQS $_{156}$ (SEQ ID NO: 82), $_{192}$ FINF $_{195}$ (SEQ ID NO:83), and $_{220}$ KETKDGFM $_{227}$ (SEQ ID NO:84) inclusive.

[0014] Preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 5 and the HCVR comprises the amino acid sequence of SEQ ID NO: 17.

[0015] It is preferred that the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention comprises a light chain having a kappa constant region and a heavy chain having an IgG4 heavy chain constant region.

[0016] The light chain is preferably encoded by the polynucleotide sequence of SEQ ID NO: 35, and the heavy chain is preferably encoded by the polynucleotide sequence of SEQ ID NO: 47.

[0017] Preferably, the monoclonal antibody according to the present invention comprises two light chains encoded by the polynucleotide sequence of SEQ ID NO: 35 and two heavy chains encoded by the polynucleotide sequence of SEQ ID NO: 47.

[0018] More preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention, has a light chain which is identical to the amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO: 35; and a heavy chain which is identical to the amino acid sequence encoded by SEQ ID NO: 47.

[0019] Preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention, comprises two light chains wherein the amino acid of the light chain is identical to the amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO: 35; and two heavy chains wherein the amino acid sequence of the heavy chain is identical to the amino acid sequence encoded by SEQ ID NO: 47.

[0020] Preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention, comprises a light chain having the amino acid sequence of SEQ ID NO:29 and a heavy chain having an IgG4 heavy chain constant region.

[0021] Even more preferably, the monoclonal antibody according to the present invention comprises two light chains having the amino acid sequence of SEQ ID NO:29 and two heavy chains having an IgG4 heavy chain constant region.

[0022] According to a second aspect of the present invention, there is provided a pharmaceutical composition, comprising the monoclonal antibody, or antigen binding fragment thereof, of the present invention, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0023] According to a third aspect of the present invention, there is provided a monoclonal antibody, or antigen-binding fragment thereof, of the present invention for use in therapy.

[0024] Preferably, the monoclonal antibody, or antigen-binding fragment thereof, of the present invention is for use in the treatment of cancer in a human.

[0025] More preferably, the monoclonal antibody, or antigen-binding fragment thereof, according to the present invention is to treat gastric, kidney, colon, colorectal, head and neck, prostate, melanoma or lung cancer

[0026] Accordingly, the present invention provides:

A monoclonal antibody, or antigen-binding fragment thereof, that:

1. a) binds an epitope within the α -chain of human c-Met, and
2. b) induces internalization of cell surface human c-Met.

[0027] Any one of the foregoing antibodies or antigen-binding fragment thereof wherein the antibody or antigen-binding fragment thereof induces hepatocyte-growth factor-independent internalization of cell surface human c-Met. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0028] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof that induces internalization of human c-Met in cells comprising a human c-Met variant containing a gain of function mutation. The gain of function mutation can be c-Met kinase domain mutation M149T or juxtamembrane domain mutation R988C.

[0029] Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 40% internalization of cell surface human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 45% internalization of cell surface human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 50% internalization of cell surface human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 55% internalization of cell surface human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 60% internalization of cell surface human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 65% internalization of human c-Met in cells. Any of the foregoing antibodies or antigen-binding fragments thereof wherein the antibody or antigen-binding fragment thereof induces at least 70% internalization of cell surface human c-Met in cells.

[0030] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which induces reduction of total c-Met in hepatocyte growth factor-independent tumor cells. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which induces reduction of total c-Met in hepatocyte growth factor-independent tumor cells comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which induces reduction of total c-Met in hepatocyte growth factor-independent tumor cells comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0031] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which induces reduction of phosphorylated c-Met in hepatocyte growth factor-independent tumor cells.

[0032] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which binds the α -chain of human c-Met at substantially the same epitope as an antibody comprising a light chain having the amino acid sequence shown in SEQ ID NO:28 and a heavy chain having the amino sequence shown in SEQ ID NO:40, or which binds the α -chain of human c-Met at substantially the same epitope as an antibody comprising a light chain having the amino acid sequence shown in SEQ ID NO:29 and a heavy chain having the amino sequence shown in SEQ ID NO:41.

[0033] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, excluding those comprising a light chain having the amino acid sequence shown in SEQ ID NO:26 and a heavy chain having the amino sequence shown in SEQ ID NO:38, wherein the epitope comprises one or more amino acid residues within $_{144}\text{HVFPHNHTADIQS}_{156}$ (SEQ ID NO: 82) inclusive.

[0034] Any one of the foregoing antibodies or antigen-binding fragments, wherein the epitope further comprises one or more amino acid residues within $_{123}\text{DTYYDD}_{128}$ (SEQ ID NO:81) inclusive.

[0035] Any one of the foregoing antibodies or antigen-binding fragments, wherein the epitope further comprises one or more amino acid residues within $_{192}\text{FINF}_{195}$ (SEQ ID NO:83) inclusive.

[0036] Any one of the foregoing antibodies or antigen-binding fragments, wherein the epitope further comprises one or more amino acid residues within $_{220}\text{KETKDGM}_{227}$ (SEQ ID NO:84) inclusive.

[0037] Any one of the foregoing antibodies or antigen-binding fragments thereof, wherein the antibody binds within an amino acid sequence selected from the group consisting of:

1. a) $_{121}\text{VVDYYDDL}_{130}$ (SEQ ID NO:77),
2. b) $_{131}\text{ISCGSVNRGTCQRHVFPNHTADIQS}_{156}$ (SEQ ID NO:78),
3. c) $_{179}\text{ALGAKVLSSVKDRFINF}_{195}$ (SEQ ID NO:79), and
4. d) $_{216}\text{VRRLKETKDGM}_{227}$ (SEQ ID NO:80), inclusive.

[0038] Any one of the foregoing antibodies or antigen-binding fragments thereof, wherein the antibody binds within an amino acid sequence selected from the group consisting of:

1. a) $_{123}\text{DTYYDD}_{128}$ (SEQ ID NO:81),
2. b) $_{144}\text{HVFPHNHTADIQS}_{156}$ (SEQ ID NO:82),
3. c) $_{192}\text{FINF}_{195}$ (SEQ ID NO:83), and
4. d) $_{220}\text{KETKDGM}_{227}$ (SEQ ID NO:84), inclusive.

[0039] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof which bind to an amino acid sequence within the epitope characterized by $_{121}\text{VVDYYDDL}_{140}$ (SEQ ID NO:77), $_{131}\text{ISCGSVNRGTCQRHVFPNHTADIQS}_{156}$ (SEQ ID NO:78), $_{179}\text{ALGAKVLSSVKDRFINF}_{195}$ (SEQ ID NO:79), and $_{216}\text{VRRLKETKDGM}_{227}$ (SEQ ID NO:80), inclusive.

[0040] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof which bind to an amino acid sequence within the epitope characterized by $_{123}\text{DTYYDD}_{128}$ (SEQ ID NO:81), $_{144}\text{HVFPHNHTADIQS}_{156}$ (SEQ ID NO: 82), $_{192}\text{FINF}_{195}$ (SEQ ID NO:83), and $_{220}\text{KETKDGM}_{227}$ (SEQ ID NO:84) inclusive.

[0041] Any one of the foregoing antibodies or antigen-binding fragments thereof, wherein the antibody binds within an amino acid sequence of $_{95}\text{CFPCQDCSSKA}_{105}$ (SEQ ID NO: 86) inclusive.

[0042] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, excluding those comprising a light chain having the amino acid sequence shown in SEQ ID NO:29 and a heavy chain having the amino sequence shown in SEQ ID

NO:41, wherein the epitope comprises one or more amino acid residues within g5CFPCQDCSSKA₁₀₅ (SEQ ID NO: 86) inclusive.

[0043] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof, that binds human c-Met, which comprises three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs),

wherein said three LCDRs and said three HCDRs are selected from the group consisting of:

1. a) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
 LCDR2 comprising the amino acid sequence GTSX₁LX₂S (SEQ ID NO:87), wherein X₁ is Y or R, and X₂ is A or R;
 LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
 HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
 HCDR2 comprising the amino acid sequence WIYPVTGDTYYX₇EX₈FKG (SEQ ID NO:90), wherein X₇ is N, I, or R, and X₈ is K or P; and
 HCDR3 comprising the amino acid sequence GYGAFX₉Y (SEQ ID NO:91), wherein X₉ is Y or F; and
2. b) LCDR1 comprising the amino acid sequence SVSSSVX₃SIYLH (SEQ ID NO:88), wherein X₃ is S or R;
 LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
 LCDR3 comprising the amino acid sequence X₄X₅YX₆GYPLT (SEQ ID NO:89), wherein X₄ is I or Q, X₅ is Q or V, and X₆ is S or R;
 HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
 HCDR2 comprising the amino acid sequence RVNPX₁₀RX₁₁X₁₂TTYNQKFEG (SEQ ID NO:92), wherein X₁₀ is N or Y, X₁₁ is G or R, and X₁₂ is G or S; and
 HCDR3 comprising the amino acid sequence X₁₃NX₁₄LDY (SEQ ID NO:93), wherein X₁₃ is T or A, and X₁₄ is W or I;
 wherein said monoclonal antibody or antigen-binding fragment thereof binds an epitope within the α -chain of said human c-Met and induces internalization of cell surface human c-Met.

[0044] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof, that binds human c-Met, which comprises three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs), wherein the antibody comprises three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (LCDRs), wherein

LCDR1 comprises the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);

LCDR2 comprises the amino acid sequence GTSX₁LX₂S (SEQ ID NO:87), wherein X₁ is Y or R, and X₂ is A or R;

LCDR3 comprises the amino acid sequence QQWSSYPYS (SEQ ID NO:51);

HCDR1 comprises the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);

HCDR2 comprises the amino acid sequence WIYPVTGDTYYX₇EX₈FKG (SEQ ID NO:90), wherein X₇ is N, I, or R, and X₈ is K or P;
 and

HCDR3 comprises the amino acid sequence GYGAFX₉Y (SEQ ID NO:91), wherein X₉ is Y or F.

[0045] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof, that binds human c-Met, which comprises three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (LCDRs), wherein

LCDR1 comprises the amino acid sequence SVSSSVX₃SIYLH (SEQ ID NO:88); wherein X₃ is S or R;

LCDR2 comprises the amino acid sequence STSNLAS (SEQ ID NO:54);

LCDR3 comprises the amino acid sequence X₄X₅YX₆GYPLT (SEQ ID NO:89), wherein X₄ is I or Q, X₅ is Q or V, and X₆ is S or R;

HCDR1 comprises the amino acid sequence GYTFTDYMH (SEQ ID NO:65);

HCDR2 comprises the amino acid sequence RVNPX₁₀RX₁₁X₁₂TTYNQKFEG (SEQ ID NO:92), wherein X₁₀ is N or Y, X₁₁ is G or R, and X₁₂ is G or S; and

[0046] HCDR3 comprises the amino acid sequence X₁₃NX₁₄LDY (SEQ ID NO:93), wherein X₁₃ is T or A, and X₁₄ is W or I.

[0047] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof, that binds human c-Met, which comprises three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs), and
wherein said three LCDRs and said three HCDRs are selected from the group consisting of:

1. a) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSYLAS (SEQ ID NO:50);
LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYNEKFKG (SEQ ID NO:60); and
HCDR3 comprising the amino acid sequence GYGAFYY (SEQ ID NO:61);
2. b) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSYLAS (SEQ ID NO:50);
LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYIEKFKG (SEQ ID NO:62); and
HCDR3 comprising the amino acid sequence GYGAFYY (SEQ ID NO:63);
3. c) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSRLRS (SEQ ID NO:52);
LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYREPFGK (SEQ ID NO:64), and
HCDR3 comprising the amino acid sequence GYGAFYY (SEQ ID NO:61);
4. d) LCDR1 comprising the amino acid sequence SVSSSVSSIYH (SEQ ID NO:53);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence IQYSGYPLT (SEQ ID NO:55);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGGTTYNQKFEG (SEQ ID NO:66), and
HCDR3 comprising the amino acid sequence TNWLDY (SEQ ID NO:67);
5. e) LCDR1 comprising the amino acid sequence SVSSSVSSIYH (SEQ ID NO:53);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence QVYSGYPLT (SEQ ID NO:56);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR12 comprising the amino acid sequence RVNPNRRGGTTYNQKFEG (SEQ ID NO:68); and
HCDR3 comprising the amino acid sequence ANWLDY (SEQ ID NO:69); and
6. f) LCDR1 comprising the amino acid sequence SVSSSVSSIYH (SEQ ID NO:57);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence QVYRGYPLT (SEQ ID NO:58);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGGTTYNQKFEG (SEQ ID NO:70); and
HCDR3 comprising the amino acid sequence ANILDY (SEQ ID NO:71); and
wherein said monoclonal antibody or antigen-binding fragment thereof binds an epitope within the α -chain of said human c-Met and induces internalization of cell surface human c-Met.

[0048] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof comprising three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (LCDRs), wherein said three LCDRs and said three HCDRs are selected from the group consisting of:

1. a) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSYLAS (SEQ ID NO:50);
LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYNEKFKG (SEQ ID NO:60); and
HCDR3 comprising the amino acid sequence GYGAFYY (SEQ ID NO:61);
2. b) LCDR1 comprising the amino acid sequence SVSSISSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSYLAS (SEQ ID NO:50);

- LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYIEKFKG (SEQ ID NO:62); and
HCDR3 comprising the amino acid sequence GYGAFY (SEQ ID NO:63);
3. c) LCDR1 comprising the amino acid sequence SVSSS1SSTNLH (SEQ ID NO:49);
LCDR2 comprising the amino acid sequence GTSRLRS (SEQ ID NO:52);
LCDR3 comprising the amino acid sequence QQWSSYPYS (SEQ ID NO:51);
HCDR1 comprising the amino acid sequence GYTFTSRYIH (SEQ ID NO:59);
HCDR2 comprising the amino acid sequence WIYPVTGDTYYREPFG (SEQ ID NO:64); and
HCDR3 comprising the amino acid sequence GYGAFY (SEQ ID NO:61).

[0049] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof comprising three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (CDRs), wherein said three LCDRs and said three HCDRs are selected from the group consisting of:

1. a) LCDR1 comprising the amino acid sequence SVSSSVSSIYLH (SEQ ID NO:53);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence IQYSGYPLT (SEQ ID NO:55);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGDTYNQKFEG (SEQ ID NO:66); and
CDR3 comprising the amino acid sequence TNWLDY (SEQ ID NO:67);
2. b) LCDR1 comprising the amino acid sequence SVSSSVSSIYLH (SEQ ID NO:53);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence QVYSGYPLT (SEQ ID NO:56);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGDTYNQKFEG (SEQ ID NO:68); and
HCDR3 comprising the amino acid sequence ANWLDY (SEQ ID NO:69); and
3. c) LCDR1 comprising the amino acid sequence SVSSSVSSIYLH (SEQ ID NO:57);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence QVYRGYPLT (SEQ ID NO:58);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGDTYNQKFEG (SEQ ID NO:70); and
HCDR3 comprising the amino acid sequence ANLDY (SEQ ID NO:71).

[0050] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof comprising three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs), wherein:

LCDR1 comprising the amino acid sequence SVSSSVSSIYLH (SEQ ID NO:53);
LCDR2 comprising the amino acid sequence STSNLAS (SEQ ID NO:54);
LCDR3 comprising the amino acid sequence IQYSGYPLT (SEQ ID NO:55);
HCDR1 comprising the amino acid sequence GYTFTDYMH (SEQ ID NO:65);
HCDR2 comprising the amino acid sequence RVNPNRGDTYNQKFEG (SEQ ID NO:66); and
HCDR3 comprising the amino acid sequence TNWLDY (SEQ ID NO:67);

[0051] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof comprising three light chain complementarity determining regions (LCDRs) and three heavy chain complementarity determining regions (HCDRs), wherein:

LCDR1 comprised the amino acid sequence SVSSSVSSIYLH (SEQ ID NO:53);
LCDR2 comprises the amino acid sequence STSNLAS (SEQ ID NO:54);

LCDR3 comprises the amino acid sequence QVYSGYPLT (SEQ ID NO:56);

HCDR1 comprises the amino acid sequence GYTFTDYMH (SEQ ID NO:65);

HCDR12 comprises the amino acid sequence RVNPNRRGTTYNQKFEG (SEQ ID NO:68); and

HCDR3 comprises the amino acid sequence ANWLDY (SEQ ID NO:69).

[0052] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and said HCVR, respectively, comprise amino acid sequences selected from the group consisting of:

1. a) SEQ ID NO:94 and SEQ ID NO:96; and
2. b) SEQ ID NO:95 and SEQ ID NO:97,

wherein said monoclonal antibody or antigen-binding fragment thereof binds an epitope within the α -chain of said human c-Met and induces internalization of cell surface human c-Met.

[0053] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises SEQ ID NO:94 and said HCVR comprises SEQ ID NO:96.

[0054] Any one of the foregoing monoclonal antibodies, or antigen-binding fragments thereof comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises SEQ ID NO:95 and said HCVR comprises SEQ ID NO:97.

[0055] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, wherein said LCVR and said HCVR comprise amino acid sequences which are selected from the group consisting of:

1. a) LCVR is SEQ ID NO: 1 and HCVR is SEQ ID NO:13;
2. b) LCVR is SEQ ID NO:2 and HCVR is SEQ ID NO:14;
3. c) LCVR is SEQ ID NO:3 and HCVR is SEQ ID NO: 15;
4. d) LCVR is SEQ ID NO:4 and HCVR is SEQ ID NO:16;
5. e) LCVR is SEQ ID NO:5 and HCVR is SEQ ID NO:17; and
6. f) LCVR is SEQ ID NO:6 and LCVR is SEQ ID NO:18.

[0056] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, wherein said LCVR and said HCVR, respectively, comprise amino acid sequences selected from the group consisting of:

1. a) LCVR is SEQ ID NO:1 and HCVR is SEQ ID NO:13;
2. b) LCVR is SEQ ID NO:2 and HCVR is SEQ ID NO:14; and
3. c) LCVR is SEQ ID NO:3 and HCVR is SEQ ID NO:15.

[0057] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, wherein said LCVR and said HCVR, respectively, comprise amino acid sequences selected from the group consisting of:

1. a) LCVR is SEQ ID NO:4 and HCVR is SEQ ID NO:16;
2. b) LCVR is SEQ ID NO:5 and HCVR is SEQ ID NO:17; and
3. c) LCVR is SEQ ID NO:6 and HCVR is SEQ ID NO:18.

[0058] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, wherein said LCVR comprises the amino acid sequence of SEQ ID NO: 4 and said HCVR comprises the amino acid sequence of SEQ ID NO: 16.

[0059] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, wherein said LCVR comprises the

amino acid sequence of SEQ ID NO: 5 and said HCVR comprises the amino acid sequence of SEQ ID NO: 17.

[0060] Any one of the foregoing monoclonal antibodies wherein said antibody comprises a light chain and a heavy chain wherein the light chain and the heavy chain comprise amino acid sequences which are selected from the group consisting of:

1. a) light chain is SEQ ID NO:25 and heavy chain is SEQ ID NO:37;
2. b) light chain is SEQ ID NO:26 and heavy chain is SEQ ID NO:38;
3. c) light chain is SEQ ID NO:27 and heavy chain is SEQ ID NO:39;
4. d) light chain is SEQ ID NO:28 and heavy chain is SEQ ID NO:40;
5. e) light chain is SEQ ID NO:29 and heavy chain is SEQ ID NO:41; and
6. f) light chain is SEQ ID NO:30 and heavy chain is SEQ ID NO:42.

[0061] Any one of the foregoing monoclonal antibodies wherein said antibody comprises a light chain and a heavy chain wherein the light chain and the heavy chain comprise amino acid sequences which are selected from the group consisting of

1. a) light chain is SEQ ID NO:25 and heavy chain is SEQ ID NO:37;
2. b) light chain is SEQ ID NO:26 and heavy chain is SEQ ID NO:38; and
3. c) light chain is SEQ ID NO:27 and heavy chain is SEQ ID NO:39.

[0062] Any one of the foregoing monoclonal antibodies wherein said antibody comprises a light chain and a heavy chain wherein the light chain and the heavy chain comprise amino acid sequences which are selected from the group consisting of:

1. a) light chain is SEQ ID NO:28 and heavy chain is SEQ ID NO:40;
2. b) light chain is SEQ ID NO:29 and heavy chain is SEQ ID NO:41; and
3. c) light chain is SEQ ID NO:30 and heavy chain is SEQ ID NO:42.

[0063] Any one of the foregoing monoclonal antibodies wherein said light chain comprises the amino acid sequence of SEQ ID NO: 28 and said heavy chain comprises the amino acid sequence of SEQ ID NO: 40.

[0064] Any one of the foregoing monoclonal antibodies wherein said light chain comprises the amino acid sequence of SEQ ID NO: 29 and said heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0065] Any one of the foregoing monoclonal antibodies wherein said antibody comprises two light chains and two heavy chains, wherein each light chain comprises the amino acid sequence of SEQ ID NO: 28 and each heavy chain comprises the amino acid sequence of SEQ ID NO: 40.

[0066] Any one of the foregoing monoclonal antibodies wherein said antibody comprises two light chains and two heavy chains, wherein each light chain comprises the amino acid sequence of SEQ ID NO: 29 and each heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0067] A monoclonal antibody or antigen-binding fragment thereof that competes with any of the foregoing c-Met monoclonal antibodies or antigen-binding fragments thereof for binding to c-Met. Such competing monoclonal antibody or antigen-binding fragment thereof can bind to the same epitope of c-Met as any one of the foregoing c-Met monoclonal antibodies or antigen-binding fragments thereof. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof competes with an antibody which comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof competes with an antibody which comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0068] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively overexpress said human c-Met. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which

induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively overexpress said human c-Met, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively overexpress said human c-Met, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0069] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively phosphorylate said human c-Met. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively phosphorylate said human c-Met, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that constitutively phosphorylate said human c-Met, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0070] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which induces reduction of total human c-Met and phosphorylated human c-Met in hepatocyte growth factor-independent tumor cells that are hepatocyte growth factor-responsive.

[0071] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which preferentially binds human c-Met extracellular domain compared to human RON extracellular domain or human PlexinA2 extracellular domain.

[0072] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which does not induce shedding of human c-Met extracellular domain. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which does not induce shedding of human c-Met extracellular domain, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which does not induce shedding of human c-Met extracellular domain, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0073] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which does not protect tumor cells expressing human c-Met from staurosporine-induced apoptosis. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which does not protect tumor cells expressing human c-Met from staurosporine-induced apoptosis, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which does not protect tumor cells expressing human c-Met from staurosporine-induced apoptosis, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0074] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which inhibits hepatocyte growth factor-dependent and hepatocyte growth factor-independent proliferation of tumor cells that express human c-Met.

[0075] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, which inhibits binding of human hepatocyte growth factor to human c-Met.

[0076] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof which does not induce HGF-like biological agonist activities. HGF-like biological agonist activities include tumor cell proliferation, tumor cell motility, tumor cell invasion, tubulogenesis, angiogenesis, and anti-apoptotic effects. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof which does not induce HGF-like biological agonist activities, comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0077] A pharmaceutical composition, comprising any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0078] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof for use in therapy. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in therapy comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in therapy comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0079] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof for use in treating a cancer in a human. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in treating a cancer in a human comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in treating a cancer in a human comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0080] Any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof for use in treating a cancer in a human in combination with another therapeutic agent. In a preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in treating a cancer in a human in combination with another therapeutic agent comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 40. In another preferred embodiment, the monoclonal antibody or antigen-binding fragment thereof for use in treating a cancer in a human in combination with another therapeutic agent comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 29 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 41.

[0081] A pharmaceutical composition comprising any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

[0082] Use of any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof for the manufacture of a medicament for treating a cancer in a human.

[0083] A method of treating a cancer, comprising administering to a human patient in need thereof an effective amount of any one of the foregoing monoclonal antibodies or antigen-binding fragments thereof.

Definitions

[0084] A full-length antibody as it exists naturally is an immunoglobulin molecule comprising 2 heavy (H) chains and 2 light (L) chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100-110 or more amino acids primarily responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

[0085] The CDRs are interspersed with regions that are more conserved, termed framework regions ("FR"). Each light chain variable region (LCVR) and heavy chain variable region (HCVR) is composed of 3 CDRs and 4 FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The 3 CDRs of the light chain are referred to as "LCDR1, LCDR2, and LCDR3" and the 3 CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3." The CDRs contain most of the residues which form specific interactions with the antigen. The numbering and positioning of CDR amino acid residues within the LCVR and HCVR regions are in accordance with the well-known Kabat numbering convention.

[0086] Light chains are classified as kappa or lambda, and are characterized by a particular constant region as known in the art. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. IgG antibodies can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4. Each heavy chain type is characterized by a particular constant region with a sequence well known in the art.

[0087] As used herein, the term "monoclonal antibody" (Mab) as applied to the present antibody compounds refers to an antibody that is derived from a single copy or clone including, for example, any eukaryotic, prokaryotic, or phage clone, and not

the method by which it is produced. Mabs of the present invention preferably exist in a homogeneous or substantially homogeneous population. Complete Mabs contain 2 heavy chains and 2 light chains. "Antigen-binding fragments" of such monoclonal antibodies include, for example, Fab fragment, Fab' fragments, F(ab')₂ fragments, single chain Fv fragments, and one-armed antibodies comprising a light chain and a heavy chain. Monoclonal antibodies and antigen-binding fragments thereof of the present invention can be produced, for example, by recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such technologies, or other technologies known in the art.

[0088] "Antibody compounds" refers to Mabs and Fabs disclosed herein. Additional antibody compounds exhibiting similar functional properties according to the present invention can be generated by conventional methods. For example, mice can be immunized with human c-Met or fragments thereof, the resulting antibodies can be recovered and purified, and determination of whether they possess binding and functional properties similar to or the same as the antibody compounds disclosed herein can be assessed by the methods disclosed in Examples 2-19, below. Antigen-binding fragments can also be prepared by conventional methods. Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, chapters 5-8 and 15, ISBN 0-87969-314-2.

[0089] The phrase "human engineered antibodies" refers to monoclonal antibodies and antigen-binding fragments in addition to the antibody compounds disclosed herein that have binding and functional properties according to the invention similar to those disclosed herein, and that have framework regions that are substantially human or fully human surrounding CDRs derived from a non-human antibody. "Framework region" or "framework sequence" refers to any one of framework regions 1 to 4. Human engineered antibodies and antigen-binding fragments encompassed by the present invention include molecules wherein any one or more of framework regions 1 to 4 is substantially or fully human, i.e., wherein any of the possible combinations of individual substantially or fully human framework regions 1 to 4, is present. For example, this includes molecules in which framework region 1 and framework region 2, framework region 1 and framework region 3, framework region 1, 2, and 3, etc., are substantially or fully human. Substantially human frameworks are those that have at least about 80% sequence identity to a known human germline framework sequence. Preferably, the substantially human frameworks have at least about 85%, about 90%, about 95%, or about 99% sequence identity to a known human germline framework sequence.

[0090] Fully human frameworks are those that are identical to a known human germline framework sequence. Human framework germline sequences can be obtained from ImMunoGeneTics (IMGT) via their website <http://imgt.cines.fr>, or from *The Immunoglobulin FactsBook* by Marie-Paule Lefranc and Gerard Lefranc, Academic Press, 2001, ISBN 012441351. For example, germline light chain frameworks can be selected from the group consisting of: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L15, L6, L8, O12, O2, and O8, and germline heavy chain framework regions can be selected from the group consisting of: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, V1-13-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51.

[0091] Human engineered antibodies in addition to those disclosed herein exhibiting similar functional properties according to the present invention can be generated using several different methods. In one approach, the parent antibody compound CDRs are grafted into a human framework that has a high sequence identity with the parent antibody compound framework. The sequence identity of the new framework will generally be at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% identical to the sequence of the corresponding framework in the parent antibody compound. In the case of frameworks having fewer than 100 amino acid residues, one, two, or three amino acid residues can be changed. This grafting may result in a reduction in binding affinity compared to that of the parent antibody. If this is the case, the framework can be back-mutated to the parent framework at certain positions based on specific criteria disclosed by Queen et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:2869. Additional references describing methods useful in humanizing mouse antibodies include U.S. Patent Nos. 4,816,397; 5,225,539, and 5,693,761; computer programs ABMOD and ENCAD as described in Levitt (1983) *J. Mol. Biol.* 168:595-620; and the method of Winter and co-workers (Jones et al. (1986) *Nature* 321:522-525; Riechmann et al. (1988) *Nature* 332:323-327; and Verhoeven et al. (1988) *Science* 239:1534-1536.

[0092] The identification of residues to consider for back-mutation can be carried out as follows.

[0093] When an amino acid falls under the following category, the framework amino acid of the human germ-line sequence that is being used (the "acceptor framework") is replaced by a framework amino acid from a framework of the parent antibody compound (the "donor framework"):

1. (a) the amino acid in the human framework region of the acceptor framework is unusual for human frameworks at that position, whereas the corresponding amino acid in the donor immunoglobulin is typical for human frameworks at that position;

2. (b) the position of the amino acid is immediately adjacent to one of the CDRs; or
3. (c) any side chain atom of a framework amino acid is within about 5-6 angstroms (center-to-center) of any atom of a CDR amino acid in a three dimensional immunoglobulin model.

[0094] When each of the amino acids in the human framework region of the acceptor framework and a corresponding amino acid in the donor framework is generally unusual for human frameworks at that position, such amino acid can be replaced by an amino acid typical for human frameworks at that position. This back-mutation criterion enables one to recover the activity of the parent antibody compound.

[0095] Another approach to generating human engineered antibodies exhibiting similar functional properties to the antibody compounds disclosed herein involves randomly mutating amino acids within the grafted CDRs without changing the framework, and screening the resultant molecules for binding affinity and other functional properties that are as good as or better than those of the parent antibody compounds. Single mutations can also be introduced at each amino acid position within each CDR, followed by assessing the effects of such mutations on binding affinity and other functional properties. Single mutations producing improved properties can be combined to assess their effects in combination with one another.

[0096] Further, a combination of both of the foregoing approaches is possible. After CDR grafting, one can back-mutate specific framework regions in addition to introducing amino acid changes in the CDRs. This methodology is described in Wu et al. (1999) J. Mol. Biol. 294:151-162.

[0097] Applying the teachings of the present invention, a person skilled in the art can use common techniques, e.g., site-directed mutagenesis, to substitute amino acids within the presently disclosed CDR and framework sequences and thereby generate further variable region amino acid sequences derived from the present sequences. Up to all naturally occurring amino acids can be introduced at a specific substitution site. The methods disclosed herein can then be used to screen these additional variable region amino acid sequences to identify sequences having the indicated *in vivo* functions. In this way, further sequences suitable for preparing human engineered antibodies and antigen-binding portions thereof in accordance with the present invention can be identified. Preferably, amino acid substitution within the frameworks is restricted to one, two, or three positions within any one or more of the 4 light chain and/or heavy chain framework regions disclosed herein. Preferably, amino acid substitution within the CDRs is restricted to one, two, or three positions within any one or more of the 3 light chain and/or heavy chain CDRs. Combinations of the various changes within these framework regions and CDRs described above are also possible.

[0098] That the functional properties of the antibody compounds generated by introducing the amino acid modifications discussed above conform to those exhibited by the specific molecules disclosed herein can be confirmed by the methods disclosed below in Examples 2-19.

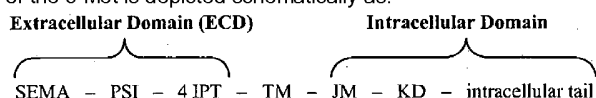
[0099] The term "epitope" refers to a specific arrangement of amino acids located on a peptide or protein to which an antibody or antibody fragment binds. Epitopes often consist of a chemically active surface grouping of molecules such as amino acids or sugar side chains, and have specific three dimensional structural characteristics as well as specific charge characteristics. Epitopes can be linear, i.e., involving binding to a single sequence of amino acids, or conformational, i.e., involving binding to two or more sequences of amino acids in various regions of the antigen that may not necessarily be contiguous. The epitopes disclosed herein can consist of, consist essentially of, or comprise the amino acid sequences disclosed in Example 3.

[0100] Monoclonal antibodies or antigen-binding fragments thereof that "compete" with the molecules disclosed herein are those that bind human c-Met at site(s) that are identical to, or overlapping with, the site(s) at which the present molecules bind. Competing monoclonal antibodies or antigen-binding fragments thereof can be identified, for example, via an antibody competition assay. For example, a sample of purified or partially purified human c-Met can be bound to a solid support. Then, an antibody compound or antigen binding fragment thereof of the present invention and a monoclonal antibody or antigen-binding fragment thereof suspected of being able to compete with such invention antibody compound are added. One of the two molecules is labeled. If the labeled compound and the unlabeled compound bind to separate and discrete sites on c-Met, the labeled compound will bind to the same level whether or not the suspected competing compound is present. However, if the sites of interaction are identical or overlapping, the unlabeled compound will compete, and the amount of labeled compound bound to the antigen will be lowered. If the unlabeled compound is present in excess, very little, if any, labeled compound will bind. For purposes of the present invention, competing monoclonal antibodies or antigen-binding fragments thereof are those that decrease the binding of the present antibody compounds to c-Met by about 50%, about 60%, about 70%, about 80%, about 85%, about 90%, about 95%, or about 99%. Details of procedures for carrying out such competition assays are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory

Press, Cold Spring Harbor, New York, pages 567-569, ISBN 0-87969-314-2. Such assays can be made quantitative by using purified antibodies. A standard curve is established by titrating one antibody against itself, i.e., the same antibody is used for both the label and the competitor. The capacity of an unlabeled competing monoclonal antibody or antigen-binding fragment thereof to inhibit the binding of the labeled molecule to the plate is titrated. The results are plotted, and the concentrations necessary to achieve the desired degree of binding inhibition are compared. Whether monoclonal antibodies or antigen-binding fragments thereof that compete with antibody compounds of the present invention in such competition assays possess the same or similar functional properties of the present antibody compounds can be determined via the methods disclosed in Examples 2-19 herein.

[0101] Monoclonal antibodies or antigen-binding fragments thereof that bind substantially the same epitope(s) of c-Met as the monoclonal antibodies or antigen-binding fragments disclosed herein are those that bind human c-Met at site(s) that are overlapping with the site(s) at which the present molecules bind. Methods that facilitate identification of monoclonal antibodies or antigen-binding fragments thereof that bind substantially the same epitope of c-Met as the c-Met monoclonal antibodies or antigen-binding fragments disclosed herein are well known in the art and are described, for example, in PCT International Publication WO 00/64946. Whether such monoclonal antibodies or antigen-binding fragments thereof that bind substantially the same c-Met epitope(s) as those disclosed herein possess the same or similar functional properties of the present antibody compounds can be determined via the methods disclosed in Examples 2-19 herein.

[0102] "c-Met" or "human c-Met" refers to any human c-Met, as well as functionally active, mutated forms thereof. The structure of the c-Met is depicted schematically as:



SEMA: Sema domain

PSI: Plexin, Semaphorins, and Integrins domain

IPT: 4 Immunoglobulins, Plexins, and Transcription factor domains

TM: Transmembrane region

JM: Juxtamembrane domain

KD: Kinase domain

[0103] In the human c-Met ECD (SEQ ID NO:75), amino acids 1-24 comprise the signal sequence. The mature protein begins at amino acid 25 (E). The Sema domain consists of approximately 500 amino acid residues at the N-terminus of c-Met, and contains the α -chain (amino acid residues 25-307) and part of the β -chain (amino acid residues 308-519).

[0104] The term "inhibit" means the ability to substantially antagonize, prohibit, prevent, restrain, slow, disrupt, eliminate, stop, reduce, or reverse the biological effects of c-Met.

[0105] The term "treating" (or "treat" or "treatment") means slowing, interrupting, arresting, controlling, stopping, reducing, or reversing the progression or severity of a symptom, disorder, condition, or disease, but does not necessarily involve a total elimination of all disease-related symptoms, conditions, or disorders.

[0106] Acute events and chronic conditions may be treated. In an acute event, an antibody or antigen-binding fragment thereof is administered at the onset of a symptom, disorder, condition, or disease, and is discontinued when the acute event ends. In contrast, a chronic symptom, disorder, condition, or disease is treated over a more protracted time frame.

[0107] The term "effective amount" refers to the amount or dose of an antibody compound of the present invention which, upon single or multiple dose administration to a patient, provides the desired treatment or prevention. Therapeutically effective amounts of the present antibody compounds can comprise an amount in the range of from about 0.1 mg/kg to about 20 mg/kg per single dose. A therapeutically effective amount for any individual patient can be determined by the health care provider by monitoring the effect of the antibody compounds on a biomarker, such as cell surface c-Met in tumor or non-tumor tissues, tumor regression, etc. Analysis of the data obtained by these methods permits modification of the treatment regimen during therapy so that optimal amounts of antibody compounds, whether employed alone or in combination with one another therapeutic agent, are administered, and so that the duration of treatment can be determined as well. In this way, the dosing/treatment regimen can be

modified over the course of therapy so that the lowest amounts of antibody compounds used alone or in combination that exhibit satisfactory tumor reducing effectiveness are administered, and so that administration of such compounds is continued only so long as is necessary to successfully treat the patient.

[0108] The antibody compounds of the present invention can be used as medicaments in human medicine, administered by a variety of routes. Most preferably, such compositions are for parenteral administration. Such pharmaceutical compositions can be prepared by methods well known in the art. See, e.g., Remington: The Science and Practice of Pharmacy, 19th ed. (1995), A. Gennaro et al., Mack Publishing Co., and comprise one or more antibody compounds disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0109] The term "tumor" refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms "cancer", "cancerous", and "tumor" are not mutually exclusive as used herein.

[0110] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by aberrant cell growth/proliferation. Examples of cancers include, but are not limited to, carcinomas, lymphomas, blastomas, sarcomas, and leukemias.

c-Met and Cancer

[0111] Deregulated c-Met pathways can be induced by transcriptional up regulation, c-Met gene amplification, specific genetic alterations, or ligand-dependent autocrine or paracrine mechanisms. The most frequent cause of constitutive c-Met activation in human tumors is increased protein expression as a consequence of transcriptional upregulation, in the absence of gene amplification. In addition, amplification of the *MET* gene, with consequent protein overexpression and constitutive kinase activation, has been reported in a number of human primary tumors, including gastric and oesophageal carcinomas, non-small-cell lung (NSCL) carcinomas, and medulloblastomas. Tumors of mesenchymal origin, such as osteosarcomas and rhabdomyosarcomas, often utilize autocrine mechanisms by producing HGF. Elevated HGF levels and overexpression of c-Met are often associated with poor clinical outcomes that include more aggressive disease, increased tumor metastasis, and shortened patient survival. Further, high levels of HGF and/or c-Met proteins in tumors confer resistance to chemotherapy and radiotherapy. In addition to abnormal HGF and c-Met expression, the c-Met pathway can be activated through genetic alternations such as c-Met mutations, gene amplification, and gene rearrangement. Missense *c-MET* mutations are found in all individuals with well-characterized hereditary papillary renal cell carcinomas (PRCC) and in a small subset (13%) of sporadic PRCC samples. Some of the mutations possess oncogenic potential due to increased kinase activity. Trisomy of chromosome 7, where both *HGF* and *c-MET* genes reside, occurs frequently in PRCC, and results in non-random duplication of the mutant *c-MET* allele. In addition, somatic *c-MET* mutations have been identified in other human cancers, including gastric, head and neck, liver, ovarian, non-small cell lung and thyroid cancers, as well as in metastases of some of these cancers. Unlike PRCC, where mutations are typically confined to the kinase domain, these mutations are often located in other regions of the receptor, for example, the juxtamembrane domain. In addition to mutation, the *c-MET* gene is often amplified in breast, liver, brain, colorectal, gastric, lung and stomach cancers, which is correlated to disease progression in some patients.

Therapeutic indications

[0112] Aberrant HGF/c-MET signaling has been documented in a wide range of human malignancies, including bladder, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, kidney, liver, lung, nasopharyngeal, ovarian, pancreatic, prostate and thyroid cancers, as well as cholangiocarcinoma, osteosarcoma, rhabdomyosarcoma, synovial sarcoma, Kaposi's sarcoma, leiomyosarcomas, and MFH/fibrosarcoma. In addition, abnormal HGF and/or c-Met expression has also been reported in hematological malignancies such as acute myelogenous leukemia, adult T-cell leukemia, chronic myeloid leukemia, lymphomas and multiple myeloma, as well as other tumors such as melanoma, mesothelioma, Wilms' tumor, glioblastomata, and astrocytomas (summarized in Liu et al. (2008) Expert Opin. Investig. Drugs 17(7):997-1011). The c-Met antibodies of the present invention can inhibit both HGF-dependent and HGF-independent tumors.

[0113] The following non-limiting examples illustrate various aspects of the present invention.

[0114] In the examples below, the humanized IgG2 and IgG4 and murine IgG (also sometimes referred to as mIgG1) control antibodies are isotype control antibodies unrelated to the present c-Met antibodies. Antibodies C8, D 11, and optD11 are murine antibodies. In all cases, human HGF is obtained from R&D Systems (#294).

Example 1**c-Met Antibodies**

[0115] The amino acid sequences of the light chain and heavy chain variable regions, the complete light and heavy chains, and the respective encoding nucleotide sequences of the foregoing, of the present human engineered antibodies are listed below in the section entitled "Amino Acid and Nucleotide Sequences." The light chain and heavy chain CDR amino acid sequences are shown in Tables 1 and 2, respectively.

Table 1. Light Chain CDRs

Antibody	CDR 1	CDR 2	CDR 3
D11-S17Y	SVSSSISSTNLH	GTSYLAS	QQWSSYPYS
	(SEQ ID NO:49)	(SEQ ID NO:50)	(SEQ ID NO:51)
D11-8B8	SVSSSISSTNLH	GTSYLAS	QQWSSYPYS
	(SEQ ID NO:49)	(SEQ ID NO:50)	(SEQ ID NO:51)
D11-C27G3	SVSSSISSTNLH	GTSRLRS	QQWSSYPYS
	(SEQ ID NO:49)	(SEQ ID NO:52)	(SEQ ID NO:51)
D11 Consensus Sequence	—	GTSX ₁ LX ₂ S	—
		(SEQ ID NO:87)	
C8-6	SVSSSVSSYLH	STSNLAS	IQYSGYPLT
	(SEQ ID NO: 53)	(SEQ ID NO:54)	(SEQ ID NO:55)
C8-H241	SVSSSVSSYLH	STSNLAS	QVYSGYPLT
	(SEQ ID NO:53)	(SEQ ID NO:54)	(SEQ ID NO:56)
C8-co-16	SVSSSVRSYLH	STSNLAS	QVYRGYPLT
	(SEQ ID NO:57)	(SEQ ID NO:54)	(SEQ ID NO: 58)
C8 Consensus Sequence	SVSSSVX ₃ SYLH	—	X ₄ X ₅ YX ₆ GYPLT
	(SEQ ID NO:88)		(SEQ ID NO: 89)

X₁ is Y or R, and X₂ is A or R;

X₃ is S or R;

X₄ is I or Q, X₅ is Q or V, and X₆ is S or R;

Table 2. Heavy Chain CDRs

Antibody	CDR 1	CDR 2	CDR 3
D11-S17Y	GYFTSRYIH	WIYPVTGDTYYNEKFKG	GYGAFYY
	(SEQ ID NO:59)	(SEQ ID NO:60)	(SEQ ID NO:61)
D11-8B8	GYFTSRYIH	WIYPVTGDTYYIEKFKG	GYGAFFY
	(SEQ ID NO:59)	(SEQ ID NO:62)	(SEQ ID NO:63)
D11-C27G3	GYFTSRYIH	WIYPVTGDTYYREPFGK	GYGAFYY
	(SEQ ID NO:59)	(SEQ ID NO:64)	(SEQ ID NO:61)
D11 Consensus Sequence	—	WIYPVTGDTYYX ₇ EX ₈ FKG	GYGAFX ₉ Y
		(SEQ ID NO:90)	(SEQ ID NO:91)
C8-6	GYFTDYMH	RVNPNRGGTTYNQKFEG	TNWLDY
	(SEQ ID NO:65)	(SEQ ID NO:66)	(SEQ ID NO:67)
C8-H241	GYFTDYMH	RVNPNRRGTTYNQKFEG	ANWLDY
	(SEQ ID NO:65)	(SEQ ID NO:68)	(SEQ ID NO:69)
	GYFTDYMH	RVNPNYRGSTTYNQKFEG	ANILDY

C8-69-16 Antibody	CDR 1	CDR 2	CDR 3
	(SEQ ID NO:65)	(SEQ ID NO:70)	(SEQ ID NO:71)
C8 Consensus Sequence	—	RVNPX ₁₀ RX ₁₁ X ₁₂ TTYNQKFEG	X ₁₃ NX ₁₄ LDY
		(SEQ ID NO:92)	(SEQ ID NO:93)

X₇ is N, I, or R, and X₈ is K or P;
X₉ is Y or F;
X₁₀ is N or Y, X₁₁ is G or R, and X₁₂ is G or S;
X₁₃ is T or A, and X₁₄ is W or I;

[0116] Consensus sequences for D11- and C8- antibody light and heavy chain variable regions are:

D11- Antibody Light Chain Variable Region Consensus Sequence (SEQ ID NO:94)

EVLVTQSPGTLSPGERATLSCSVSSISSTNLHWYQKPGQAPRLLIY
GTSX₁LX₂SGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQWSSYPYSGF
GGTKLEIK

wherein X₁ is Y or R, and X₂ is A or R;

C8- Antibody Light Chain Variable Region Consensus Sequence (SEQ ID NO:95)

DIQMTQSPSSLSASVGDRTVITCSVSSSVX₃SIYLHWYQKPGKAPKLLIY
STSNLASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCX₄X₅YX₆GYPLTFG
GGTKVEIK

wherein X₃ is S or R, X₄ is I or Q, X₅ is Q, or V, and X₆ is S or R;

D11-Antibody Heavy Chain Variable Region Consensus Sequence (SEQ ID NO:96)

QVQLVQSGAEVKKPGSSVKVSKCASGYTFTSRYIHVVRQAPGGLEWMGW
IYPVTGDTYYX₇EX₈FKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGY
GAFX₉YWGQGTLLTVS

wherein X₇ is N, I, or R, X₈ is K or P, and X₉ is Y or F;

C8- Antibody Heavy Chain Variable Region Consensus Sequence (SEQ ID NO:97)

QVQLVQSGAEVKKPGASVKVSKCASGYTFTDYMHVVRQAPGGLEWMGR
VNPX₁₀RX₁₁X₁₂TTYNQKFEGRVMTTDTSTSTAYMELSLRSDDTAVYYCARX₁₃
NX₁₄LDYWGQGTLLTVS

wherein X₁₀ is Y or N, X₁₁ is G or R, X₁₂ is S or G, X₁₃ is A or T, and X₁₄ is I or W.

[0117] Antibodies are transiently expressed in HEK293 EBNA cells (Edge BioSystems, #90500130) using standard transfection procedures. Transfected cells are cultured in standard serum-free medium containing geneticin (G418) and tobramycin for 48 to 120 hours at 37°C after transfection. Antibodies are purified on a 60 mL rProtein A Sepharose column (Amersham Biosciences, #17-1279-04) by following the manufacturer's instructions, and further concentrated and purified by size exclusion chromatography (XK50/60 Superdex200, Pharmacia) with phosphate buffered saline (PBS), pH 7.4, as the mobile phase. Antibodies are then filtered using Millev-GV, PVDF membranes, 0.22 µm, 33mm, (Millipore, # SLGV033RS), and stored at 4 to 8°C.

[0118] Murine IgG1 c-Met antibody 5D5 (U.S. Patent No. 5,686,292), discussed in many of the examples below, is isolated and purified from hybridoma HB-11895 obtained from the American Type Culture Collection, Manassas, VA, as described above.

Example 2

Binding Kinetics of c-Met Antibodies to Various c-Met Extracellular Domains

[0119] The extracellular domains (ECDs) of human, cynomolgus monkey, and rat c-Met sequences are expressed as Fc fusion

proteins with a flab- and His-tag (Flis-tag) at the C-terminus of the Fc (SEQ ID NOs:72-74). These c-Met ECD Fc fusion proteins are separately transiently expressed in HEK293 EBNA cells and purified as described in Example 1.

[0120] A Biacore® 2000 instrument is used to measure the binding kinetics of c-Met antibodies to human, cynomolgus monkey, and rat c-Met ECDs. Measurements are performed at 25°C. Samples are dissolved in HBS-EP buffer (150 mM sodium chloride, 3 mM EDTA, 0.005% (w/v) surfactant P-20, and 10 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) at pH 7.4; #BR-1001-88). F(ab')₂ fragment of goat anti human IgG, F(ab')₂ fragment specific (Jackson ImmunoResearch Inc, #109-006-097) is immobilized on flow cells 1 to 4 of a CM5 sensor chip at a level of 4000 response units (RUs) using amine coupling chemistry to capture anti-c-Met antibodies.

[0121] Binding is evaluated using multiple cycles. Each cycle is performed at a flow rate of 50 µL/min., and consists of the following steps: injection of about 10 µL of a c-Met antibody at 10 µg/mL aiming at a capture of 40-100 RUs, injection of 250 µL of human, cynomolgus, or rat c-Met-Flis-Fc ECD (starting at 100 nM and using two-fold serial dilutions for each cycle) followed by 20 min. for dissociation, and regeneration using about 30 µL of 10 mM glycine hydrochloride, pH 1.5. Association and dissociation rates for each cycle are evaluated using a "1:1 (Langmuir) binding" model in the BIAevaluation software, version 4.1. For binding of antibody D11-S17Y to rat c-Met-Flis-Fc ECD, a heterogeneous ligand model is used to fit the data adequately; therefore, two binding affinities are obtained.

[0122] The results are shown in Tables 3-5 below.

Table 3

Binding Kinetics and Affinity of c-Met Antibodies to Human c-Met-Flis-Fc ECD			
Antibody	k_{on} (1/Ms)	k_{off} (1/s)	K_D (nM)
D11-8B8	$1.0 \pm 0.1 \times 10^5$	$0.5 \pm 0.2 \times 10^{-4}$	0.5 ± 0.2
D11-C27G3	$6.4 \pm 0.2 \times 10^4$	$0.9 \pm 0.2 \times 10^{-4}$	1.4 ± 0.3
D11-S17Y	$0.7 \pm 0.1 \times 10^5$	$2.8 \pm 0.1 \times 10^{-4}$	4.2 ± 0.9
C8-H241	$1.1 \pm 0.3 \times 10^5$	$<10^{-5}$	<0.1
C8-6	$1.6 \pm 0.4 \times 10^3$	$3 \pm 2 \times 10^{-4}$	4 ± 1
C8-co16	$1.1 \pm 0.2 \times 10^5$	$0.3 \pm 0.2 \times 10^{-4}$	0.3 ± 0.1

Table 4

Binding Kinetics and Affinity of c-Met Antibodies to Cynomolgus Monkey c-Met-Flis-Fc ECD			
Antibody	k_{on} (1/Ms)	k_{off} (1/s)	K_D (nM)
D11-8B8	$0.78 \pm 0.02 \times 10^5$	$2.23 \pm 0.07 \times 10^{-4}$	2.9 ± 0.2
D11-C27G3	$0.5 \pm 0.1 \times 10^5$	$3.2 \pm 0.4 \times 10^{-4}$	6.5 ± 0.7
D11-S17Y	$0.70 \pm 0.08 \times 10^5$	$3.6 \pm 0.5 \times 10^{-4}$	5.1 ± 0.2
C8-H241	$0.80 \pm 0.06 \times 10^5$	$<10^{-5}$	<0.2
C8-6	$1.4 \pm 0.5 \times 10^5$	$4.5 \pm 0.2 \times 10^{-4}$	3.6 ± 1.1
C8-co16	$1.03 \pm 0.02 \times 10^5$	$<10^{-5}$	<0.1

Table 5

Binding Kinetics and Affinity of c-Met Antibodies to Rat c-Met-Flis-Fc ECD						
Antibody	k_{on} (1/Ms)	k_{off} (1/s)	K_D (pM)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (nM)
D11-8B8	$2.1 \pm 0.2 \times 10^5$	$1.9 \pm 0.3 \times 10^{-4}$	0.89 ± 0.04			
D11-C27G3	$1.3 \pm 0.1 \times 10^5$	$3.4 \pm 0.5 \times 10^{-4}$	2.7 ± 0.2			
D11-S17Y	0.66×10^5	189×10^{-4}	286	2.5×10^5	3.0×10^{-4}	1.2

[0123] These data demonstrate that antibodies C8-H241, C8-6, and C8-co16 bind both human and cynomolgus monkey c-Met ECDs with similar affinity, but not rat c-Met ECD. Additional data (not shown) indicate that these antibodies do not bind mouse c-Met ECD at up to 100 nM of antibody with 1 µg/mL ECD coated on ELISA plates. Antibodies D11-8B8, D11-C27G3, and D11-

S17Y, however, bind human, cynomolgus monkey, and rat c-Met ECDs.

Example 3

Epitope Mapping

[0124] The epitopes of the present c-Met antibodies are mapped by a combination of hydrogen-deuterium exchange mass spectrometry (HDXMS) (Yamada et al. (2002) *Rapid Commun. Mass Spectrom.* 16(4):293-299) and diethyl pyrocarbonate (DEPC) labeling (Mendoza et al. (2008) *Analy. Chem.* 80(8):2895-2904). Hydrogen-deuterium exchange reaction of human c-Met Sema domain is carried out in the presence or absence of c-Met antibodies. Sema domain regions that gain less deuterium in the presence of an antibody than in its absence are identified as the epitope(s) for the antibody. DEPC can react with amino groups of surface-exposed lysine or histidine residues in the Sema domain, forming ethyl carbamate lysine or histidine. If these amino acids are located in the epitope region, they will be protected, and will not react with DEPC upon antibody binding. This helps to further localize and/or confirm the epitope regions determined by HDXMS.

[0125] Expression and Purification of c-Met Sema Domain. The Sema domain of human c-Met is expressed with a Flis tag at the C-terminus (SEQ ID NO:76) in HEK293 EBNA cells and purified as described in Examples 1 and 2. The purified protein is then stored at 4°C in PBS at pH 7.4. This domain binds to the c-Met antibodies of the present invention with affinity similar to that of full length human c-Met ECD, indicating that the epitopes for these antibodies are located in this region of human c-Met.

[0126] Deglycosylation and Desialylation of the c-Met Sema Domain. 100 µL of 1.2 mg/mL human c-Met Sema domain solution are treated with 1 µL of PNGase F solution (Prozyme, GKE-5006B) at 37°C overnight for de-N-glycosylation. LC/MS analysis demonstrates that most of the protein is deglycosylated after this treatment. Separately, 100 µL of 1.2 mg/mL human c-Met Sema domain solution are treated with 2 µL of 10 U/mL neuraminidase solution (Roche, Cat. # 10 269 611 001) at 37°C for 1 hour to desialylate the Sema domain.

[0127] Formation of c-Met Sema Domain/Antibody Complexes. 10 µL of deglycosylated c-Met Sema domain solution (1.2 mg/mL) are mixed with an aliquot containing 29 µg protein of antibody solution (2.07 µL of C8-H241, 2.01 µL of D11-8B8, or 3.87 µL of an unrelated control Mab), and then diluted with 1X PBS solution to a final volume of 40 µL. Separately, 5 µL of desialylated human c-Met Sema domain solution (1.2 mg/mL) are mixed with an aliquot containing 14 µg protein of antibody solution (1.04 µL of C8-H241, 1.01 µL of D11-8B8, or 1.94 µL of the unrelated control Mab), and then diluted with 1X PBS solution to a final volume of 15 µL. Each of the mixed solutions of each antibody is then subjected to HDXMS analysis.

[0128] HDXMS Assays. 4 µL of deglycosylated or desialylated c-Met Sema domain/antibody mixture are mixed with 16 µL of 100% D₂O (Acros, Code 166310500; 80% D during exchange), and incubated at ambient temperature for 90 seconds. The exchange is then quenched with 50 µL of 0.5% (v/v) formic acid in water at 0°C. The quenched solution is immediately treated with 2 µL of 5 mg/mL (v/v) pepsin solution (Sigma, Cat. # P6887) at 0°C for 3.5 or 4 min. The digested solution is immediately manually injected onto an RP-HPLC column (Polymer Laboratories, Part #1912-1802; 2.1 x50mm, 1000 Å pore size, 8 µm particle size). The HPLC buffer stream from the HPLC pump (Waters, 2795 HPLC) passes through a metal tube (approximately 1 mL) to a manual injector. The column eluate is then passed to a Micromass LCT Premier or SYNAPT mass spectrometer. The metal tube, injector loop, and column are submerged in an ice water bath.

[0129] The column is equilibrated with 99% A (0.05% (v/v) aqueous TFA (trifluoroacetic acid) and 1% B (0.04% (v/v) TFA in acetonitrile) at a flow rate of 0.2 mL/min. An isocratic gradient elution is performed for 1 min., from 1 to 10% B over 1 min., to 40% B over 12 min., to 90% B over 4 min. with a 3 min. hold, and then rapidly returned to the initial conditions. The mass spectrometry is performed on a Micromass LCT Premier Mass Spectrometer with a positive spray, W mode, and the following settings: a capillary voltage of 1.5 kV, a cone voltage of 100 V, Aperture 1 of 25 V, a mass range of 200 to 2000, a desolvation temperature of 150°C, and a desolvation gas flow of 500 L/h. The mass spectrum of each peptic peptide of c-Met is obtained after D/H exchange with or without c-Met antibody. The average mass of each peptide is calculated according to the isotopic distribution of the most intense ion peak.

[0130] DEPC Labeling of c-Met/Antibody Complexes. 8.3 µL of 1.2 mg/mL human c-Met Sema domain solution are mixed with an antibody solution (24 µg protein: 1.71 µL of C8-H241, 1.67 µL of D11-8B8, or 3.2 µL of unrelated control Mab), and 1X PBS solution to a final volume of 76 µL. Each c-Met/antibody mixture is treated with 4 µL of 10 mg/mL (w/v) DEPC in isopropanol at ambient temperature for 5 min. and then quenched with 10 µL of 20 mg/mL histidine in 0.1 M Tris-HCl buffer, pH 8, and 10 µL

of 0.2 mg/mL lysine in 0.1 M Tris-HCl buffer, pH 8. Each solution is mixed with 5 μ L of 0.2 mg/mL (w/v) porcine trypsin solution (Promega, Cat. # V528A), and half of the mixture is mixed with 0.5 μ L of 50 mg/mL (w/v) dithiothreitol solution. Each sample solution is incubated at 37°C for 5 hours and then treated with 0.5 μ L of PNGase F solution for an additional hour. Each digested solution is acidified with 2 μ L of 10% (v/v) acetic acid solution. 2 μ L of 100 mg/mL TCEP (tris(2-carboxyethyl) phosphine hydrochloride (Sigma, Cat. # C4702-2G) solution are added to the unreduced digest without added dithiothreitol. Each of the solutions is subjected to LC/MS analysis using a Waters Acquity UPLC and Waters SYNAPT Mass spectrometer. The HPLC uses a Waters Acquity UPLC BEH C8 column (2.1 $\times$ 50mm, 1.7 μ m, Waters, part #186002877) at 60 °C, and peptides are eluted with an acetonitrile gradient in a water/acetonitrile/TFA HPLC mobile phase system. A 45 min. run time is used for the digests. The column is equilibrated with 99% A (0.05% (v/v) TFA aqueous solution) and 1% B (0.04% (v/v) TFA in acetonitrile) at a flow rate of 0.2 mL/min. A gradient elution is performed in isocratic state for 2 min., from 1 to 25% B over 25 min., to 45% B over 10 min., to 90% B over 1 min., with 1.5 min. hold (at the same period of time, flow rate of 0.3 mL/min.), and then rapidly returned to 1% B.

[0131] Results. Mab C8-H241 appears to bind a conformational epitope comprising four regions of the c-Met Sema domain, located in the α -chain of the human c-Met extracellular domain (amino acid residues 25-307 of SEQ ID NO:75):

121VVDYYDDQL₁₃₀ (SEQ ID NO:77),

131ISCGSVNRGTCQRHVFPNHTADIQS₁₅₆ (SEQ ID NO:78),

179ALGAKVLSSVKDRFINFF₁₉₆ (SEQ ID NO:79), and

216VRRLKETKDGM₂₂₇ (SEQ ID NO:80).

[0132] More particularly, Mab C8-H241 binds c-Met by interacting with one or more amino acid residues within:

123DTYYDD₁₂₈ (SEQ ID NO:81) inclusive,

144HVFPHNHTADIQS₁₅₆ (SEQ ID NO: 82) inclusive,

192FINF₁₉₅ (SEQ ID NO:83) inclusive, and

220KETKDGM₂₂₇ (SEQ ID NO:84) inclusive.

[0133] Binding of Mab C8-H241 to the region 144HVFPHNHTADIQS₁₅₆ (SEQ ID NO: 82) renders it capable of binding both human (SEQ ID NO:75) and cynomolgus monkey (amino acids 25 to 932 of SEQ ID NO:73) c-Met extracellular domain with comparable affinity, but not rat or mouse c-Met, up to 100 nM of antibody in binding assays.

[0134] Mab D11-8B8 binding to the α -chain of the c-Met Sema domain appears to be localized to one region, i.e., amino acid residues within a linear epitope within the amino acid sequence 84YKTGPVLEHPDCFCQDCSSKANL₁₀₇ (SEQ ID NO:85) inclusive, more particularly the region 95CFPCQDCSSKA₁₀₅ (SEQ ID NO:86) inclusive. The epitope for Mab D11-8B8 is further confirmed by epitope extraction experiments (Dhungana et al. (2009) Methods Mol. Biol. 524:87-101). c-Met Sema domain is digested with porcine trypsin (Promega) and the digest is then mixed with biotinylated Mab D11-8B8, using the EZ-Link™ Sulfo-NHS-LC-Biotin kit (Pierce, Prod. #1754210), to bind the c-Met peptides. Biotinylated D11-8B8 with or without bound c-Met peptides is captured by high capacity Streptavidin agarose resin (Thermo Scientific, Prod. # 20359). The bound peptides are released by 0.15% formic acid (v/v) in H₂O, and then identified by LC/MS.

Example 4

Preferential Binding of Antibodies to c-Met vs. RON and PlexinA2 ECDs

[0135] The human proteins with the greatest sequence identity to c-Met are RON and Plexin A2. This experiment compares the specificity of c-Met antibody binding to c-Met, RON, and PlexinA2 ECDs.

[0136] Wells of 96-well EIA/RIA high binding plates (Costar, #2592) are coated with 100 μ L of 1 μ g/mL human c-Met extracellular domain (ECD)-Fc-Flis fusion (SEQ ID NO:72), RON-ECD-Fc (R&D Systems, #1947-MS), or PlexinA2-ECD-Fc (Abnova, Taipei, Taiwan #H00005362-P01) in coating buffer (BioFX Labs, # COAT-1000-01) overnight at 4°C. The wells are aspirated and non-specific binding sites are blocked by adding 200 μ L of blocking buffer (Tris-buffered saline, pH 8.0, with 0.05% (v/v) polysorbate 20 (Tween-20) (TBS-T) (BioFX Labs, # WSHW-1000-01) plus 1% (w/v) bovine serum albumin (BSA) (Jackson Immuno, #001-000-162) and incubating for 1 hour at room temperature. After the plates are washed three times with wash buffer (TBS-T), 100 μ L/well of 1:6 serial dilutions of c-Met antibodies in blocking buffer (starting from 100 μ g/mL) are added and incubated at room temperature for 2 hours. The plates are washed and incubated with 100 μ L/well of HRP-conjugated goat anti-human F(ab)₂ IgG (Jackson ImmunoResearch Labs #109-036-097) in blocking buffer for 90 min. After the plates are washed, 100 μ L/well of substrate solution (BioFx, #TMBW-1000-01) are added and the plates are incubated for 10 min. at room temperature. 100 μ L/well of stop solution (BioFx, # LSTP-1000-01) are added to stop the reaction. The colorimetric signals are developed and read at 450 nm using a SpectraMax 190 plate reader (Molecular Devices, Sunnyvale, CA). c-Met antibody binding to c-Met, RON and PlexinA2 ECDs is proportional to color signal production.

[0137] As shown in Table 6, both C8 and D11 c-Met antibodies of the present invention preferentially bind to human c-Met ECD compared to RON ECD or PlexinA2 ECDs.

Table 6

Preferential Binding of c-Met Antibodies to Human c-Met ECD vs. RON and PlexinA2 ECDs									
Antibody dose (ng/mL)	Average A450 nm								
	C8-H241			C8-6			C8-co16		
	c-Met ECD	RON ECD	Plexin A2	c-Met ECD	RON ECD	Plexin A2	c-Met ECD	RON ECD	Plexin A2
0.000	0.300	0.098	0.092	0.322	0.110	0.109	0.335	0.106	0.104
0.002	0.317	0.088	0.082	0.326	0.106	0.099	0.369	0.100	0.094
0.010	0.317	0.081	0.090	0.335	0.097	0.095	0.374	0.096	0.078
0.060	0.484	0.104	0.099	0.551	0.087	0.096	0.446	0.089	0.082
0.357	0.902	0.091	0.097	0.813	0.080	0.107	0.907	0.083	0.095
2.143	2.861	0.101	0.103	2.415	0.098	0.106	2.888	0.114	0.092
12.860	4.000	0.079	0.083	4.000	0.087	0.085	4.000	0.102	0.069
77.160	4.000	0.085	0.079	4.000	0.090	0.078	4.000	0.084	0.096
462.963	4.000	0.090	0.104	4.000	0.088	0.086	4.000	0.103	0.092
2777.778	4.000	0.085	0.092	4.000	0.088	0.094	4.000	0.095	0.114
16666.667	4.000	0.117	0.125	4.000	0.124	0.118	4.000	0.198	0.284
100000.000	4.000	0.267	0.310	4.000	0.170	0.171	4.000	0.421	0.983
Standard Error									
0.000	0.006	0.015	0.007	0.011	0.000	0.004	0.003	0.005	0.011
0.002	0.003	0.006	0.002	0.012	0.005	0.006	0.023	0.000	0.006
0.010	0.002	0.000	0.005	0.001	0.004	0.009	0.015	0.012	0.002
0.060	0.055	0.001	0.002	0.144	0.004	0.005	0.029	0.003	0.002
0.357	0.004	0.004	0.002	0.022	0.005	0.003	0.005	0.007	0.000
2.143	0.032	0.004	0.005	0.041	0.004	0.003	0.128	0.002	0.007
12.860	0.000	0.001	0.012	0.000	0.000	0.007	0.000	0.004	0.004
77.160	0.000	0.002	0.014	0.000	0.008	0.007	0.000	0.003	0.001
462.963	0.000	0.004	0.003	0.000	0.006	0.001	0.000	0.013	0.001
2777.778	0.000	0.004	0.002	0.000	0.004	0.001	0.000	0.007	0.000
16666.667	0.000	0.005	0.004	0.000	0.004	0.003	0.000	0.003	0.002

Standard Error									
100000.00 0	0.000	0.008	0.012	0.000	0.002	0.003	0.000	0.011	0.093
D11-8B8			D11-C27G3			D11-S17Y			
c-Met ECD	RON ECD	Plexin A2	c-Met ECD	RON ECD	Plexin A2	c-Met ECD	RON ECD	Plexin A2	
0.297	0.097	0.081	0.2844	0.0791	0.0771	0.31475	0.1129		0.10795
0.299	0.082	0.078	0.2708	0.07065	0.07965	0.3091	0.09705		0.09345
0.304	0.074	0.078	0.2904	0.0715	0.0763	0.31405	0.0868		0.0986
0.445	0.094	0.073	0.45965	0.0695	0.06605	0.37355	0.0857		0.09455
1.314	0.073	0.074	1.43965	0.07085	0.0792	0.78915	0.08475		0.0924
2.416	0.069	0.073	2.5266	0.0655	0.0742	2.1432	0.1085		0.08235
3.931	0.079	0.075	4	0.07835	0.0641	4	0.0825		0.0768
4.000	0.079	0.066	4	0.06725	0.076	4	0.08195		0.07575
4.000	0.071	0.077	4	0.0981	0.1045	4	0.08185		0.0783
4.000	0.088	0.093	4	0.20445	0.30325	4	0.09255		0.0955
4.000	0.165	0.181	4	0.67565	1.33475	4	0.1274		0.1491
4.000	0.544	0.498	3.9211	2.30295	3.37085	4	0.23775		0.3146
Standard Error									
0.006	0.003	0.003	0.0087	0.0017	0.0106	0.00515	0.0012		0.00035
0.011	0.002	0.002	0.0194	0.00595	0.00185	0.0228	0.00065		0.01725
0.012	0.002	0.001	0.0051	0.0018	0.0017	0.01195	0.0058		0.0079
0.007	0.017	0.003	0.01495	0.0006	0.00335	0.00375	0.0013		0.00035
0.092	0.007	0.004	0.02935	0.00695	0.0017	0.04195	0.00075		0.0039
0.044	0.002	0.001	0.2742	0.0002	0.0015	0.0841	0.0054		0.00015
0.069	0.005	0.002	0	0.01505	0.0043	0	0.0029		0.0061
0.000	0.007	0.000	0	0.00275	0.0066	0	0.00445		0.00455
0.000	0.005	0.004	0	0.0063	0.0032	0	0.00485		0.0089
0.000	0.003	0.005	0	0.00975	0.00535	0	0.00705		0.0055
0.000	0.007	0.004	0	0.03125	0.03495	0	0.0007		0.0035
0.000	0.016	0.006	0.0789	0.07335	0.14345	0	0.00865		0.004

Example 5**c-Met Antibodies Block HGF/c-Met Binding**

[0138] *In vitro* binding assays are used to determine inhibition of HGF binding to c-Met by the present c-Met antibodies.

[0139] Wells of 96-well EIA/RIA high binding plates (Costar, #2592) are coated with 100 μ L of human c-Met ECD-Fc-Flis (SEQ ID NO:72) (2 μ g/mL) in Dulbecco's phosphate buffered saline (DPBS) overnight at room temperature; washed four times with wash buffer (Tris-buffered saline, pH 8.0, with 0.05% (v/v) polysorbate 20 (TWEEN[®]-20) (TBS-T) (BioFX Labs, # WSHW-1000-01) in a plate washer; blocked by adding 300 μ L of blocking buffer (TBS-T plus 1% (w/v) bovine serum albumin (BSA) (Jackson Immuno, #001-000-162); and incubating for 60 min. at 37°C. Blocking buffer is then removed from the wells and 50 μ L of antibodies in blocking buffer at final concentrations as indicated in Table 7 are added into each well, respectively. Blocking buffer is added to the HGF-only control wells. The plates with c-Met antibodies are incubated for 90 min. at 37°C. 50 μ L of human hepatocyte

growth factor (HGF) (R&D Systems, #294) in blocking buffer at a final concentration of 10 ng/mL are then added to each well except the antibody-only control wells. The plates containing the c-Met antibody/HGF mixture are incubated on a plate shaker for two hours at room temperature. The wells are then washed four times with TBS-T in a plate washer. Next, 100 μ L of biotinylated anti-HGF antibody (R&D Systems, # BAF294) in blocking buffer at a final concentration of 100 ng/mL are added into each well. The plates are incubated for 90 min. at room temperature. The wells are again washed four times with TBS-T in a plate washer. 100 μ L of a 1:200 dilution of streptavidin-horseradish peroxidase (HRP) (R&D Systems, DY998) in blocking buffer are added to each well. The plates are incubated for 30 min. at room temperature. The wells are washed four times with TBS-T in a plate washer. 100 μ L/well of substrate solution (BioFx, #TMBW-1000-01) are then added, and the plates are incubated for 10 min. at room temperature. To stop the reaction, 100 μ L/well of stop solution (BioFx, # LSTP-1000-01) are added. The samples are read at a wavelength of 450-570 nm on a microplate reader (Spectra, MAX 190) and no background is subtracted.

[0140] As shown in Table 7, both C8 and D11 c-Met antibodies of the present invention block human HGF/c-Met binding.

Table 7

Inhibition of Human HGF Binding to Human c-Met by C8- and D11- Antibodies								
	AVG A450 nm							
Antibody dose (ng/mL)	hlgG2	D11-8B8	D11-27G3	D11-S17Y	hlgG4	C8-6	C8-H241	C8-co16
0.00	2.43	2.43	2.43	2.43	2.61	2.61	2.61	2.61
0.48	2.46	2.51	2.37	2.15	2.41	2.56	2.45	2.05
1.91	2.87	2.48	2.31	1.98	2.49	2.59	2.46	2.18
7.63	2.70	2.41	2.27	2.08	2.88	2.64	2.53	2.20
30.52	2.41	2.32	2.38	2.07	2.63	2.42	2.42	2.08
122.07	2.52	1.92	1.60	1.69	2.44	2.00	1.77	1.30
488.28	2.53	1.30	0.94	1.29	2.44	1.33	0.73	0.70
1953.13	2.43	1.43	0.97	1.23	2.27	1.08	0.68	0.60
7812.50	2.50	1.24	0.91	1.12	2.49	0.95	0.70	0.57
31250.00	2.50	1.31	0.94	1.17	2.67	0.98	0.77	0.56
125000.00	2.43	1.38	0.89	1.35	3.00	1.32	0.69	0.38
	STDErr							
0.00	0.06	0.06	0.06	0.06	0.10	0.10	0.10	0.10
0.48	0.02	0.13	0.01	0.09	0.24	0.02	0.14	0.15
1.91	0.27	0.08	0.08	0.03	0.00	0.03	0.16	0.12
7.63	0.14	0.01	0.21	0.08	0.14	0.03	0.06	0.09
30.52	0.09	0.02	0.31	0.09	0.16	0.01	0.03	0.01
122.07	0.09	0.07	0.03	0.02	0.08	0.10	0.02	0.03
488.28	0.00	0.04	0.04	0.02	0.01	0.02	0.00	0.01
1953.13	0.13	0.16	0.02	0.05	0.00	0.01	0.01	0.01
7812.50	0.04	0.01	0.01	0.02	0.25	0.07	0.01	0.02
31250.00	0.06	0.02	0.02	0.04	0.03	0.03	0.03	0.03
125000.00	0.07	0.03	0.01	0.08	0.13	0.47	0.01	0.00
Abbreviations: AVG = average; STDErr = Standard Error								

Example 6

c-Met Antibodies Induce Weak c-Met Phosphorylation Compared to Hnatocyte Growth Factor and Agonist Mab 5D5

[0141] Upon stimulation with HGF, the A549 lung carcinoma cell line exhibits increased c-Met phosphorylation at tyrosine residue 1349. A phosphorylated c-Met (p-Met) ELISA assay is used to measure the agonistic activity of various c-Met antibodies in the absence of HGF, as well as of Mab 5D5 and HGF itself.

[0142] A549 cells (ATCC, #CCL-185) are cultured in Ham's F12K + 2 mM glutamine (Invitrogen, # 21127-022) + 10% FBS medium (Invitrogen, #10082). Cells are plated at 6×10^4 cells/well in the full serum medium as above in 96-well plates and incubated overnight at 37°C under 5% (v/v) CO₂. The medium is removed from the wells and the cells are starved in 100 µL of Ham's F12K + 2 mM glutamine medium + 0.5% FBS for six hours at 37°C under 5% (v/v) CO₂. Antibodies or HGF are diluted in the starvation culture medium, added at final concentrations as indicated in Table 8, and incubated for 15 min. at 37°C. The medium is aspirated and cells are lysed in 50 µL lysis buffer (10 mM Tris (Invitrogen, #15567-027), 150 mM NaCl, 2 mM ethylenediaminetetraacetic acid (EDTA) (Invitrogen, #15575-038), 50 mM NaF (Sigma, #S1504), 1% (v/v) octylphenoxy polyethoxy ethanol (TRITON®-X 100; Sigma, #T8787), 2 mM sodium orthovanadate (EMD Chemicals, Gibbstown, NJ, #567540), protease inhibitor (Sigma, St. Louis, MO; #P8340), phosphatase inhibitor cocktail 1 (Sigma #P2850), and phosphatase inhibitor cocktail II (Sigma #P5726)) per well and incubated on ice for 15-20 min. Cell lysates are used in the ELISA assay described below to determine the phosphorylation of c-Met at residue Y1349.

[0143] c-Met capture antibody is diluted in Bup H coating buffer (Thermo Fisher Scientific, Waltham, MA, #28382) to 2 µg/mL, added to ELISA plates (Greiner Bio-One, Monroe, NC, #655081) and incubated overnight at 4°C. The wells are aspirated, washed three times with TBS-T (BioFX, Owings Mills, MD, WSH-1000-01), and then blocked with 200 µL of blocking buffer (TBS-T plus 2% (w/v) BSA) for 1 hour at room temperature. The plates are washed three times with TBS-T. Next, 25 µL of cell lysates plus 75 µL blocking buffer are added, and the plates are incubated overnight at 4°C. The plates are then washed three times with TBS-T. 100 µL of 0.5 µg/mL of pY1349 c-Met polyclonal antibody (Cell Signaling Technology, Danvers, MA, #3133) in blocking buffer are added to each well, and incubated for 2 hours at room temperature. The plates are then washed three times with TBS-T. 100 µL of 1/10,000 diluted peroxidase-conjugated goat anti-rabbit IgG polyclonal antibody (Jackson ImmunoResearch Laboratories, West Grove, PA, #111-035-144) in blocking buffer are added to each well and incubated 1 hour at room temperature. The plates are then washed three times with TBS-T. 100 µL of 3,3',5,5'-tetramethylbenzidine solution (BioFX, #TMBW-1000-01) are added to each well, followed by the addition of 100 µL stop solution (BioFX, #LSTP-1000-01). The plates are read at 450 nm on a SpectraMax M5 plate reader (Molecular Devices, Sunnyvale, CA) and sample values are determined using SOFTmax Pro 4.8 software (Molecular Devices).

[0144] The results are shown in Table 8.

Table 8

Effect of c-Met Antibodies, HGF, and Agonist Mab 5D5 on c-Met Phosphorylation in A549 Cells			
Ab Conc. (µg/mL)	p-Met signal C8-H241	p-Met signal C8-6	p-Met signal hlgG4
30	0.333	0.272	0.061
10	0.418	0.334	0.077
3.333	0.450	0.328	0.068
1.113	0.465	0.365	0.087
0.370	0.340	0.211	0.082
0.123	0.304	0.127	0.067
0.041	0.130	0.125	0.268
0.014	0.078	0.105	0.074
0.005	0.074	0.070	0.074
0.002	0.070	0.081	0.117
HGF Conc. (ng/mL)	p-Met signal	Ab Conc. (ng/mL)	p-Met signal Mab 5D5
300	10.615	5	3.290
100	6.129		
33.33333	2.267		
11.11111	1.0667		
3.703704	0.461		

HGF Conc. (ng/mL)	p-Met signal	Ab Conc. (ng/mL)	p-Met signal Mab 5D5
1.234568	0.211		
0.411523	0.142		
0.137174	0.128		
0.045725	0.100		
0.015242	0.148		

[0145] The data demonstrate that HGF and agonist c-Met Mab 5D5 strongly stimulate c-Met phosphorylation, while present c-Met Mabs C8-H241 and C8-6 weakly stimulate c-Met phosphorylation. Similar results are obtained in HCT116, H460, and MDA-MB-231 cell lines.

[0146] Mab D11-8B8 yields similar results.

Example 7

c-Met Antibodies inhibits HGF-Induced c-Met Phosphorylation

[0147] Binding of HGF to c-Met results in tyrosine phosphorylation of c-Met molecules and activation of the c-Met signaling pathway. In this example, human colon cancer cell line HCT116, which is responsive to HGF, is used to assess the inhibition of HGF-induced phosphorylation at tyrosine residues 1230, 1234, and 1235 of c-Met by the present c-Met antibodies.

[0148] HCT116 cells (ATCC, Manassas, VA, #CCL-247) are resuspended to 150,000 cells/mL in McCoy's 5A medium (Invitrogen, Carlsbad, CA, #16600-082) plus penicillin/streptomycin (Invitrogen, #15140-122) with 10% (v/v) fetal bovine serum (FBS) (Invitrogen, #10082-147). 0.2 mL of the resuspended HCT116 cells are added to 96-well microtiter plates (Corning, Lowell, MA, #3596) at 30,000 cells/well, and the cells are then incubated for 48 hours at 37°C under 5% (v/v) CO₂. The culture medium is then aspirated and the cells are starved in 100 µL of McCoy's 5A medium plus penicillin/streptomycin with 0.1% (w/v) BSA for 24 hours at 37°C under 5% (v/v) CO₂. 25 µL of sodium azide (final concentration of 0.01% (w/v)) (Sigma, #S2002) are added, followed immediately by adding 25 µL of 8X c-Met antibody dilutions to McCoy's 5A medium plus penicillin/streptomycin with 0.1% (w/v) BSA, and the cells are incubated for 30 min. at 37°C under 5% (v/v) CO₂. 50 µL of HGF at a final concentration of 200 ng/mL are added to each well and the cells are incubated for an additional 15 min. at 37°C under 5% (v/v) CO₂. The medium is then aspirated and 50 µL of cell lysis buffer are added (10 mM Tris (Invitrogen, #15567-027), 150 mM NaCl, 2 mM ethylenediaminetetraacetic acid (EDTA) (Invitrogen, #15575-038), 50 mM NaF (Sigma, #S1504), 1% (v/v) octylphenoxypolyethoxy ethanol (TRITON®-X100; Sigma, #T8787), 2 mM sodium orthovanadate (EMD Chemicals, Gibbstown, NJ, #567540), and complete protease inhibitor, EDTA free (Roche, Basel, Switzerland, #11836170001). Cells are incubated in the lysis buffer at room temperature for 15-30 min. Cell lysates are assayed for c-Met tyrosine phosphorylation by ELISA as follows.

[0149] c-Met capture antibody is diluted in coating buffer (BioFX, Glendora, CA, COAT-1000-01) to 2 µg/mL. 110 µL of the diluted antibody are added per well to ELISA plates (Greiner Bio-One, Monroe, NC, #655081) and the plates are incubated overnight at 4°C. The wells are aspirated, washed twice with TBS-T, and then blocked with 200 µL of blocking buffer (TBS-T plus 2% (w/v) BSA) for 1 hour. The plates are washed twice with TBS-T. Next, 25 µL of cell lysates plus 75 µL blocking buffer or 100 µL of MKN45 cell lysate dilutions (diluted with blocking buffer, as a standard) are added, and the plates are incubated for 2 hours at room temperature. The plates are then washed four times with TBS-T. 100 µL of 0.5 µg/mL of pYpY1230/1234/1235 c-Met polyclonal antibody (Invitrogen, #44-888G) in blocking buffer are then added to each well, and the plates are incubated for 2 hours at room temperature. Next, the plates are washed four times with TBS-T. 100 µL of 1/12,000 diluted peroxidase-conjugated goat anti-rabbit IgG polyclonal antibody (Jackson ImmunoResearch Laboratories, West Grove, PA, #111-035-144) in blocking buffer are then added, and the mixture is incubated for 1 hour at room temperature. The plates are then washed six times with TBS-T. 100 µL of 3,3',5,5'-tetramethylbenzidine solution (BioFX, #TMBW-1000-01) are added to each well, followed by the addition of 100 µL stop solution (BioFX, #LSTP-1000-01). The plates are read at 450 nm with a 570 nm correction using a SpectraMax 190 plate reader (Molecular Devices, Sunnyvale, CA). The standard curve is established using 4-parameter analysis, and sample values are determined using SOFTmax Pro 3.1.2 software (Molecular Devices).

[0150] The percentage of inhibition of c-Met tyrosine phosphorylation is set at the average of HGF treatment without c-Met antibody addition (0% inhibition), and 100% inhibition is set at the average of sodium azide treatment (no HGF or c-Met antibody treatment).

[0151] Table 9 shows the average of triplicate treatments per experiment for three experiments with standard errors. The data demonstrate that five of six c-Met antibodies of the present invention significantly inhibit HGF-induced tyrosine phosphorylation of c-Met compared to that of the human IgG2 and IgG4 isotype controls.

Table 9

Percent Inhibition of HGF-Induced c-Met Tyrosine Phosphorylation By C8-and D11- Antibodies													
		Antibody doses:											
		10 µg/mL		2 µg/mL		0.4 µg/mL		0.08 µg/mL		0.016 µg/mL		0.0032 µg/mL	
Ab treatment	isotype	average	sterr	average	sterr	average	sterr	average	sterr	average	sterr	average	sterr
D11-8B8	IgG2	19.56	4.68	40.74	8.24	35.04	6.43	10.52	7.41	-6.68	9.48	-10.37	6.79
D11- C27G3	IgG2	1.25	7.55	31.78	7.71	38.10	4.97	20.79	5.72	5.73	8.95	9.72	7.09
D11- S17Y	IgG2	16.73	8.72	31.39	6.43	15.91	6.05	-3.24	10.54	2.53	8.52	9.48	8.51
C8-H241	IgG4	60.08	5.27	62.20	2.10	59.09	3.05	22.09	4.92	14.68	12.40	-12.33	10.18
C8-co-16	IgG4	65.40	3.94	58.96	3.37	45.08	3.44	9.77	9.14	-2.89	10.95	-10.72	5.41
C8-6	IgG4	14.88	10.78	27.94	3.80	16.83	4.36	7.79	7.68	-6.06	8.84	-11.34	8.65
5D5	mIgG1	64.12	3.31	63.75	4.44	42.55	4.27	11.87	7.73	-3.50	9.70	-6.07	5.68
hIgG2	isotype control	6.24	5.31	17.53	5.74	9.31	6.56	-1.58	8.16	9.49	6.77	-10.21	6.78
hIgG4	isotype control	-1.47	5.76	-6.62	9.07	-16.07	7.01	-21.70	9.09	-7.96	10.97	-14.40	7.37
mIgG1	isotype control	5.46	6.31	9.76	9.27	13.43	8.18	-10.59	10.31	-5.42	10.53	-9.76	8.42
		ave	sterr										
untreated		100.00	0.98										
HGF	200 ng/mL	0.001	2.76										
% inhibition of HGF stimulated phospho-Met as measured by ELISA													

Examples 8

Induction of c-Met Internalization by c-Met Antibodies

[0152] The experiments described in this example employ fluorescence-activated cell sorting (FACS) analysis to demonstrate that the present c-Met antibodies bind to cell surface c-Met molecules and induce c-Met internalization. The MKN45 cells employed constitutively express high levels of total c-Met, and exhibit HGF-independent phosphorylation of c-Met as a result of *MET* gene amplification. c-Met internalization appears to induce c-Met degradation (see Examples 10 and 19), resulting in inhibition of the c-Met signaling pathway.

[0153] Wells of 6-well tissue culture plates (Costar, #3598) are seeded with 1.5×10^5 human gastric tumor MKN45 cells (Japan Health Sciences Foundation, Health Science Research Resource Bank, #JCRB0254) in 2 mL of culture medium (RPMI-1640

(Invitrogen, #11835); 10% (v/v) FBS (Invitrogen, #10082); 2 mM L-glutamine (Invitrogen, #25030); 100 U/500mL penicillin G, and 100 µg/500 mL streptomycin (Invitrogen, #15140)). The plates are incubated for 24 hours at 37°C under 95% relative humidity and 5% (v/v) CO₂. Antibodies are then added to the wells at a final concentration of 5 µg/mL. After overnight treatment, the culture medium is removed from the wells and replaced with 1 mL of enzyme-free cell dissociation solution (Chemicon, #S-014-B). The cells are collected into centrifuge tubes after being incubated for 5 min. at room temperature, and washed once in culture medium followed by one more wash in binding buffer (DPBS with 1% (w/v) BSA and 0.01% (w/v) sodium azide). Before staining cells, a c-Met antibody that recognizes a different epitope from the present c-Met antibodies is labeled by using an Alexa Fluor 488 Monoclonal Antibody Labeling Kit (Molecular Probes, Eugene, OR, #A-20181) according to the supplier's instructions. 100 µL of binding buffer containing 2 µg/mL of the Alexa Fluor 488-labeled antibody are added to the cells, which are then incubated for 60 min. on ice. The cells are then washed once with binding buffer and resuspended in DPBS containing 2 µg/mL propidium iodide (to stain the dead cells). The amount of c-Met molecules remaining on the cell surface is analyzed by FACS analysis, and 10,000 events are acquired for each sample.

[0154] The mean fluorescence intensity on the cell surface reflects the quantity of c-Met molecules that remain on the cell surface after treatment with c-Met antibodies.

[0155] The data from one representative experiment are shown in Table 10.

Table 10

Effect of C8- and D11- Antibodies on c-Met Internalization as Determined by FACS Analysis										
Antibody (µg/mL)	Mean Fluorescence		D11-C27G3	D11-S17Y	hlgG4	C8-6	C8-H241	C8-co16	mlgG	5D5
	hlgG2	D11-8B8								
5.00	130.25	44.66	51.09	56.35	135.03	67.88	57.63	56.16	136.47	92.87

[0156] The data demonstrate that the mean fluorescence intensity on the surface of cells treated with the present c-Met antibodies is lower than that in cells treated with a corresponding IgG isotype control antibody or mlgG antibody, indicating that the present c-Met antibodies induce c-Met internalization. Moreover, the mean fluorescence intensity on the surface of the cells treated with the present c-Met antibodies is lower than that in cells treated with control agonist c-Met antibody 5D5. % internalization may be calculated as follows

$$\% \text{ internalization} = [1 - (\text{mean fluorescence of test antibody divided by mean fluorescence of isotype antibody control})] \text{ multiplied by } 100].$$

[0157] The internalization data suggest that the present antibodies induce dimerization of human c-Met. The data in Examples 9 and 19 demonstrate that C8- and D11- antibodies also induce degradation, and reduce phosphorylation, of c-Met.

[0158] Complementary internalization results are obtained by confocal microscopy using fluorescently labeled murine C8 antibody in MKN45 and Caki-1 cells.

[0159] Using C8-H241, C8-6, C8-co-16, and murine D11 antibodies, similar internalization results are obtained in cynomolgus monkey NIH3T3 cells transfected with nucleic acid encoding cynomolgus monkey c-Met.

[0160] C8-H241, C8-6, C8-co-16, and optD11 antibodies also induce internalization of c-Met in NIH3T3 cells transfected with nucleic acid encoding human c-Met kinase domain mutation M1149T. Antibodies C8-H241, C8-6, C8-co-16, and murine D11 also induce internalization of c-Met in non-small cell lung cancer H 1437 cells containing c-Met juxtamembrane domain mutation R988C. Both mutations cause gain-of function constitutive activation of the c-Met.

Example 9

Antibody Inhibition of Ligand-Independent Tumor Cell Proliferation *In Vitro*

[0161] The inhibition of tumor cell growth *in vitro* by c-Met antibodies in HGF-independent MKN45 cells in the absence of HGF

ligand is examined in this assay.

[0162] c-Met and isotype control antibodies are diluted with culture medium (RPMI-1640 (Invitrogen, #11835), 10% (v/v) FBS, 2 mM L-glutamine (Invitrogen, #25030), 100 U/500mL penicillin G, and 100 µg/500 mL streptomycin (Invitrogen, #15140)) to achieve 2X the final concentrations indicated in Table 11, and 50 µL of the 2X antibody solutions are added to each well of 96-well tissue culture plates (PerkinElmer#1450-517). MKN45 cells (Japan Health Sciences Foundation, Health Science Research Resource Bank, #JCRB0254) are maintained in the medium indicated above, and are resuspended to 1×10^5 cells/mL in the same medium. 50 µL of this MKN45 resuspension are added to each well to achieve 5×10^3 cells/well. The plates are then incubated for 48 hours at 37°C under 95% relative humidity and 5% (v/v) CO₂. For the last six hours of the culture, the cells are pulsed with ³H-thymidine (MP Biomedicals, Solon, OH #24066) at 1 µCi/well at 37°C, 95% relative humidity, 5% (v/v) CO₂. The medium is then removed and the cells are washed once with DPBS. After this, 200 µL of Optiphase Supermix (PerkinElmer, #1200-439) are added to each well. The plates are sealed and incubated for at least one hour at room temperature. ³H-thymidine incorporated in the cells is counted for one min. using a scintillation counter.

[0163] The data from one representative experiment are shown in Table 11.

Table 11

Inhibition of ³ H-Thymidine Incorporation in MKN45 Cells by Various C8- and D11- Antibodies										
	AVG CPM									
Antibody dose										
(mg/mL)	hlgG2	D11-8B8	D11-27G3	D11-S17Y	hlgG4	C8-co16	C8-H241	C8-6	mIgG	5D5
20000.0	45054	11239	18407	19752	50628	11738	11425	16387	52448	35086
3333.3	49384	11441	16920	21239	54026	12956	12063	18216	53670	38195
555.6	51720	11925	15987	20936	54204	13476	13217	18334	54655	39496
92.6	47562	11094	14550	21911	54264	12419	11962	23041	52241	39607
15.4	50488	24402	28685	39695	53806	22528	23150	44771	51329	49766
2.6	48491	44741	47034	49868	54765	53465	48761	54598	55463	54967
0.4	46468	43334	43998	45304	55330	47485	46645	53389	51549	49563
0.1	44822	41578	41515	44566	53856	45725	44418	51668	47709	51883
0.0	50427	50427	44213	44213	48708	51478	51478	48708	50300	50300
	STDErr									
20000.0	2927	114	1265	1206	2491	262	654	282	1845	764
3333.3	2462	732	641	689	1421	388	386	314	1310	1491
555.6	2166	605	578	267	4364	281	341	1116	1192	534
92.6	1835	22	150	564	1733	352	636	475	1036	370
15.4	2144	2024	941	463	1376	207	1771	422	1281	968
2.6	2587	1914	1133	1910	1978	2164	1945	444	919	2577
0.4	2041	650	1177	2551	1501	378	2392	162	438	1943
0.1	1628	1734	1817	2402	678	1340	2442	1589	2092	3143
0.0	1203	1203	841	841	1377	886	886	1377	777	777
Abbreviations: AVG = average; CPM = count per minute; STDErr = Standard Error										

[0164] These data demonstrate that various C8- and D11- c-Met antibodies of the present invention inhibit HGF-independent MKN45 cell proliferation as evidenced by a reduction in ³H-thymidine incorporation. Similar results are obtained in SNU5 and NUGC-4 tumor cells, which each exhibit constitutive overexpression and Phosphorylation of c-Met.

Example 10**Reduction of Phosphorylated and Total c-Met, and Lack of Shedding of c-Met Extracellular Domain, in Response to c-Met Antibodies**

[0165] This example investigates whether treatment of MKN45 cells with c-Met antibodies of the present invention results in reduction of phosphorylated c-Met (p-Met) and total c-Met. In addition, this assay is used to determine if c-Met antibody treatment induces the shedding of c-Met ECD into MKN45-conditioned medium.

[0166] c-Met and isotype control antibodies are diluted with culture medium (RPMI-1640 (Invitrogen, #11835), 10% (v/v) FBS (Invitrogen, #10082), 2 mM L-glutamine (Invitrogen, #25030), 100 U/500mL penicillin G, and 100 µg/500 mL streptomycin (Invitrogen, #15140)) to achieve 2X the final concentrations indicated in Table 12, and 50 µL of the 2X antibody solutions are added to each well of 96-well tissue culture plates (Costar, #3596). MKN45 cells (Japan Health Sciences Foundation, Health Science Research Resource Bank, #JCRB0254) are maintained in the medium indicated above and are resuspended to 1×10^5 cells/mL in the same medium. 50 µL of this MKN45 resuspension are added to each well to achieve 5×10^3 cells/well. The plates are then incubated for 24 hours at 37°C under 95% relative humidity and 5% (v/v) CO₂, and cell lysates are prepared as described in Example 7. In addition, the conditioned medium from each treatment is collected for c-Met-ECD quantitation. p-Met and total c-Met levels in the cell lysates are determined by ELISA, and normalized to lysate protein concentration (as determined by BCA, Pierce #23225).

Phosphorylated c-Met

[0167] Phosphorylation of c-Met at tyrosine residues 1230, 1234, and 1235 is determined as described in Example 7.

Total c-Met and c-Met ECD Shedding

[0168] For the total c-Met and c-Met ECD ELISAs, a c-Met capture antibody is diluted in coating buffer (BioFX, Glendora, CA, COAT-1000-01) to 2 µg/mL. 110 µL of the diluted antibody are added per well to ELISA plates (Greiner Bio-One, Monroe, NC, #655081) and the plates are incubated overnight at 4°C. The wells are aspirated, washed twice with TBS-T, and then blocked with 200 µL of blocking buffer (TBS-T plus 2% (w/v) BSA) for 1 hour at room temperature. The plates are then washed twice with TBS-T. Next, MKN45 cell lysates, MKN45 conditioned medium, or c-Met extracellular domain (ECD) (SEQ ID NO:75) (as a standard), are added, and the plates are incubated for 2 hours at room temperature. The plates are then washed four times with TBS-T. 100 µL of 0.5 µg/mL of a biotinylated second c-Met antibody (Mab 5D5) that binds a different c-Met epitope from the capture antibody diluted in blocking buffer are then added to each well, and the plates are incubated for 2 hours at room temperature. Next, the plates are washed four times with TBS-T. 100 µL of 1/12,000 diluted peroxidase-conjugated streptavidin (Jackson ImmunoResearch Laboratories, West Grove, PA, #016-030-084) in blocking buffer are then added, and the mixture is incubated for 1 hour at room temperature. The plates are then washed six times with TBS-T. 100 µL of 3,3',5,5'-tetramethylbenzidine solution (BioFX, #TMBW-1000-01) are added to each well, followed by the addition of 100 µL stop solution (BioFX, #LSTP-1000-01). The plates are read at 450 nm with a 570 nm correction using a SpectraMax 190 plate reader (Molecular Devices, Sunnyvale, CA). The standard curve is established using 4-parameter analysis, and sample values are determined using SOFTmax Pro 3.1.2 software (Molecular Devices).

[0169] As shown in Table 12, the p-Met and total c-Met ELISA data reveal that Mab C8-H241 treatment maximally reduces p-Met by 77% and total c-Met by approximately 67%. D11-8B8 treatment maximally reduces p-Met by approximately 75% and total c-Met by 63%.

[0170] As noted in Example 8, these data demonstrate that C8- and D11- antibodies induce c-Met degradation and reduce phosphorylation of c-Met.

[0171] The data in Table 12 also indicate that treatment with C8-H241 and D11-8B8 c-Met antibodies does not induce cleavage and shedding of the c-Met ECD.

Table 12

Effect of C8- and D11- Antibodies on Phosphorylated c-Met, Total c-Met, and Shedding of c-Met Extracellular Domain in MKN45 Cell Lysates and Conditioned Medium								
Percent Inhibition of MKN45 Phosphorylated c-Met								
	C8-H241		hlgG4		D11-8B8		hlgG2	
Mab Dose (ng/mL)	ave	stdev	ave	stdev	ave	stdev	ave	stdev
10000	77.0	2.4	-2.1	10.9	74.8	3.4	14.0	7.1
1000	74.1	1.3	11.1	9.7	72.8	2.0	-4.6	10.9
100	71.7	2.5	13.4	13.3	69.1	3.7	-7.6	24.4
10	42.3	3.0	5.8	11.3	37.6	5.5	6.1	11.0
	ave	stdev						
untreated	0.0	8.0						
Percent Inhibition of MKN45 Total c-Met								
	C8-H241		hlgG4		D11-8B8		hlgG2	
Mab Dose (ng/mL)	ave	stdev	ave	stdev	ave	stdev	ave	stdev
10000	63.1	1.6	-23.7	4.1	63.0	7.0	14.1	9.1
1000	66.7	4.3	10.4	16.0	62.7	0.6	-2.4	22.4
100	61.5	3.4	-3.7	14.4	62.9	2.5	7.3	9.1
10	32.3	4.9	-3.4	13.5	34.5	8.4	15.1	7.0
	ave	stdev						
untreated	0.0	25.9						
Level of c-Met ECD in MKN45-Conditioned Medium (ng/mL)								
	C8-H241		hlgG4		D11-8B8		hlgG2	
Mab Dose (ng/mL)	ave	stdev	ave	stdev	ave	stdev	ave	stdev
10000	5.1	0.5	7.4	0.7	6.2	0.2	7.0	0.1
1000	6.1	0.8	7.6	0.4	7.2	0.5	7.2	0.5
100	5.4	0.4	7.6	0.8	6.9	1.6	7.2	0.6
10	6.6	0.2	8.4	1.1	6.2	0.4	7.2	0.1
	ave	stdev						
untreated	8.3	1.0						

Example 11**Agonist Activity of Antibodies in Caki-1. Tumor Cells in the Absence of HGF**

[0172] Caki-1 renal carcinoma cells proliferate in response to HGF. The activation of c-Met in Caki-1 cells by c-Met antibodies in the absence of HGF is examined in this example to assess the agonist activity of c-Met antibodies of the present invention.

[0173] Wells of 96-well tissue culture plates are seeded with 5,000 human kidney clear cell carcinoma Caki-1 cells (ATCC, #HTB-46) in McCoy's 5A culture medium (Invitrogen, #16600) supplemented with 10% (v/v) FBS, 2 mM L-glutamine (Invitrogen,

#25030), 100 U/500mL penicillin G and 100 µg/500 mL streptomycin (Invitrogen, #15140). After culture for 24 hours, cells are starved in low serum medium (0.5% (v/v) FBS) for another 24 hours. The cells are then cultured in the presence of anti-c-Met and control antibodies in low serum medium at final concentrations as indicated in Table 13 for 24 hours at 37°C, 95% relative humidity, 5% (v/v) CO₂. For the last six hours of the culture, the cells are pulsed with ³H-thymidine (MP Biomedicals, Solon, OH #24066) at 1 µCi/well at 37°C, 95% relative humidity, 5% (v/v) CO₂. Next, the medium is removed and the cells are washed once with DPBS. After this, 200 µL of Optiphase Supermix (PerkinElmer, #1200-439) are added to each well. The plates are then sealed and incubated for at least one hour at room temperature. ³H-thymidine incorporated in the cells is counted for one min. using a scintillation counter.

[0174] The data from one representative experiment are shown in Table 13.

Table 13

Effect of C8- and D11- Antibodies on ³H-Thymidine Incorporation in Caki-1 Cells in the Absence of HGF										
	AVG CPM									
Antibody dose (ng/mL)	hlgG2	D11- 8B8	D11- 27G3	D11- S17Y	hlgG4	C8-co16	C8- H241	C8-6	mlgG	5D5
20000.0	14658	15866	16054	18616	13704	13112	12797	13194	14224	19893
3333.3	14034	15730	15765	17897	13023	13829	12702	13193	13469	19018
555.6	14048	13997	14536	16620	12393	11359	12116	13494	13200	20043
92.6	14113	13705	14718	15342	12934	11563	12142	12793	13761	15588
15.4	14473	13488	13836	14579	13271	12111	13020	13670	13638	11748
2.6	15517	14097	13325	14867	13858	13713	14407	14126	13766	12520
0.4	14341	14411	13596	14618	13412	14080	14142	14601	14357	12896
0.1	16947	15319	17690	15899	13547	15567	15530	16121	13797	14383
0.0	14992	14992	15237	15237	14622	13889	14622	13889	14531	14531
	STDErr									
20000.0	398	737	549	345	219	642	268	96	465	807
3333.3	358	959	538	466	84	1086	380	382	927	954
555.6	343	809	705	284	478	437	216	4	397	505
92.6	428	502	728	237	447	292	445	212	706	394
15.4	232	737	729	160	487	267	305	107	514	318
2.6	386	173	295	404	339	299	291	711	91	221
0.4	357	568	508	392	317	556	656	281	331	323
0.1	262	550	1108	326	381	601	583	536	229	145
0.0	310	310	394	394	364	554	364	554	238	238

Abbreviations: AVG = average; CPM = count per minute; STDErr = Standard Error

[0175] These data demonstrate that c-Met antibodies C8-H241, C8-6, C8-co-16, and D11-8B8 do not significantly increase the uptake of thymidine-[methyl-³H] in Caki-1 cells compared to that of the IgG isotype controls. D11-C27G3 and D11-S17Y exhibit a low, variable, but statistically significant stimulation of thymidine-[methyl-³H] uptake in Caki-1 cells compared to that of the IgG isotype control. The control c-Met agonist antibody 5D5 induces stronger thymidine-[methyl-³H] uptake than that of the present c-Met antibodies in Caki-1 cells under the same experimental conditions.

Examples 12

Agonist Activity of Antibodies in Primary Human Hepatocytes in the Absence of HGF

[0176] The agonist activity of the present c-Met antibodies is further assessed in primary human hepatocytes (PHH), which are HGF-responsive, in the absence of HGF.

[0177] Cryopreserved, plateable PHH cells (KQG Celsis, Chicago, IL, RD#00002) are thawed at 37°C and resuspended to 175,000 cells/mL in InVitroGRO CP medium (Celsis, #Z99029) with torpedo antibiotic mix (Celsis, #Z99000). 0.2 mL of resuspended PHH cells are added per well to collagen I coated 96-well microtiter plates (BD, Franklin Lakes, NJ, #354407) at 35,000 cells/well, and the cells are incubated for 24 hours at 37°C, 5% (v/v) CO₂. The culture medium is then aspirated and 150 µL of InVitroGRO HI medium (Celsis, #Z99009) with torpedo antibiotic mix plus 0.1% (w/v) BSA are added per well, plus 50 µL of c-Met and control antibodies in a final concentration range of 10 µg/mL to 0.0032 µg/mL, or HGF at a final concentration of 200 ng/mL, in InVitroGRO HI medium with torpedo antibiotic mix plus 0.1% (w/v) BSA. Cells are incubated for 48 hours at 37°C, 5% (v/v) CO₂, and 10 µL of 0.1 mCi thymidine-[methyl-³H]/mL (MP Biomedicals, Solon, OH, #24066) are added per well for the last 6 hours of incubation. Assay plates are frozen at -70°C, thawed at 37°C, and harvested onto UniFilter-96, GF/C plates (Perkin Elmer, Waltham, MA, #6005174) using a Filtermate Harvester (Perkin Elmer). The UniFilter plates are dried, 20 µL of Microscint 0 scintillant (Perkin Elmer, #6013611) are added per well, and plates are counted on a 1450 Microbeta liquid scintillation counter (Perkin Elmer).

[0178] Table 14 shows the average of triplicate treatments with standard deviations, and is representative of three repeat experiments.

Table 14

Effect of Various C8- and D11- Antibodies on ³ H-Thymidine Incorporation in Primary Human Hepatocytes in the Absence of HGF													
		Doses:											
		10 µg/ml		2 µg/mL		0.4 µg/mL		0.08 µg/mL		0.016 µg/mL		0.0032 µg/mL	
Ab treatment	isotype	average	stdev	average	stdev	average	stdev	average	stdev	average	stdev	average	stdev
D11-8B8	IgG2	1703.7	140.1	1427.0	120.3	1231.0	232.4	1122.0	188.3	715.3	25.8	611.0	61.5
D11-C27G3	IgG2	2145.7	171.0	1874.0	443.4	1753.0	199.8	1283.3	131.6	892.0	109.3	692.7	23.0
D11-S17Y	IgG2	3155.0	594.2	2566.0	173.1	1911.0	348.3	1458.7	132.7	919.7	47.5	726.3	131.7
C8-H241	IgG4	671.0	61.0	710.3	81.8	681.3	13.7	669.3	77.0	630.0	37.2	625.0	65.5
C8-co-16	IgG4	952.0	36.0	822.0	88.4	670.0	23.3	767.3	12.6	715.7	12.5	828.7	85.2
C8-6	IgG4	1042.3	91.3	892.3	107.0	801.7	77.4	792.3	48.4	769.7	109.9	736.3	43.1
5D5	mIgG1	4978.0	59.9	4912.3	287.7	3763.7	292.1	3320.7	40.1	1716.3	324.1	821.7	175.3
hIgG2	isotype control	650.0	39.4	643.7	11.7	711.7	16.6	836.0	61.0	748.3	57.7	799.7	80.3
hIgG4	isotype control	647.3	77.1	735.0	33.8	717.3	19.4	819.0	44.2	848.3	75.1	806.7	79.7
mIgG1	isotype control	616.7	24.8	581.0	81.8	601.0	82.0	596.0	78.6	588.7	43.0	675.0	73.0
		ave	stdev										
HGF	200 ng/mL	6292.7	733.0										
untreated		615.1	83.9										

[0179] The data demonstrate that compared with the IgG isotype controls, present c-Met antibodies C8-H241 does not significantly increase thymidine-[methyl-³] uptake in PHH cells; C8-6, C8-co-16, D11-8B8, D11-C27G3, and D11-S17Y exhibit a

low, variable, but statistically significant stimulation of thymidine-[methyl- ^3H] uptake. However, the agonist activity of the present c-Met antibodies is significantly lower than that of the 5D5 control c-Met antibody. Agonist antibody 5D5 stimulates PHH proliferation in a dose-dependent manner, with a 5-fold increase at a concentration of 3 $\mu\text{g/mL}$. At 200 $\mu\text{g/mL}$, HGF stimulates a 5-fold increase in ^3H -thymidine uptake. Mab C8-H241 does not induce proliferation even when used at 10 $\mu\text{g/mL}$.

[0180] Similar results are obtained in human renal epithelial HK2 cells, which also proliferate in response to HGF stimulation.

Example 13

Effect of Antibodies on Tubular Morphogenesis in HepG2 Cells in the Absence of HGF

[0181] HGF induces tubular morphogenic changes in HepG2 cells grown in MatrigelTM (Becton-Dickinson, #354234), an extracellular matrix material containing components of the basement membrane. In this experiment, the HGF-like agonist activity of antibodies of the present invention in inducing tubular morphogenic changes in HepG2 cells is assessed.

[0182] HepG2 cells (ATCC, #HB-8065) are cultured in DMEM supplemented with 10% FBS. 100 μL of a MatrigelTM solution (MatrigelTM, Becton-Dickinson) diluted in Opi-MEM (Invitrogen, #31985) supplemented with 10% (v/v) FBS, 2 mM L-glutamine (Invitrogen, #25030), 100 U/500mL penicillin G and 100 $\mu\text{g}/500\text{ mL}$ streptomycin (Invitrogen, #15140) are plated in wells of 96-well tissue culture plates (Costar, #3596). After the MatrigelTM solution solidifies, 2000 HepG2 cells in 50 μL of culture medium supplemented with 10% serum are added. Next, c-Met and control antibodies at a final concentration of 50 $\mu\text{g/mL}$, or HGF at a final concentration of 50 ng/mL, are added to the cells. The cells are grown for 4 days at 37°C in a humidified atmosphere containing 5% (v/v) CO_2 . After 4 days, the top medium is removed and replaced with 50 μL of 1 mg/mL p-Iodonitro-tetrazolium violet (Sigma, #18377) in PBS, and the cells are incubated for another 48 hours under the same conditions. Photographs are taken of the stained 32 mm area, and analyzed using Image-Pro Plus 6 (Media Cybernetics, Inc., MD).

[0183] The data from one representative experiment, for antibodies at 50 $\mu\text{g/mL}$, are shown in Table 15.

Table 15

Effect of C8- Antibodies on Tubular Morphogenesis in HepG2 Cells							
Antibody (50 $\mu\text{g}/\text{ml}$)	hlgG4	C8-H241	C8-co16	C8-6	mlgG	5D5	NGF (50ng/ml)
Tubular Morphogenesis	no stimulation	no stimulation	no stimulation	1.2	1.2	4.9	5.4
Agonist activity (fold stimulation)							

[0184] These data demonstrate that HGF and control agonist antibody 5D5 induce approximately 5-fold tubular morphogenic changes in HepG2 cells as compared to the isotype control. In contrast, present c-Met antibodies C8-H241 and C8-co16 do not induce significant tubular morphogenic changes in HepG2 cells under the same conditions, while c-Met antibody C8-6 induces only a low level of stimulation.

[0185] Similar results are obtained with Mab D11-8-B8.

Example 14

Effect of Antibodies on Cell Motility: DU145 Scatter Assay and H441 Cell Scratch Assay

[0186] Upon stimulation with HGF, DU145 prostate cancer cells dissociate from each other and H441 cells fill in a scratch made in a confluent cell layer. H441 cells exhibit a high level of c-Met expression and constitutive phosphorylation of this receptor, but are still HGF-responsive. The following experiments assess the agonist effect of antibodies of the present invention on cell motility

in a scatter assay and a scratch assay.

DU145 Cell Scatter Assay

[0187] DU 145 cells (ATCC, # HTB-81) grown in MEM medium (Invitrogen, #11095) + 10% FBS (Invitrogen, #10082) at 37°C under 5% (v/v) CO₂ are plated at 2×10^3 cells/well in 70 µL volume in black ViewPlate 96-well plates (Perkin Elmer, Waltham, MA, #6005182) and incubated overnight at 37°C under 5% (v/v) CO₂. c-Met and control antibodies are diluted in the cell culture medium and added at a final concentration of 20 µg/mL, and HGF is added at a final concentration of 20 ng/mL, each in 30 µL volume with twelve replicates, and incubated for 48 hours at 37°C under 5% (v/v) CO₂. The medium is then aspirated and cells are fixed in 2% formaldehyde for 15 min. at room temperature. Wells are washed three times with PBS, and 50 µL of 5 U/mL Alexa Fluor 488 phalloidin (Invitrogen, #A12379) are added for 30 min. at room temperature. Wells are washed three times with PBS, and 50 µL of 15 µM propidium iodide (Invitrogen, #P3566) are added. The plate is subsequently read on an Acumen Explorer™ laser-scanning fluorescence microplate cytometer (TTP Labtech Ltd, Cambridge, MA) using Jockyss software in order to determine the percent of DU145 cells in colonies.

[0188] The results are shown in Table 16.

Table 16

Effect of C8- and D11- Antibodies on DU145 Cell Scattering									
	Percent of DU145 Cells in Colonies								
	C8-H241	C8-6	C8-co-16	hlgG4	D11-8B8	hlgG2	5D5	HGF	Untreated
Average	24.13	23.29	23.69	24.41	25.57	25.67	14.45	8.15	26.53
Std. Dev.	3.35	1.37	2.30	2.02	1.98	3.13	0.34	1.23	2.44

[0189] The data demonstrate that agonist c-Met Mab 5D5 and HGF, but not c-Met Mabs C8-H241, C8-co-16, C8-6, or D11-8B8, significantly stimulate DU145 cell scattering/motility.

H441 Cell Scratch Assay

[0190] For the H441 Scratch assay, H441 cells (ATCC, # HTB-174) are grown in RPMI-1640 (Invitrogen, #11835); 10% (v/v) FBS (Invitrogen, #10082); 2 mM L-glutamine (Invitrogen, #25030); 100 U/500mL penicillin G, and 100 µg/500 mL streptomycin (Invitrogen, # 15140)), and seeded at 1×10^6 cells/2mL/well in wells of 6-well tissue culture plates (Costar, #3598) in the culture medium. The plates are incubated for 3 days under 95% relative humidity and 5% (v/v) CO₂. The medium is then aspirated, and the cells are starved in low serum medium (0.5% (v/v) FBS in RPMI medium) for 16 hours. The confluent cell layers on the bottom of the wells are scratched with 5 mL pipette tips in the middle of each well, and floating cells are aspirated. The remaining cells are washed 1X with low serum medium. Low serum medium is added, and the scratched areas are imaged using a bright field microscope with a 4X objective. These gaps are defined as Gaps at 0 hours.

[0191] The testing antibodies are added to the cells at a final concentration of 10 µg/mL, followed by incubation at 37°C under 5% CO₂ (v/v) for 16 hours. HGF is tested at a final concentration of 200 ng/mL. Each treatment group is tested at least in duplicate wells. The scratched areas are imaged again using a bright field microscope at 16 hours. These gaps are defined as Gaps at 16 hours.

[0192] The effect of c-Met antibodies or HGF on the movement of H441 cells to fill the gaps are calculated as follows:

Average percentage change =

$$\frac{\text{Treatment group (Gap at 0 hour - Gap at 16 hours)}}{\text{Average medium group (Gap at 0 hour - Gap at 16 hours)}} \times 100$$

Average medium group (Gap at 0 hour - Gap at 16 hours)

[0193] The results are shown in Table 17.

Table 17

Effect of C8- antibodies in H441 Scratch Assay		
Antibody (10 µg/mL)	Avg. %	St. Dev.
Medium	100	7
hlgG4	98	9
C8-H241	98	9
C8-6	102	4
mlgG1	98	18
Mab 5D5	244	4
HGF (200 ng/mL)	364	9

[0194] The data demonstrate that agonist c-Met Mab 5D5 and HGF stimulate movement of H441 cells/filling in of the scratched areas. Under the same conditions, c-Met Mabs C8-H241 and C8-6 do not stimulate H441 cell motility.

Example 15

Effect of c-Met Antibodies on HepG2 Cell Invasiveness

[0195] HGF and agonist c-Met antibodies stimulate invasion of c-Met bearing cells. This example examines the agonist activity of the present c-Met antibodies in a cell invasion assay employing HepG2 cells, which are HGF-responsive in an invasion assay.

[0196] HepG2 cells (ATCC, #H-8065) are starved overnight in serum-free MEM medium (Invitrogen, #11095) and then 5×10^4 cells in a total volume of 500 µL are added to each well of the top chamber of a matrigel invasion chamber (BD, Franklin Lakes, NJ, #354483), with the bottom chamber containing antibodies in a total volume of 750 µL of serum-free medium at a concentration of 10 µg/mL, or HGF at 50 ng/mL in serum-free medium, followed by incubation for forty-eight hours at 3.7°C under 5% (v/v) CO₂. Non-invading cells are removed from the top chamber with a swab, followed by membrane fixation with 95% ethanol and staining with 0.2% (w/v) crystal violet. After washing and drying, the number of invading cells is counted using Image-Pro Plus 6 Manual Tag (Media Cybernetics, Inc., MD) software analysis of photographs taken of stained cells with a 2.5X objective.

[0197] The results are summarized in Table 18.

Table 18

Effect of C8-, C8, and D11 Antibodies on HepG2 Cell Invasiveness								
Antibody Concentration hlgG4 (µg/mL)	Average Cell Number Per 2.5x Field							
		C8-H241	C8	mlgG1	optD11	5D5	HGF (50 ng/mL)	Medium
10.00	5.5	3.5	4.3	5.5	19.8	85.0	509.5	3.5
	Std. Err.							
	0.5	0.9	1.3	0.5	4.1	20.4	4.5	0.5

[0198] The data demonstrate that agonist c-Met Mab 5D5 and HGF, but not c-Met Mabs C8-H241 and (murine) C8, stimulate HepG2 invasion. Murine c-Met Mab optD11 weakly induces HepG2 cell invasion.

Example 16

C8- and D11- Antibodies Do Not Protect Caki-1 Cells

from Staurosporine-Induced Apoptosis

[0199] HGF and agonist c-Met antibodies protect cells from staurosporine-induced cell death. This example examines the agonist activity of c-Met antibodies of the present invention in a staurosporine-induced apoptosis assay employing HGF-responsive Caki-1 cells.

[0200] Caki-1 cells (ATCC, #HTB-46) are grown as described in Example 11, seeded at 1×10^4 cells/well in 96 well plates (Costar, #3596) in culture medium, and pre-treated with antibodies (diluted from 30000 ng/mL to 3 ng/mL in the cell culture medium), or HGF (diluted from 225 ng/mL to 0.02 ng/mL), for one hour followed by treatment with 0.1 μ M staurosporine (final concentration) for forty-eight hours at 37° C. The medium is aspirated and the cells are lysed for 30 min. with 0.2 mL of the lysis buffer component of the Cell Death Detection ELISA kit (Roche Applied Science, Indianapolis, IN, #11774425001). This kit utilizes 20 μ L of each lysate to measure cell death by detection of cytoplasmic histone-associated DNA fragments as determined by the absorption at 450 nm. A higher optical density at 450 nm indicates greater apoptosis.

[0201] The results shown in Table 19 demonstrate that HGF, but not c-Met Mabs C8-H241, C8-6, and D11-8B8, protects Caki-1 cells from staurosporine-induced apoptosis.

Table 19

Effect of c-Met Antibodies on Staurosporine-Induced Apoptosis in Caki-1 Cells								
Antibody dose (ng/mL)	Average A450 nm							
	hlgG4	C8-H241	C8-6	HGF	hlgG2	D11-8B8	Medium	STS*
3	0.95	0.83	1.09	0.97 (0.02 ng/mL)	0.95	1.02	0.24	0.87
30	0.98	0.84	1.02	0.93 (0.23 ng/mL)	0.91	0.91		
300	0.87	0.86	0.97	0.73 (2.25 ng/mL)	0.95	0.81		
3000	0.98	0.85	0.92	0.58 (22.5 ng/mL)	0.95	0.91		
30000	0.91	0.90	0.96	0.45 (225 ng/mL)	0.94	0.87		
	STDErr							
3	0.03	0.02	0.19	0.02	0.07	0.01	0.01	0.03
30	0.03	0.01	0.14	0.06	0.00	0.11		
300	0.10	0.03	0.06	0.03	0.02	0.02		
3000	0.04	0.01	0.12	0.01	0.06	0.02		
30000	0.00	0.01	0.13	0.06	0.04	0.03		
*STS: Staurosporine								

Example 17**Effect of C8- Antibodies on Angiogenesis**

[0202] HGF and agonist c-Met antibodies stimulate angiogenesis. c-Met antibodies of the present invention are evaluated for this functional agonist property in the ADSC/ECFC co-culture tube formation assay. Adipose-derived stem cells (ADSC) express HGF; endothelial colony forming cells (ECFC) form tubes in response to stimulation by HGF.

[0203] ADCS (Lonza, Allendale, NJ, # PCT-5006) are dissociated, resuspended in basal medium (MCDB-131 medium (Sigma, St. Louis, MO #M8537)) + 30 μ g/mL L-ascorbic acid 2-phosphate (Sigma #A8960), 1 μ M dexamethasone (Sigma #D4902), 50 μ g/mL tobramycin (Sigma #T4014), 10 μ g/mL Cell Prime r-transferrin AF (Millipore #9701) + 10 μ g/mL Nuclein (Lilly human recombinant

insulin)), plated at 4×10^4 cells/well in 96-well plates, and incubated overnight at 37°C under 5% (v/v) CO₂. The medium is aspirated and 500 µg/mL sodium heparin (Sigma, #H3393) are added in basal medium at 100 µL/well; the cells are then incubated for 1 hour at 37°C. The wells are aspirated, washed once with 100 µL basal medium, and ECFC are added as follows: ECFC

[0204] (EndGenitor Technologies, Inc., Indianapolis, IN #EGT-ECFC100506) are dissociated, washed in basal medium, resuspended in basal medium, and added at 4×10^3 cells/well on top of ADSC in 96-well plates. After 4 hours incubation at 37°C, HGF and antibodies are diluted in the cell culture medium and added to separate wells at the following final concentrations: HGF:100 ng/mL; antibodies: 10 µg/mL. The HGF antibody (R&D Systems #AB-294-NA) is also added at 10 µg/mL final concentration. The cells are incubated for an additional 4 days at 37°C. The wells are aspirated, and 100 µL/well of 1% paraformaldehyde are added, followed by incubation for 20-30 min. Cells are washed three times with PBS-BSA (0.1% BSA, Invitrogen #15260-037) and treated with 50 µL of 1 µg/mL anti-human CD31 antibody (R&D Systems, #AF806) for 1 hour at 37°C or overnight at 4°C. Cells are washed twice with PBS-BSA and treated with 50 µL of 4 µg/mL anti-sheep IgG AlexaFluor488 conjugate (Invitrogen, #A11015) for 1 hour at room temperature. Cells are washed twice with PBS-BSA and stained with 100 µL of Hoechst3342 dye and read on a Cellomics ArrayScan (Thermo Fisher Scientific, Waltham, MA). vHCS View Version 1.4.6 software is used to determine total tube areas, which are used to evaluate the effect of the various antibodies and HGF on stimulation of angiogenesis.

[0205] The results are shown in Table 20.

Table 20

Effect of C8- Antibodies on Tube Formation in ECFC Cells								
Total Tube Area								
	Basal Medium	hlgG4	C8-H241	C8-6	mIgG1	5D5	HGF Ab	HGF
Avg.	67753.3	90134.3	22979.7	65224.0	125538.3	147237.3	22824.3	212104.7
Std. Dev.	24221.6	17741.1	604.9	18275.9	34702.4	18748.1	6586.0	16588.5

[0206] The results demonstrate that C8-H241 and C8-6 do not stimulate tube formation compared to the medium or their corresponding isotype control antibodies, whereas HGF and agonist Mab 5D5 significantly stimulate tube formation.

Example 18

Inhibition of HGF-Independent and HGF-Dependent Tumor Cell Growth in Xenograft Models

[0207] The inhibition of HGF-independent and HGF-dependent tumor cell growth by c-Met antibodies of the present invention is examined in *in vivo* assays employing MKN45 cell and U87MG (human glioblastoma) cell mouse xenograft models, respectively. MKN45 cells constitutively express high levels of c-Met and c-Met phosphorylation in the absence of HGF. U87MG cells secrete HGF in an autocrine manner, and are HGF-responsive.

[0208] MKN45 cells (Japan Health Sciences Foundation, Health Science Research Resource, #JCRB0254) are expanded in culture as described in Example 8, trypsinized to single cells, harvested, and resuspended in PBS. Two million MKN45 cells in PBS are injected subcutaneously into the rear flank of athymic nude mice (Harlan, Indianapolis, IN). c-Met antibodies and corresponding IgG2 and IgG4 antibodies are diluted in PBS, pH 7.2, and administered on a weekly basis by intravenous injection starting from 3 or 7 days after tumor cell implantation at 1, 5, or 20 mg/mL. Inhibition of tumor cell growth is determined by three dimensional caliper measurement of tumor volumes twice weekly during the course of treatment. Body weight is measured as a general measurement of toxicity.

[0209] U87MG cells (ATCC, #HTB-14) are grown in MEM (Invitrogen, #11095) at 37°C, expanded in culture, trypsinized to single cells, harvested, and resuspended in PBS (Invitrogen, # 14190). Five million cells are injected subcutaneously into the rear flank of athymic nude mice (Harlan, Indianapolis, IN). c-Met antibodies are diluted in PBS, and administered on a weekly basis by intravenous injection at the doses indicated in Table 22 starting 7 days after tumor cell implantation. Control IgG4 antibody is administered at 10 mg/kg. Inhibition of tumor cell growth is determined by three dimensional caliper measurement of tumor volumes twice weekly during the course of treatment. Body weight is measured as a general measurement of toxicity.

[0210] The anti-tumor efficacy of four antibodies, D11-8B8, C8-H241, C8-6, and C8-Co-16 in the MKN45 cell xenograft model is summarized in Table 21. "Maximum % Inhibition" represents the percent inhibition of tumor growth compared to treatment with corresponding control antibody (0% inhibition).

[0211] When dosed at 5 mg/kg or 20 mg/kg, all four c-Met antibodies produce significant inhibition of MKN45 tumor cell growth as compared to their corresponding IgG isotype controls.

Table 21

Effect of C8- and D11- Antibodies On HGF-Independent MKN45 Tumor Growth <i>In Vivo</i>			
Antibody	Dose level (mg/kg)	Maximum % Inhibition	p value
D11-8B8	5	53	p<0.05
	20	56	p<0.01
C8-H241	1	39	NS
	5	63	p<0.01
	20	51	p<0.05
C8-6	1	60	p<0.001
	5	59	p<0.01
	20	73	p<0.001
C8-Co-16	1	36	NS
	5	60	p<0.001
	20	85	p<0.001

[0212] A dose-dependent inhibition of tumor cell growth by C8-H241 is also observed in the HGF-dependent U87MG cell xenograft model, as summarized in Table 22. "Maximum % Inhibition" represents the percent inhibition of tumor growth compared to treatment with corresponding IgG4 control antibody (0% inhibition).

Table 22

Effect of C8-H:241 Antibody On HGF-Dependent U87MG Tumor Growth <i>In Vivo</i>			
Antibody	Dose level (mg/kg)	Maximum % Inhibition	p value
C8-H241	0.1	45.2	NS
C8-H241	0.3	86.8	p<0.001
C8-H241	1	91.9	p<0.001
C8-H241	3	91	p<0.001
C8-H241	10	94.8	p<0.001

[0213] At 5 and 20 mg/kg, C8-H241 antibody also inhibits H441 non-small cell lung cancer xenograft tumor growth 58% and 60%, respectively. H441 cells exhibit a high level of c-Met expression and constitutive phosphorylation of c-Met, but are still responsive to HGF.

Example 19

Antibody Reduction of Total and Phosphorylated c-Met in MKN45 Xenograft Tumors

[0214] The *in vivo* activity of c-Met antibody C8-H241 on total c-Met and phosphorylated c-Met in mice bearing MKN45 (HGF-independent) xenograft tumors is investigated in this example. A dose-dependent reduction of both total c-Met and phosphorylated c-Met (at tyrosine 1349) is observed 24 hours after antibody administration.

[0215] MKN45 cells are expanded in culture as described in Example 8, trypsinized, and harvested. Two million MKN45 cells in PBS are injected subcutaneously into the rear flank of athymic nude mice (Harlan, Indianapolis, IN). c-Met antibody C8-H241 is diluted in PBS, pH 7.2, and administered by intravenous injection eight days after tumor cell implantation at 2.5, 5, 10, 20, and 40 mg/kg. Control antibody hlgG4 is administered at 40 mg/kg. After 24 hours of treatment, tumors are removed, flash frozen, stored temporarily at -80°C, and lysed in lysis buffer (5 mM ethylenediaminetetraacetic acid (EDTA), 5 mM ethyleneglycol-bis(b-aminoethyl)-N,N,N',N'-tetracetic acid (EGTA), 50 mM HEPES, 20 mM sodium pyrophosphate (ThermoFisherScientific, #S390-500), 150 mM NaCl, 20 mM NaF, 1% (v/v) octylphenoxy polyethoxy ethanol (TRITON®-X 100), complete protease inhibitor, EDTA free (Roche, Basel, Switzerland, # 1836153) phosphatase inhibitor cocktail I (Sigma #P2850), and phosphatase inhibitor cocktail II (Sigma #P5726)).

Total c-Met ELISA

[0216] For the total c-Met ELISA, a c-Met capture antibody is diluted in Bup H coating buffer (Thermo Fisher Scientific, Waltham, MA, #28382) to 2 µg/mL. 100 µL of the diluted antibody is added per well to ELISA plates (ThermoFisherScientific, Waltham, MA #439454), and the plates are incubated overnight at 4°C. The wells are aspirated, washed twice with TBS-T, and then blocked with 200 µL of blocking buffer (TBS-T plus 2% (w/v) BSA) for 1 hour at room temperature. The plates are washed twice with TBS-T. Next, dilutions of tumor Lysates or c-Met extracellular domain (amino acids 25-932 of SEQ ID NO:75) are added, and the plates are incubated overnight at 4°C. The plates are then washed three times with TBS-T. 100 µL of 0.5 µg/mL of biotinylated Mab 5D5 (as second c-Met antibody that binds a different c-Met epitope from the capture antibody) diluted in blocking buffer are then added to each well, and the plates are incubated for 2 hours at room temperature. Next, the plates are washed three times with TBS-T. 100 µL of 1/10,000 diluted peroxidase-conjugated streptavidin (Jackson ImmunoResearch Laboratories, West Grove, PA, #016-030-484) in blocking buffer are then added, and the mixture is incubated for 1 hour at room temperature. The plates are then washed three times with TBS-T. 100 µL of 3,3',5,5'-tetramethylbenzidine solution (BioFX, #TMBW-1000-01) are added to each well, followed by the addition of 100 µL stop solution (BioFX, #LSTP-1000-01). The plates are read at 450 nm using a SpectraMax 250 plate reader (Molecular Devices, Sunnyvale, CA) with SOFTmax Pro 3.1.2 software (Molecular Devices).

Phosphorylated c-Met ELISA

[0217] For the phospho-c-Met ELISA, a c-Met capture antibody is diluted in Bup H coating buffer (Thermo Fisher Scientific, Waltham, MA, #28382) to 2 µg/mL. 100 µL of the diluted antibody are added per well to ELISA plates (ThermoFisherScientific, Waltham, MA #439454), and the plates are incubated overnight at 4°C. The wells are aspirated, washed twice with TBS-T, and then blocked with 200 µL of blocking buffer (TBS-T plus 2% (w/v) BSA) for 1 hour at room temperature. The plates are washed twice with TBS-T. Next, MKN45 cell lysates are added, and the plates are incubated overnight at room temperature. The plates are then washed three times with TBS-T. 100 µL of 0.5 µg/mL anti-pY1349 c-Met antibody (Cell Signaling Technology, Danvers, Massachusetts, #3121) diluted in blocking buffer are then added to each well, and the plates are incubated for 2 hours at room temperature. Next, the plates are washed three times with TBS-T. 100 µL of 1/10,000 diluted peroxidase conjugated anti-rabbit IgG (Jackson ImmunoResearch Laboratories, West Grove, PA, #111-035-144) in blocking buffer are then added, and the mixture is incubated for 1 hour at room temperature. The plates are then washed three times with TBS-T. 100 µL of 3,3',5,5'-tetramethylbenzidine solution (BioFX, #TMBW-1000-01) are added to each well, followed by the addition of 100 µL stop solution (BioFX, #LSTP-1000-01). The plates are read at 450 nm using a SpectraMax 250 plate reader (Molecular Devices, Sunnyvale, CA) with SOFTmax Pro 3.1.2 software (Molecular Devices).

[0218] The results are shown in Table 23.

[0219] The data demonstrate that *in vivo* treatment of MKN45 Xenograft tumors with Mab C8-H241 for 24 hours maximally reduces total c-Met by approximately 43%, and phosphorylated c-Met by approximately 73%, under these conditions.

Table 23

Reduction of Total and Phosphorylated c-Met in MKN45 Xenograft Tumors After 24 Hour Treatment with c-Met antibody C8-H241 <i>In Vivo</i>							
Reduction of Total c-Met							
% Inhibition		C8-H241					hlgG4
	PBS	2.5 mpk	5 mpk	10 mpk	20 mpk	40 mpk	40 mpk
average % inhibition	-88.51	-8.43	4.26	25.07	42.85	30.62	0.00
st. dev. % inhibition	62.63	-8.43	36.84	26.88	17.67	35.95	41.23
Reduction of Phosphorylated c-Met							
% Inhibition		C8-H241					hlgG4
	PBS	2.5 mpk	5 mpk	10 mpk	20 mpk	40 mpk	40 mpk
average % inhibition	12.16	22.89	17.56	53.21	67.04	73.42	0.00
st. dev. % inhibition	23.89	22.89	37.05	9.90	6.58	7.04	48.81
mpk: mg/kg							

[0220] Amino Acid and Nucleotide Sequences

Light Chain Variable Region Amino Acid Sequences

[0221]

D11-S17Y (SEQ ID NO:1)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSYLAS
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIK

D11-8B8 (SEQ ID NO:2)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSYLAS
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIK

D11-C27G3 (SEQ ID NO:3)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSRLRS
GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIK

C8-6 (SEQ ID NO:4)

DIQMTQSPSSLSASVGDRTITCSVSSSVSSIYHWHYQQKPGKAPKLLIYSTSNLAS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCIQYSGYPLTFGGGTKVEIK

C8-H241 (SEQ ID NO:5)

DIQMTQSPSSLSASVGDRTITCSVSSSVSSIYHWHYQQKPGKAPKLLIYSTSNLAS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQVYSGYPLTFGGGTKVEIK

C8-co-16 (SEQ ID NO:6)

DIQMTQSPSSLSASVGDRTITCSVSSSVRSIYHWHYQQKPGKAPKLLIYSTSNLA
SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQVYRGYPLTFGGGTKVEIK

Light Chain Variable Region Nucleic Acid Sequences

[0222]

D11-S17Y (SEQ ID NO:7)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCCTATCTGGCTTCTGGCATCCCA
 GACAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAA

D11-8B8 (SEQ ID NO:8)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCCTACCTGGCTTCTGGCATCCCA
 GACAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAA

D11-C27G3 (SEQ ID NO:9)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCCAGACTGAGATCTGGCATCCCA
 GACAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAA

C8-6 (SEQ ID NO:10)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAGTGTCAAGTATAAGTTCCATTTACTTGCAGTGGTATCAGCAGAAA
 CCAGGGAAAGCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCA
 TCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAACTTACTACTGTATTTCAGTACAGTGGTTACCCGCTCACGTTTCGGC
 GGAGGGACCAAGGTGGAGATCAAA

C8-H241 (SEQ ID NO:11)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAGTGTCAAGTATAAGTTCCATTTACTTGCAGTGGTATCAGCAGAAA
 CCAGGGAAAGCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCA
 TCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAACTTACTACTGTACAGGTGTACAGTGGTTACCCGCTCACGTTTCGGC
 GGAGGGACCAAGGTGGAGATCAAA

C8-co-16 (SEQ ID NO:12)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAGTGTCAAGTGTACGTTCCATTTACTTGCAGTGGTATCAGCAGAAA
 CCAGGGAAAGCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCA
 TCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAACTTACTACTGTACAGGTGTACAGGTTACCCGCTCACGTTTCGGC
 GGAGGGACCAAGGTGGAGATCAAA

Heavy Chain Variable Region Amino Acid Sequences

[0223]

D11-S17Y (SEQ ID NO:13)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRYIHVVRQAPGQGLEWMGWIYP
VTGDTYYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYGAFYYW
GQGLTVTVS

D11-8B8 (SEQ ID NO:14)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRYIHVVRQAPGQGLEWMGWIYP
VTGDTYYIEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYGAFYYWG
QGLTVTVS

D11-C27G3 (SEQ ID NO:15)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRYIHVVRQAPGQGLEWMGWIYP
VTGDTYYREPFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYGAFYYWG
QGLTVTVS

C8-6 (SEQ ID NO:16)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
NPNRRGGTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARTNWL
WGQGTITVTVS

C8-H241 (SEQ ID NO:17)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
NPNRRGGTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARANWL
WGQGTITVTVS

C8-co-16 (SEQ ID NO:18)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
NPYRGSTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARANIL
WGQGTITVTVS

Heavy Chain Variable Region Nucleic Acid Sequences

[0224]

D11-S17T (SEQ ID NO:19)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATTATCCTGTAACCTGGTGATACTTACTAC
AACGAGAAGTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAC
GGAGCTTTTACTACTGGGGCCAGGGCACCTGGTCACCGTCTCC

D11-8B8 (SEQ ID NO:20)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATTATCCTGTAACCTGGTGATACTTACTAC
ATCGAGAAGTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAT
GGTGCTTTTCTACTGGGGCCAGGGCACCTGGTCACCGTCTCC

D11-C27G3 (SEQ ID NO:21)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATTATCCTGTAACCTGGTGATACTTACTAC
AGAGAGCCTTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAT
GGGGCTTTTACTACTGGGGCCAGGGCACCTGGTCACCGTCTCC

C8-6 (SEQ ID NO:22)

CAGGTTCAAGCTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAAGGTC
 TCCTGCAAGGCTTCTGGTTACACCTTTACCGACTACTACATGCACTGGGTGCGTCAGGCC
 CCTGGTCAAGGCTTGTAGTGGATGGGTCGTGTTAATCCTAACCGGGGTGGTACTACCTAC
 AACCAGAAATTCGAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTACGAAC
 TGGCTTGACTACTGGGGCCAGGGCACCACCGTCACCGTCTCC

C8-H241 (SEQ ID NO:23)

CAGGTTCAAGCTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAAGGTC
 TCCTGCAAGGCTTCTGGTTACACCTTTACCGACTACTACATGCACTGGGTGCGTCAGGCC
 CCTGGTCAAGGCTTGTAGTGGATGGGTCGTGTTAATCCTAACCGGAGGGGTACTACCTAC
 AACCAGAAATTCGAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTACGAAC
 TGGCTTGACTACTGGGGCCAGGGCACCACCGTCACCGTCTCC

C8-co-16 (SEQ ID NO:24)

CAGGTTCAAGCTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAAGGTC
 TCCTGCAAGGCTTCTGGTTACACATTCACTGACTACTACATGCACTGGGTGCGTCAGGCC
 CCTGGTCAAGGCTTGTAGTGGATGGGTCGTGTTAATCCTTATCGGGGTAGTACTACCTAC
 AACCAGAAATTCGAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTACGAAC
 ATTCTTGACTACTGGGGCCAGGGCACCACCGTCACCGTCTCC

Complete Light Chain Amino Acid Sequences

D11-S17Y kappa (SEQ ID NO:25)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSYLA
 GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

D11-8B8 kappa (SEQ ID NO:26)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSYLA
 GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

D11-C27G3 kappa (SEQ ID NO:27)

EIVLTQSPGTLISLSPGERATLSCSVSSSISSTNLHWYQQKPGQAPRLLIYGTSRLRS
 GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQWSSYPYSFGQGTKLEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

C8-6 kappa (SEQ ID NO:28)

DIQMTQSPSSLSASVGDRTITCSVSSSVSSYLHWYQQKPGKAPKLLIYSTSNLAS
 GVPSRFSGSGSGTDFTLTISLQPEDFATYYCIQYSGYPLTFGGGTKVEIKRTVAAP

SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
 KDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

C8-h241 kappa (SEQ ID NO:29)

DIQMTQSPSSLSASVGDRTITCSVSSSVSSYLHWYQQKPGKAPKLLIYSTSNLAS
 GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQVYSGYPLTFGGGTKVEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

C8-co-16 kappa (SEQ ID NO:30)

DIQMTQSPSSLSASVGDRTITCSVSSSVRSYLHWYQQKPGKAPKLLIYSTSNLA
 SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQVYRGYPLTFGGGTKVEIKRTVA
 APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
 DSKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Complete Light Chain Nucleic Acid Sequences

[0225]

D11-S17Y LC (SEQ ID NO:31)

GAAATTGTGTTGACGACAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTGAGCTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCCTACCTGGCTTCTGGCATCCCA
 GACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGTAATAACTTC
 TATCCAGAGAGGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

D11-8B8 LC (SEQ ID NO:32)

GAAATTGTGTTGACGACAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTGAGCTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCCTACCTGGCTTCTGGCATCCCA
 GACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGTAATAACTTC

TATCCAGAGAGGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

D11-C27G3 LC (SEQ ID NO:33)

GAAATTGTGTTGACGACAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
 CTCTCCTGCAGTGTGAGCTCAAGTATAAGTTCCACCAACTTACACTGGTACCAGCAGAAA
 CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGCACATCAGACTGAGATCTGGCATCCCA
 GACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
 CCTGAAGATTTTGCAGTGTATTACTGTCAACAGTGGAGTAGTTACCCGTACAGTTTCGGC
 CAAGGGACCAAGTTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGTAATAACTTC
 TATCCAGAGAGGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

C8-6 LC (SEQ ID NO:34)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAGTGTGAGCTCAAGTGTATAGTTCCATTACTTGCAGTGGTATCAGCAGAAA
 CCAGGGAAAGCCCCTAAGCTCCTGATCTATAGCACATCCAAGTGGCTTCTGGAGTCCCA
 TCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAGTGTATTACTGTATTCAGTACAGTGGTTACCCGCTCAGGTTTCGGC
 GGAGGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGTAATAACTTC
 TATCCAGAGAGGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

C8-H241 LC (SEQ ID NO:35)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAGTGTGAGCTCAAGTGTATAGTTCCATTACTTGCAGTGGTATCAGCAGAAA
 CCAGGGAAAGCCCCTAAGCTCCTGATCTATAGCACATCCAAGTGGCTTCTGGAGTCCCA
 TCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAGTGTATTACTGTCAAGTCTACAGTGGTTACCCGCTCAGGTTTCGGC
 GGAGGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGTAATAACTTC
 TATCCAGAGAGGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

C8-co16 LC (SEQ ID NO:36)

GACATCCAGATGAUCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
 ATCACTTGCAAGTGTCAAGTGTACGTTCCATTTACTTGCACTGGTATCAGCAGAAA
 CCAGGGAAAGCCCTAAGCTCCTGATCTATAGCACATCCAACCTGGCTTCTGGAGTCCCA
 TCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
 CCTGAAGATTTTGCAACTTACTACTGTCAGGTGTACAGGGGTACCCGCTCACGTTCCGGC
 GGAGGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGTGAATCTGGAACGCTCTGTTGTGTGCCTGCTGAATAACTTC
 TATCCCAGAGAGGCCAAAGTACAGTGGAGGTGGATAACGCCCTCCAATCGGGTAACTCC
 CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG
 ACGCTGAGCAAGACAGACTACGAGAAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAG
 GGCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGC

Complete Heavy Chain Amino Acid Sequences

[0226]

D11-S17Y IgG2 (SEQ ID NO:37)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRVYHWRQAPGQGLEWMGWYYP
 VTGDTYYNEKFKGRVTITADKSTSTAYMELSSLRSEDAVYYCARGYGAFYYW
 GQGTILVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
 LTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVER
 KCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN
 WYVDGMEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYCKVSNKGL
 PAPIETISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYT
 QKSLSLSPG

D11-8B8 IgG2 (SEQ ID NO:38)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRVYHWRQAPGQGLEWMGWYYP
 VTGDTYYIEKFKGRVTITADKSTSTAYMELSSLRSEDAVYYCARGYGAFYYWG
 QGTILVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
 TSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVERK
 CCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW
 YVDGMEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYCKVSNKGLP
 APIETISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG

QPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQ
 KSLSLSPG

D11-C27G3 IgG2 (SEQ ID NO:39)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRVYHWRQAPGQGLEWMGWYYP
 VTGDTYYREFPKGRVTITADKSTSTAYMELSSLRSEDAVYYCARGYGAFYYWG
 QGTILVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
 TSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVERK
 CCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW
 YVDGMEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYCKVSNKGLP
 APIETISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
 QPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQ
 KSLSLSPG

C8-6 IgG2 (SEQ ID NO:40)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
 NPNRRGGTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARTNWLDY
 WGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 ALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDKTV
 RKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN
 WYVDGMEVHNAKTKPREEQFNSTFRVVSIVLTVVHVDWLNKEYKCKVSNKGL
 PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPMLDSGDSFLLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT
 QKSLSLSPG

C8-H241 IgG2 (SEQ ID NO:41)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
 NPNRRGGTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARANWLDY
 WGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 ALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDKTV
 RKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN
 WYVDGMEVHNAKTKPREEQFNSTFRVVSIVLTVVHVDWLNKEYKCKVSNKGL

PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPMLDSGDSFLLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT
 QKSLSLSPG

C8-co-16 IgG2 (SEQ ID NO:42)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHVVRQAPGQGLEWMGRV
 NPYRGSTTYNQKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARANWLDY
 GGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 ALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDKTV
 KCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN
 WYVDGMEVHNAKTKPREEQFNSTFRVVSIVLTVVHVDWLNKEYKCKVSNKGL
 PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPMLDSGDSFLLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT
 QKSLSLSPG

Complete Heavy Chain Nucleic Acid Sequences

[0227]

D11-S17Y IgG2 HC (SEQ ID NO:43)

CAGGTGCAGCTGGTGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTC
 TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
 CCTGGACAAGGCTTGAGTGGATGGGATGGATTATCCTGTAAGTGGTGATCTACTAC
 AACGAGAAGTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
 ATGGAGCTGAGCAGCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAT
 GGGGCTTTTACTACTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCCGCTCCACCAAG
 GGCCCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCC
 CTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCAGGTGACGGTGTCTGGAACTCAGGC
 GCCCTGACCAGCGCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCC
 CTCAGCAGCGTGGTGACCTGCCCCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
 GTAGATCACAAGCCCAAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAATGTTGTGTC
 GAGTGCCACCGTGCCAGCACACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCA
 AAACCCAAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGGAC
 GTGAGCCAGCAAGACCCGAGGTCCAGTTCAACTGGTACGTGGACGGCATGGAGGTGCAT
 AATGCCAAGACAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCTCGTGTGGTCAGCGTC
 CTCACCGTCTGTCAACGAGTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
 AAAGGCTTCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAA
 CCACAGGTGTACACCTGCCCCCATCCCGGAGGAGATGACCAAGAACCGGTGAGCTG
 ACCTGCTGTGTCAAAGGCTTCTACCCAGCGACATCGCGTGGAGTGGGAGAGCAATGGG
 CAGCCGAGAAACACTACAGACCAACCTCCCATCTGAGTCTGAGCTCCGACGGCTCTTCTTC
 CTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC

TCCGTGATGCATGAGGCTCTGCACAACCACTACACAGAAAGAGCCTCTCCCTGTCTCCG
 GGT

D11-8B8 IgG2 HC (SEQ ID NO:44)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTC
 TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
 CCTGGACAAGGGTTGAGTGGATGGGATGGATTATCCTGTAACCTGGTGATACTTACTAC
 ATCGAGAAGTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
 ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAT
 GGTGCTTTTTTCTACTGGGGCCAGGGCACCTTGGTCACCGTCTCCTCCGCCTCCACCAAG
 GGCCCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCC
 CTGGGCTGCCTGGTCAAGGACTACTTCCCGGAACCGGTGACGGTGTCTGTGGAACCTCAGGC
 GCCCTGACCAGCGGGCTGCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCC
 CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
 GTAGATCACAAAGCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAATGTGTGTCTC
 GAGTGCCACCCGTGCCAGCACCCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCA
 AAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTGGTGGAC
 GTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCATGGAGGTGCAT
 AATGCCAAGACAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTTCAGCGTC
 CTCACCGTGTGACCCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
 AAAGGCTCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAA
 CCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGAACAGGTTCAGCCTG
 ACCTGCTGGTCAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGG
 CAGCCGAGAACTACAAGACCACCTCCCATGCTGGACTCCGACGGCTCCTTCTTC
 CTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGCTCTTCTCATGC
 TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCG
 GGT

D11-C27G3 IgG2 HC (SEQ ID NO:45)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTC
 TCCTGCAAGGCTTCTGGCTACACCTTCACAAGTAGGTATATACACTGGGTGCGACAGGCC
 CCTGGACAAGGGTTGAGTGGATGGGATGGATTATCCTGTAACCTGGTGATACTTACTAC
 AGAGAGCCTTTCAAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
 ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTAC
 GGAGCTTTTTTACTACTGGGGCCAGGGCACCTTGGTCACCGTCTCCTCCGCCTCCACCAAG
 GGCCCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCC
 CTGGGCTGCCTGGTCAAGGACTACTTCCCGGAACCGGTGACGGTGTCTGTGGAACCTCAGGC
 GCCCTGACCAGCGGGCTGCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCC
 CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC
 GTAGATCACAAAGCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAATGTGTGTCTC
 GAGTGCCACCCGTGCCAGCACCCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCA
 AAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTGGTGGAC
 GTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCATGGAGGTGCAT
 AATGCCAAGACAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTTCAGCGTC
 CTCACCGTGTGACACAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC

AAAGGCTCCAGCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAA
 CCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGAACAGGTTCAGCCTG
 ACCTGCTGGTCAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGG
 CAGCCGAGAACTACAAGACCACCTCCCATGCTGGACTCCGACGGCTCCTTCTTC
 CTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGCTCTTCTCATGC
 TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCG
 GGT

C8-6 IgG4 HC (SEQ ID NO:46)

CAGGTTACAGCTGGTGCAGTCTGGTGTGAGGTGAAGAAGCCTGGTGCCCTCAGTGAAGGTC
 TCCTGCAAGGCTTCTGGTTACACCTTACCAGTACTACATGCACCTGGGTGCGTCAGGCC
 CCTGTCAAGGCTTGTAGTGGATGGGTCTGTGTTAATCCTAACCGGGGTGGTACTACTTAC
 AACCAGAAATTCAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTACGAAC
 TGGCTTGACTACTGGGGCCAGGGCACCCGTACCGTCTCCTCCGCCTCCACCAAGGGC
 CCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTG
 GGCTGCTGGTCAAGGACTACTTCCCGAACCCGTGACGGTGTCTGTGGAACCTCAGGCGCC
 CTGACCAGCGGCTGCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCCCTC
 AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTA
 GATCAACAAGCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCA
 TGCCCCACCTGCCAGCACCTGAGGCCGCCGGGGGACCATCAGTCTTCTGTTCCTCCCA
 AAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTGGTGGAC
 GTGAGCCAGGAAGACCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCAT
 AATGCCAAGACAAGCCGCGGGAGGAGCAGTTCAACAGCACGTAACCGTGTGGTTCAGCGTC
 CTCACCGTCTGCACAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
 AAAGGCTCCCGTCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG
 CCACAGGTGTACACCTGCCCCCATCCCGAGGAGAGATGACCAAGAACAGGTTCAGCCTG
 ACCTGCTGGTCAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAAGCAATGGG
 CAGCCGAGAACTACAAGACCAGCCTCCCGTGTGGACTCCGACGGCTCCTTCTTC
 CTCTACAGCAGGTAAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGC
 TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTG
 GGT

C8-H241 IgG4 HC (SEQ ID NO:47)

CAGGTTCAAGCTGGTGCAGTCTGGTGCTGAGGTGAAGAAGCCTGGTGCCTCAGTGAAGGTC
 TCCTGCAAGGCTTCTGGTTACACATTCACTGACTACTACATGCAGTGGGTGCGTCAGGCC
 CCTGGTCAAGGCTTGTAGTGGATGGGTGCTGTTAATCCTAACCGGAGGGGTACTACCTAC
 AACCAAGAAATTCGAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTGCGAAC
 TGGCTTGACTACTGGGGCCAGGGCACCACCGTCACCGTCTCCTCCGCTCCACCAAGGGC
 CCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTG
 GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCTGGAAGTCAAGGCGCC
 CTGACCAGCGCGGTGCACACCTTCCCCGGTGTCTACAGTCTCAGGACTCTACTCCCTC
 AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTA
 GATCACAAGCCAGCAACACCAAGGTGGACAAGAGTTGAGTCCAAATATGGTCCCCCA
 TGCCCAACCTGCCAGCACCTGAGGCCGCCGGGGACCATCAGTCTTCTGTTCCTCCCA

AAACCCAAGGACACTCTCATGATCTCCCCGACCCCTGAGGTACAGTGCCTGGTGGTGGAC
 GTGAGCCAGGAAGACCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCAT
 AATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAGTACCGTGTGGTCAGCGTC
 CTCACCGTCTTGACACAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
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 CCACAGGTGTACACCTGCCCCCATCCAGGAGGAGATGACCAAGAACAGGTGAGCCTG
 ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAAAGCAATGGG
 CAGCCGGAAGAACACTACAAGACCACGCTCCCGTGTGGACTCCGACGGCTCCTTCTTC
 CTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGC
 TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTG
 GGT

C8-co16 IgG4 HC (SEQ ID NO:48)

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 TCCTGCAAGGCTTCTGGTTACACATTCACTGACTACTACATGCAGTGGGTGCGTCAGGCC
 CCTGGTCAAGGCTTGTAGTGGATGGGTGCTGTTAATCCTTATCGGGGTAGTACTACCTAC
 AACCAGAAATTCGAGGGCCGTGTACCATGACCACAGACACATCCACGAGCACAGCCTAC
 ATGGAGCTGCGTAGCCTGCGTTCTGACGACACGGCCGTGTATTACTGTGCGCGTGCGAAC
 ATTCTTGACTACTGGGGCCAGGGCACCACCGTCACCGTCTCCTCCGCTCCACCAAGGGC
 CCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTG
 GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCTGGAAGTCAAGGCGCC
 CTGACCAGCGCGGTGCACACCTTCCCCGGTGTCTACAGTCTCAGGACTCTACTCCCTC
 AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTA
 GATCACAAGCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCA
 TGCCCAACCTGCCAGCACCTGAGGCCGCCGGGGACCATCAGTCTTCTGTTCCTCCCA
 AAACCCAAGGACACTCTCATGATCTCCCCGACCCCTGAGGTACAGTGCCTGGTGGTGGAC
 GTGAGCCAGGAAGACCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCAT
 AATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAGTACCGTGTGGTCAGCGTC
 CTCACCGTCTTGACACAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
 AAAGGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAGGCCAAAGGGCAGCCCCGAGAG
 CCACAGGTGTACACCTGCCCCCATCCAGGAGGAGATGACCAAGAACAGGTGAGCCTG
 ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAAAGCAATGGG
 CAGCCGGAAGAACACTACAAGACCACGCTCCCGTGTGGACTCCGACGGCTCCTTCTTC
 CTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGC
 TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTG
 GGT

Human cMet-ECD-Fc-Flis (SEQ ID NO:72)

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQN
 VILHEHHIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPQDCSSKANLSG
 GVWKNINMALVVDYIYDDQLISCGSVNRGTCQRHVFPNHNTADIQSEVHCIFS
 PQIEPSQCPDCVVSALGAKVLSSVKDRFINFFVGNNTINSSYFPDHPHLSISVRLK
 ETKDGMFLTDQSYIDVLEPRDSYPIKYVHAFESNNFIYFLTVQRETLDAQTFHT

RIIRFCSINSLGHSYMEMPLECILTEKRKKRSTKKEVFNLQAAYVSKPGAQLARQI
 GASLNDILFGVFAQSKPDSAEPMDSAMCAPIKYVNDFFNKIVNKNVRCLO
 HFYGPNEHCNFRNLLRNSSGCEARRDEYRTEFTTALQRVDLFMGQFSEVLLTSI
 STFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLDLSHPVSPEVIVEHTLNQ
 NGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGWCHDKCVRSEECLS
 GTWTQQICLPAIYKVFNSAPLEGGTRLTICGWDFGFRNNKFDLKKTRVLLGNE
 SCTLTLSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVITSISP
 YGPMAGGTLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTISTEFA
 VKLKIDLANRETSIFSREDPIVYEHPTKSFISGGSTITGVGKNLNSVSVPRMVINV
 HEAGRNFVACQHRNSSEIICCTTPSLQQLNLQLPLKTKAFFMLDGLSKYFDLIY
 VHNPFVKPFEPVPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKNSCENIHLHSE
 AVLCTVPNDLLKLNSLNIWQKQAISSVTLGKVTVQPDQNTLEVLFQGPDIPEKS
 CDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
 NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIETISKAKGQPREPQEYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES
 NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
 TQKSLSLSPGKRJ**DYKDDDDKHVHHHHHH**

[0228] Bold, italicized amino acids represent the signal sequence; bold underlined amino acids represent the Flis tag.

Cynomolgus Monkey cMet-ECD-Fc-Flis (SEQ ID NO:73)

MKAPAVLVPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETAIQN
 VILHEHHIFLGATNYIYVLNEEDLQKVAEYKTPVLEHPDCFPQCDCSSKANLSG
 GVWKNINMALVVDYTYDDQLISCGSVNRGTCQRHVFPNHTADIQSEVHCIFS
 PQIEEPNQPCDCVVSALGAKVLSSVKDRFINFFVGNNTINSSYPHHPHLSISVRRLK
 ETKDGMFLTDQSYIDVLPFRDSYPIKYIHAFESNNFIYFLTVQRETLNAQTFHTR
 IIRFCSINSLGHSYMEMPLECILTEKRKKRSTKKEVFNLQAAYVSKPGAQLARQI
 GASLNDILFGVFAQSKPDSAEPMDSAMCAPIKYVNDFFNKIVNKNVRCLO
 HFYGPNEHCNFRNLLRNSSGCEARRDEYRAEFTTALQRVDLFMGQFSEVLLTSI
 STFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLDLSHPVSPEVIVEHPLNQ
 NGYTLVVTGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGWCHDKCVRSEECPS
 GTWTQQICLPAIYKVFTSAPLEGGTRLTICGWDFGFRNNKFDLKKTRVLLGNE
 SCTLTLSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPHITSISP
 YGPMAGGTLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTISTEFA
 VKLKIDLANRETSIFSREDPIVYEHPTKSFISGGSTITGVGKNLNSVSVPRMVINV
 HEAGRNFVACQHRNSSEIICCTTPSLQQLNLQLPLKTKAFFMLDGLSKYFDLIY
 VHNPFVKPFEPVPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKNSCENIHLHSE
 AVLCTVPNDLLKLNSLNIWQKQAISSVTLGKVTVQPDQNTLEVLFQGPDIPEKS
 CDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
 NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIETISKAKGQPREPQEYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES
 NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
 TQKSLSLSPGKRJ**DYKDDDDKHVHHHHHH**

[0229] Bold, italicized amino acids represent the signal sequence; bold underlined amino acids represent the Flis tag.

Rat cMet-ECD-Fc-Flis (SEQ ID NO:74)

MKAPTALAPGILLLLTLAQRSHGECKEALVKSEMNVNMKYQLPNFTAETPIHN
VVLHGHHIYL GATNYIYVLNDKDLQKVSEFKTGPVVEHPDCFCQDCSSKANVS
GGVWKDNVNMALLVDITYDDQLISCGSVNRGTCQRHVLPDAAADIQSEVHC
MFSPLAEESGQCPDCVVSALGAKVLLSEKDRFINFFVGNTINSSYPDYSLHSISV
RRLKETQDGFKFLTDQSYIDVLPFRDSYPIKYIHAFESNHFYFLTVQKETLDAQT
FHTRIIRFCSVDSGLHSYMEMPLECILTEKRRKRSTREEVFNLQAAYVSKPGANL
AKQIGASPYDDILYGVFAQSKPDSAEPMNRSVCAFPKIYVNDFFNKIVNKNNV
CLQHFYGNHEHCFNRILLRNSSGCEVRSDEYRTEFTTALQRVDLFMGRLNHVL
LTSISTFIKGLTIANLGTSEGRFMQVVSRTAHFTPHVNFLDSYPVSPEVIVEHP
SNQNGYTLVVTGKKITKIPLNGLGCGHFQSCSQCLSAPYFIQCGWCHNRCVHSNE
CPSGTWTQEICLPAVYKVFPTSAPLEGGTMLTICGWDFGFKNNKFDLRKTKVLL
GNESTLTLESTNTLKTCTVGPAMSEHFNVSVIVSNSRETTQYSAFSYVDPVITSI
SPRYGPHAGGTLTLTGKYLNSGNSRHISIGGKTCTLKSVDLSILECYTPGHTVSA
EFPVKLIKIDLADRVTSSFSYREDPVVSEIHPTKSFISGGSTITGIGKNLSVSTPKLV
IEVHDVG VNYTVACQHRSSSEIICCTTPSLQQLDLQLPLKTKAFFLLDGILSKHFDL
TYVHDPMPFKPFEPVPMISMGNENVVEIKGDDIDPEAVKGEVLKVGKNSCENLH

WHSEALLCTVPSDLLKLNGGELNIEWKQAVSSTVLGKVIVQPDQNFALVLFQ
PDIEPKSCDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQEQYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
ALHNHYTQKSLSLSPGKRIDYKDDDDKHVHHHHHH

[0230] Bold, italicized amino acids represent the signal sequence; bold underlined amino acids represent the Flis tag.

Human c-Met ECD (SEQ ID NO:75)

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQN
VILHEHHIFL GATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFCQDCSSKANLSG
GVWKDNINMALVVDITYDDQLISCGSVNRGTCQRHVFPNHTADIQSEVHCIFS
PQIEEPSQCPDCVVSALGAKVLSVVKDRFINFFVGNTINSSYPDPHPLHSISVRLK
ETKDGFMFLTDQSYIDVLPFRDSYPIKYVHAFESNHFYFLTVQRETLDQTFHT
RIIRFCSINSGLHSYMEMPLECILTEKRRKRSTKKEVFNLQAAYVSKPGAQLARQI
GASLNDLILFGVFAQSKPDSAEPMDRSAMCAFPKIYVNDFFNKIVNKNNVRLCQ
HFYGNHEHCFNRILLRNSSGCEARRDEYRTEFTTALQRVDLFMGQFSEVLLTSI
STFIKGLTIANLGTSEGRFMQVVSRSRGPSTPHVNFLDSHPVSPEVIVEHTLNQ
NGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCWCHDKCVRSEECLS
GTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNKFDLKKTRVLLGNE
SCTLTLESTMTNLKTCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVITSISP
YGPMAGGTLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTISTEFA
VKLIKIDLANRETSIFSREDPIVYIEIHPTKSFISGGSTITGVGKNLSVSVPRMVINV
HEAGRNFTVACQHRNSSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIY
VHNVPVKPFEPVPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKNSCENIHLHSE
AVLCTVPNDLLKLNSLNEWKQAISSTVLGKVIVQPDQNFT

[0231] Bold, italicized amino acids represent the signal sequence.

Human c-Met Sema Domain with Flis tag (SEQ ID NO:76)

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQN
VILHEHHJFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFCQDCSSKANLSG
GVWKNINMALVVDITYDDQLISCGSVNRGTCQRHVFPNHNTADIQSEVHCIFS
PQIEEPSQCPDCVVSALGAKVLSSVKDRFINFFVGNINSSYFPDHPHLSISVRLK
ETKDGFMFLTDQSYIDVLPEDRDSYPIKYVHAFESNNFYFLTQVRETLDQTFHT
RJIRFCSINSLHSYMEMPLECILTEKRKKRSTKKEVFNLQAAYVSKPGAQLARQI
GASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPKIYVNDFFNKIVNKNVRLCLQ
HPYGPNEHCFNRTLRLNSSGCEARRDEYRTEFTTALQRVDLFMGQFSEVLLTSI
STFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLDSDHPVSPEVIVEHTLNQ
NGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGWCHDKCVRSEECLS
GTWTQQICLDYKD*DDDKHVHHHHHH***

[0232] Bold, italicized amino acids represent the signal sequence; bold underlined amino acids represent the Flis tag

C8- Antibody Epitopes in the Human c-Met Extracellular Domain

121VVDITYDDQL₁₃₀ (SEQ ID NO:77)

131ISCGSVNRGTCQRHVFPNHNTADIQS₁₅₆ (SEQ ID NO:78)

179ALGAKVLSSVKDRFTNF₁₉₅ (SEQ ID NO:79)

216VRLKETKDGFM₂₂₇ (SEQ ID NO:80)

123DITYDD₁₂₈ (SEQ ID NO:81)

144HVFPNHNTADIQS₁₅₆ (SEQ ID NO: 82)

192FINF₁₉₅ (SEQ ID NO:83)

220KETKDGFM₂₂₇ (SEQ ID NO:84)

D11- Antibody Epitopes in the Human c-Met Extracellular Domain

84YKTGPVLEHPDCFCQDCSSKANL₉₅ (SEQ ID NO:85)

95CFPCQDCSSKA₁₀₅ (SEQ ID NO:86)

Consensus CDR Sequences

[0233]

D11- Antibody Light Chain CDR2

GTSX₁LX₂S (SEQ ID NO:87), wherein X₁ is Y or R; and X₂ is A or R;

C8-Antibody Light Chain CDR1

SVSSSVX₃SIYLH (SEQ ID NO:88), wherein X₃ is S or R;

C8- Antibody Light Chain CDR3

X₄X₅YX₆GYPLT (SEQ ID NO:89), wherein X₄ is I or Q, X₅ is Q or V, and X₆ is S or R;

D11-Heavy Chain Antibody CDR2

WIYPVTGDTYYX₇EX₈FKG (SEQ ID NO:90), wherein X₇ is N, I, or R, and X₈ is K or P;

D11- Antibody Heavy Chain CDR 3

GYGAFX₉Y (SEQ ID NO:91), wherein X₉ is Y or F;

C8- Antibody Heavy Chain CDR 2

RVN_{PX}₁₀R_X₁₁X₁₂TTYNQKFEG (SEQ ID NO:92), wherein X₁₀ is N or Y, X₁₁ is G or R, and X₁₂ is G or S;

C8- Antibody Heavy Chain CDR3

X₁₃NX₁₄LDY (SEQ ID NO:93), wherein X₁₃ is T or A, and X₁₄ is W or I;

Consensus Light Chain Variable Region Sequences

[0234]

D11- Antibody Light Chain Variable Region Consensus Sequence (SEQ ID NO:94)

EIVLTQSPGTL_SSLSPGERATL_SCSVSSSISSTNLHWYQQKPGQAPRLLIY

GTSX₁LX₂SGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQWSSYPYSFG

QGTKLEIK

wherein X₁ is Y or R, and X₂ is A or R;

C8- Antibody Light Chain Variable Region Consensus Sequence (SEQ ID NO:95)

DIQMTQSPSSLSASVGDRVTITCSVSSSVX₃SIYLHWYQQKPGKAPKLLIY

STSNLASGVPSRFS_GSGSGTDFTLTIS_SLQPEDFATYYCX₄X₅YX₆GYPLTFG

GGTKVEIK

wherein X₃ is S or R, X₄ is I or Q, X₅ is Q, or V, and X₆ is S or R;

Consensus Heavy Chain Variable Region Sequences

[0235]

D1.1-Antibody Heavy Chain Variable Region Consensus Sequence (SEQ ID NO:96)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSRYIH_WVRQAPGQGLEWMGW

IYPVTGDTYYX₇EX₈FKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGY

GAFX₉YWGQGLTVTS

wherein X₇ is N, I, or R, X₈ is K or P, and X₉ is Y or F;

C8- Antibody Heavy Chain Variable Region Consensus Sequence (SEQ ID NO:97)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMH_WVRQAPGQGLEWMGR

VNPX₁₀RX₁₁X₁₂TTYNQKFEGRV_TMTTDTSTSTAYMELRSLRSDDTAVYYCARX₁₃

NX₁₄LDYWGQGLTVTVS

wherein X₁₀ is Y or N, X₁₁ is G or R, X₁₂ is S or G, X₁₃ is A or T, and X₁₄ is I or W.

SEQUENCE LISTING

[0236]

<110> Eli Lilly and Company

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<150> 61/116825 <151> 2008-11-21

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Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Thr Ser Tyr Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
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Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

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

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Thr Ser Tyr Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

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

Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

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

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Thr Ser Arg Leu Arg Ser Gly Ile Pro Asp Arg Phe Ser
 50 55 60

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

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

Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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Asp Arg Val Thr Ile Thr Cys Ser Val Ser Ser Ser Val Ser Ser Ile
 20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
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Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ile Gln Tyr Ser Gly Tyr Pro
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Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
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 1 5 10 15

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 20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Val Tyr Ser Gly Tyr Pro
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 1 5 10 15

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 20 25 30

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 35 40 45

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
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cctggccagg ctcccaggct cctcatctat ggcacatcct atctggcttc tggcatccca 180

gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240

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<223> Synthetic Construct

<400> 8

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccaggga aagagccacc	60
ctctcctgca gtgtcagctc aagtataagt tccaccaact tacactggta ccagcagaaa	120
cctggccagg ctcccaggct cctcatctat ggcacatcct acctggcttc tggcatccca	180
gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag	240
cctgaagatt ttgcagtgtg ttactgtcaa cagtggagta gttaccogta cagtttcggc	300
caagggacca agttggagat caaa	324

<210> 9

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 9

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccaggga aagagccacc	60
ctctcctgca gtgtcagctc aagtataagt tccaccaact tacactggta ccagcagaaa	120
cctggccagg ctcccaggct cctcatctat ggcacatcca gactgagatc tggcatccca	180
gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag	240
cctgaagatt ttgcagtgtg ttactgtcaa cagtggagta gttaccogta cagtttcggc	300
caagggacca agttggagat caaa	324

<210> 10

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 10

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgca gtgtcagctc aagtgttaagt tccatttact tgcactggta tcagcagaaa	120
ccagggaag cccctaagct cctgatctat agcacatcca acttggcttc tggagtccca	180
tcaagggttca gtggcagtggt atctgggaca gatttcactc tcaccatcag cagtctgcaa	240
cctgaagatt ttgcaactta ctactgtatt cagtacagtg gttaccogct cagtttcggc	300
ggagggacca agttggagat caaa	324

<210> 11

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 11

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gacatccaga tgaccagtc tccatctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgca gtgtcagctc aagtgttaagt tccatttact tgcactggta tcagcagaaa    120
ccagggaag cccctaagct cctgatctat agcacatcca acttggttc tggagtccca      180
tcaaggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagtctgcaa    240
cctgaagatt ttgcaactta ctactgtcag gtgtacagtg gttacccgct cacgttcggc    300
ggagggaacca aggtggagat caaa                                           324

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<210> 12

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 12

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gacatccaga tgaccagtc tccatctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgca gtgtcagctc aagtgtacgt tccatttact tgcactggta tcagcagaaa    120
ccagggaag cccctaagct cctgatctat agcacatcca acttggttc tggagtccca      180
tcaaggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagtctgcaa    240
cctgaagatt ttgcaactta ctactgtcag gtgtacaggg gttacccgct cacgttcggc    300
ggagggaacca aggtggagat caaa                                           324

```

<210> 13

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 13

```

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

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

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

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

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

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

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

Thr Val Ser
      115

```

<210> 14

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 14

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

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

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

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

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

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

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

Thr Val Ser
 115

<210> 15

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 15

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

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

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

Gly Trp Ile Tyr Pro Val Thr Gly Asp Thr Tyr Tyr Arg Glu Pro Phe
 50 55 60

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

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

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

Thr Val Ser
 115

<210> 16

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 16

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Val Asn Pro Asn Arg Gly Gly Thr Thr Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Val Ser

<210> 17

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 17

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Val Asn Pro Asn Arg Arg Gly Thr Thr Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Val Ser

<210> 18

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 18

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

Val Ser

<210> 19

<211> 345

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 19

caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc	60
tcctgcaagg cttctggcta caccttcaca agtaggtata tacactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atttaccctg taactggtga tacttactac	180
aacgagaagt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctac	300
ggagcttttt actactgggg ccagggcacc ctggtcaccg tctcc	345

<210> 20

<211> 345

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 20

caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc	60
tcctgcaagg cttctggcta caccttcaca agtaggtata tacactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atttaccctg taactggtga tacttactac	180
atcgagaagt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctat	300
ggagcttttt tctactgggg ccagggcacc ctggtcaccg tctcc	345

<210> 21

<211> 345

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 21

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caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc      60
tcctgcaagg cttctggcta caccttcaca agtaggtata tacactgggt gcgacaggcc      120
cctggacaag ggccttgagt gatgggatgg attatcctg taactggtga taettactac      180
agagagcctt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac      240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctat      300
ggggcttttt actactgggg ccagggcacc ctggtcaccg tctcc                        345

```

<210> 22

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 22

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caggttcagc tgggtgcagtc tgggtgctgag gtgaagaagc ctgggtcctc agtgaaggtc      60
tcctgcaagg cttctggcta cacctttacc gactactaca tgcactgggt gcgtcaggcc      120
cctggtcaag gtcttgagt gatgggtcgt gttaatccta accggggtgg tactacctac      180
aaccagaaat tcgagggccg tgtcaccatg accacagaca catccacgag cacagcctac      240
atggagctgc gtgacctgag ttctgacgac acggccgtgt attactgtgc gcgtacgaac      300
tggcttgact actggggcca gggcaccacc gtcaccgtct cc                        342

```

<210> 23

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 23

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caggttcagc tgggtgcagtc tgggtgctgag gtgaagaagc ctgggtcctc agtgaaggtc      60
tcctgcaagg cttctggcta cacctttacc gactactaca tgcactgggt gcgtcaggcc      120
cctggtcaag gtcttgagt gatgggtcgt gttaatccta accggagggg tactacctac      180
aaccagaaat tcgagggccg tgtcaccatg accacagaca catccacgag cacagcctac      240
atggagctgc gtgacctgag ttctgacgac acggccgtgt attactgtgc gcgtgcgaac      300
tggcttgact actggggcca gggcaccacc gtcaccgtct cc                        342

```

<210> 24

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 24

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caggttcagc tgggtgcagtc tgggtgctgag gtgaagaagc ctgggtcctc agtgaaggtc      60
tcctgcaagg cttctggcta cacattcaact gactactaca tgcactgggt gcgtcaggcc      120
cctggtcaag gtcttgagt gatgggtcgt gttaatcctt atcggggtag tactacctac      180
aaccagaaat tcgagggccg tgtcaccatg accacagaca catccacgag cacagcctac      240
atggagctgc gtgacctgag ttctgacgac acggccgtgt attactgtgc gcgtgcgaac      300
attcttgact actggggcca gggcaccacc gtcaccgtct cc                        342

```

<210> 25

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 25

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

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

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Thr Ser Tyr Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

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

Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
100 105 110

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

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

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 26

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 26

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

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

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Thr Ser Tyr Leu Ala Ser Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
 85 90 95
 Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 27

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 27

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

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Thr Ser Arg Leu Arg Ser Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
 85 90 95
 Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 28

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 28

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 Ser Val Ser Ser Ser Val Ser Ser Ile

20 25 30
 Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ile Gln Tyr Ser Gly Tyr Pro
 85 90 95
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 29

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 29

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 Ser Val Ser Ser Ser Val Ser Ser Ile
 20 25 30
 Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Val Tyr Ser Gly Tyr Pro
 85 90 95
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 30

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 30

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 Ser Val Ser Ser Ser Val Arg Ser Ile
 20 25 30
 Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Val Tyr Arg Gly Tyr Pro
 85 90 95
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 31

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 31

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccaggga aagagccacc 60
 ctctcctgca gtgtcagctc aagtataagt tccaccaact tacactggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggcacatcct acctggcttc tggcatocca 180
 gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtg ttactgtcaa cagtggagta gttaccogta cagtttcggc 300
 caagggacca agttggagat caaacgaact gtggctgcac catctgtctt catcttcocg 360
 ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
 tatcccagag agggcaaaagt acagtggaag gtggataacg cctccaatc gggtaactcc 480
 caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540
 acgctgagca aagcagacta cgagaacac aaagtctacg cctgcgaagt caccatcag 600
 ggcctgagct cgcccgac aaagagcttc aacaggggag agtgc 645

<210> 32

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 32

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gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc      60
ctctcctgca gtgtcagctc aagtataagt tccaccaact tacactggta ccagcagaaa      120
cctggccagg ctcccaggct cctcatctat ggcacatcct acctggcttc tggcatocca      180
gacagggtca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag      240
cctgaagatt ttgcagtgtg ttactgtcaa cagtggagta gttaccgta cagtttcggc      300
caagggacca agttggagat caaacgaact gtggctgcac catctgtctt catcttcccg      360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataaactc      420
tatcccagag agggcaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc      480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg      540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag      600
ggcctgagct cgcccgctac aaagagcttc aacaggggag agtgc      645

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<210> 33

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 33

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gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc      60
ctctcctgca gtgtcagctc aagtataagt tccaccaact tacactggta ccagcagaaa      120
cctggccagg ctcccaggct cctcatctat ggcacatcca gactgagatc tggcatocca      180
gacagggtca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag      240
cctgaagatt ttgcagtgtg ttactgtcaa cagtggagta gttaccgta cagtttcggc      300
caagggacca agttggagat caaacgaact gtggctgcac catctgtctt catcttcccg      360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataaactc      420
tatcccagag agggcaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc      480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg      540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag      600
ggcctgagct cgcccgctac aaagagcttc aacaggggag agtgc      645

```

<210> 34

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 34

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgca gtgtcagctc aagtgtaatc tccatttact tgcactggta tcagcagaaa    120
ccagggaag cccctaagct cctgatctat agcacatcca acttggcttc tggagtccca    180
tcaaggttca gtggcagtg atctgggaca gatttcactc tcaccatcag cagtctgcaa    240
cctgaagatt ttgcaactta ctactgtatt cagtacagtg gttacccgct caggttcggc    300
ggagggaacca aggtggagat caaacgaact gtggctgcac catctgtctt catcttcccg    360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc    420
tatccagag agggcaaaagt acagtggaag gtggataacg cctccaatc gggtaactcc    480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg    540
acgctgagca aagcagacta cgagaacac aaagtctacg cctgcgaagt caccatcag    600
ggcctgagct cggccgtcac aaagagcttc aacaggggag agtgc    645

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<210> 35

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 35

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgca gtgtcagctc aagtgtatcc tccatttact tgcactggta tcagcagaaa    120
ccagggaag cccctaagct cctgatctat agcacatcca acttggcttc tggagtccca    180

tcaaggttca gtggcagtg atctgggaca gatttcactc tcaccatcag cagtctgcaa    240
cctgaagatt ttgcaactta ctactgtcaa gtctacagtg gttacccgct caggttcggc    300
ggagggaacca aggtggagat caaacgaact gtggctgcac catctgtctt catcttcccg    360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc    420
tatccagag agggcaaaagt acagtggaag gtggataacg cctccaatc gggtaactcc    480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg    540
acgctgagca aagcagacta cgagaacac aaagtctacg cctgcgaagt caccatcag    600
ggcctgagct cggccgtcac aaagagcttc aacaggggag agtgc    645

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<210> 36

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 36

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgca gtgtcagctc aagtgtacgt tccatttact tgcactggta tcagcagaaa    120
ccagggaag cccctaagct cctgatctat agcacatcca acttggcttc tggagtccca    180
tcaaggttca gtggcagtg atctgggaca gatttcactc tcaccatcag cagtctgcaa    240
cctgaagatt ttgcaactta ctactgtcag gtgtacaggg gttacccgct caggttcggc    300
ggagggaacca aggtggagat caaacgaact gtggctgcac catctgtctt catcttcccg    360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc    420
tatccagag agggcaaaagt acagtggaag gtggataacg cctccaatc gggtaactcc    480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg    540
acgctgagca aagcagacta cgagaacac aaagtctacg cctgcgaagt caccatcag    600
ggcctgagct cggccgtcac aaagagcttc aacaggggag agtgc    645

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<210> 37

<211> 441

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 37

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Arg

20 25 30

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

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

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

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

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

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
 130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

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

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
 180 185 190

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

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
 210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
 225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
 260 265 270

Tyr Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
 290 295 300
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 305 310 315 320
 Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
 325 330 335
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 340 345 350
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 355 360 365
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 370 375 380
 Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
 385 390 395 400
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 405 410 415
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 420 425 430
 Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440

<210> 38

<211> 441

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 38

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

50 55 60
 Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Tyr Gly Ala Phe Phe Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125
 Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
 130 135 140
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
 180 185 190
 Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
 195 200 205
 Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
 225 230 235 240
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 245 250 255
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
 260 265 270
 Tyr Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 275 280 285
 Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
 290 295 300
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 305 310 315 320
 Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
 325 330 335
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 340 345 350
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 355 360 365
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 370 375 380
 Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
 385 390 395 400
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 405 410 415
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 420 425 430
 Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440

<210> 39

<211> 441

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 39

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

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

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

Gly Trp Ile Tyr Pro Val Thr Gly Asp Thr Tyr Tyr Arg Glu Pro Phe
50 55 60

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

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

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

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

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

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

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

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

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

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 370 375 380

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
 385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 420 425 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440

<210> 40

<211> 440

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 40

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Val Asn Pro Asn Arg Gly Gly Thr Thr Tyr Asn Gln Lys Phe
 50 55 60

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

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

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

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro

115 120 125
 Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
 130 135 140
 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 145 150 155 160
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 165 170 175
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
 180 185 190
 Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
 195 200 205
 Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
 210 215 220
 Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 225 230 235 240
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 245 250 255
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 260 265 270
 Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 275 280 285
 Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
 290 295 300
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 305 310 315 320
 Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
 325 330 335
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 340 345 350
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 355 360 365
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 370 375 380
 Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
 385 390 395 400
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 405 410 415
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 420 425 430
 Lys Ser Leu Ser Leu Ser Pro Gly
 435 440

<210> 41

<211> 440

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 41

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

145 150 155 160
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 165 170 175
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
 180 185 190
 Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
 195 200 205
 Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
 210 215 220
 Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 225 230 235 240
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 245 250 255
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 260 265 270
 Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 275 280 285
 Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
 290 295 300
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 305 310 315 320
 Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
 325 330 335
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 340 345 350
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 355 360 365
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 370 375 380
 Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
 385 390 395 400
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 405 410 415
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 420 425 430
 Lys Ser Leu Ser Leu Ser Pro Gly
 435 440

<210> 42

<211> 440

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 42

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

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

<210> 43

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 43

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caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc      60
tectgcaagg cttctggcta caccctcaca agtaggtata tacactgggt gcgacaggcc      120
cctggacaag ggcttgagtg gatgggatgg atttatcctg taactggtga tacttactac      180
aacgagaagt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac      240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctat      300
ggggcttttt actactgggg ccagggcacc ctggtcacog tctcctcccg ctccaccaag      360
ggcccatcgg tcttcccgct agcgcctctc tccaggagca cctccgagag cacagccgcc      420
ctgggctgco tgggtcaagga ctacttcccc gaaccggtga cgggtgctgt gaactcaggc      480
gccctgacca gcggcgtgca caccctcccg gctgtcctac agtcctcagg actctactcc      540
ctcagcagcg tgggtgacogt gccctccagc aacttcggca ccagagccta cacctgcaac      600
gtatgatcaca agcccagcaa caccaggtg gacaagacag ttgagcgcaa atgtttgtgc      660
gagtgcacac cgtgcccagc accacctgtg gcaggaccgt cagtcttctt cttcccccca      720
aaacccaagg acaccctcat gatctcccg acccctgagg tcacgtgctg ggtgggtggac      780
gtgagccacg aagaccccg ggtccagttc aactggtacg tggacggcat ggaggtgcat      840
aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc      900
ctcaccgtcg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac      960
aaaggcctcc cagcccccac cgagaaaacc atctccaaaa ccaaggggca gccccgagaa     1020
ccacagggtg acaccctgcc cccatcccg gaggagatga ccaagaacca ggtcagcctg     1080
acctgcctgg tcaagggtt ctaccccagc gacatcgccg tggagtggga gagcaatggg     1140
cagccggaga acaactacaa gaccacacdt cccatgctgg actccgacgg ctecttcttc     1200
ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc     1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctcog     1320
ggt

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<210> 44

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 44

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caggtgcagc tgggtcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc      60
tcctgcaagg cttctggcta caccttcaca agtaggtata tacactgggt gcgacaggcc      120
cctggacaag ggcttgagtg gatgggatgg atttatcctg taactgggta tacttactac      180
atcgagaagt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac      240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctat      300
ggtgcttttt tctactgggg ccagggcacc ctggtcaccg tctcctccgc ctccaccaag      360
ggcccatcgg tcttcccgtc agcgcctgc tccaggagca cctccgagag cacagccgcc      420
ctgggctgcc tgggtcaaggc ctactcccc gaaccgggta cgggtgcgtg gaactcaggc      480
gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc      540
ctcagcagcg tggtgaccgt gccctccagc aacttcggca cccagaccta cacctgcaac      600
gtagatcaca agcccagcaa caccaagggtg gacaagacag ttgagcgcaa atgttggtgc      660
gagtgcccac cgtgcccgag accacotgtg gcaggaccgt cagtcttctc cttcccccca      720
aaacccaagg acacccctcat gatctcccgg acccctgagg tcacgtgcgt ggtgggtggac      780
gtgagccaag aagaccccga ggtccagttc aactggtaag tggacggcat ggaggtgcat      840
aatccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc      900
ctcaccgtcg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac      960
aaaggcctcc cagcccccac cgagaaaacc atctccaaaa ccaaagggca gccccagaaa     1020
ccacagtggt acacccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg     1080
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg     1140
cagccggaga acaactacaa gaccacacct cccatgctgg actccgacgg ctecttcttc     1200
ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc     1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctccg     1320
ggt                                             1323

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<210> 45

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 45

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caggtgcagc tgggtcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc      60
tcctgcaagg cttctggcta caccttcaca agtaggtata tacactgggt gcgacaggcc      120
cctggacaag ggcttgagtg gatgggatgg atttatcctg taactgggta tacttactac      180
agagagcctt tcaagggcag agtcacgatt accgcggaca aatccacgag cacagcctac      240

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggctac      300
ggagcttttt actactgggg ccagggcacc ctggtcaccg tctcctccgc ctccaccaag      360
ggcccatogg tcttcccgct agcgccctgc tccaggagca cctccgagag cacagccgcc      420
ctgggctgcc tggccaagga ctacttccc gaaccgggtga cgggtgtcgtg gaactcaggg      480
gccctgacca gcggcgtgca caccctcccg gctgtcctac agtcctcagg actctactcc      540
ctcagcagcg tggtgaccgt gccctccagc aacttoggca ccagacctc caccctgcaac      600
gtagatcaca agcccagcaa caccaagggtg gacaagacag ttgagcgcaa atgttgtgtc      660
gagtgcacc acgtgccagc accacctgtg gcaggaccgt cagtcttctc cttcccccca      720
aaacccaagg acacccctcat gatctcccg acccctgagg tcacgtgcgt ggtgggtggac      780
gtgagccacg aagaccocga ggtccagttc aactggtacg tggacggcat ggaggtgcat      840
aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttcctgtg ggtcagcgtc      900
ctcaccgtcg tgcaccagga ctggctgaac ggcaaggagt acaagtgcga ggtctcacaac      960
aaaggcctcc cagcccccat cgagaaaacc atctccaaaa ccaaggggca gccccgagaa     1020
ccacaggtgt acacccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg     1080
acctgcctgg tcaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg     1140
cagccggaga acaactacaa gaccacacct cccatgctgg actccgacgy ctccttcttc     1200
ctctacagca agctcacctg ggacaagagc aggtggcagc aggggaacgt cttctcatgc     1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctccg     1320
gggt                                              1323

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<210> 46

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 46

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tcctgcaagg cttctggtta caccctttacc gactactaca tgcactgggt gcgtcaggcc     120
cctgggtcaag gtcttgagtg gatgggtcgt gttaatccta accgggggtg tactacctac     180
aaccagaaat tcgagggccg tgtcaccatg accacagaca catccacgag cacagccctac     240
atggagctgc gtagcctgcg ttctgacgac acggccgtgt attactgtgc gcgtacgaac     300
tggcttgact actggggcca gggcaccacc gtcaccgtct cctccgcctc caccaagggg     360
ccatcggtct tcccgtagc gccctgctcc aggagcacct ccgagagcac agccgccctg     420
ggctgcctgg tcaaggacta cttccccgaa ccgggtgacgg tgtcgtggaa ctcaggcgcc     480

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ctgaccagcg gcggtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcacga agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagagagttg agtccaaata tggccccca 660
tgccccacct gccacgaccc tgaggccgcc gggggaccat cagtcttctc gttcccccca 720
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gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat 840
aatgccaaga caaagccgcg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc 900
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 960
aaaggcctcc cgtcctccat cgagaaaacc atctccaaag ccaaagggca gccccgagag 1020
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acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga aagcaatggg 1140
cagccggaga acaactacaa gaccacgcct cccgtgctgg actcogacgg ctcttcttc 1200
ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc 1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctctg 1320
ggt 1323

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<210> 47

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 47

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cctggtcaag gtcttgagtg gatgggtcgt gttaatccta accggagggg tactacctac 180
aaccagaaat tcgagggdgc tgtcaccatg accacagaca catccacgag cacagcctac 240
atggagctgc gtagectgcg ttctgacgac acggccgtgt attactgtgc gcgtgcgaac 300
tggcttgact actggggcca gggcaccaac gtacdcgtct cctccgcctc caaccaagggc 360
ccatcggtct tcccgtagc gccctgctcc aggagcacct ccgagagcac agccgccctg 420
ggctgcctgg tcaaggacta cttcccga aacgggtgacgg tgtcgtggaa ctcaggcgcc 480
ctgaccagcg gcggtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 540
agcagcgtgg tgaccgtgcc ctccagcagc ttgggcacga agacctacac ctgcaacgta 600
gatcacaagc ccagcaacac caaggtggac aagagagttg agtccaaata tggccccca 660
tgccccacct gccacgaccc tgaggccgcc gggggaccat cagtcttctc gttcccccca 720
aaacccaagg acactctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 780

gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat 840
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ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 960
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ccacaggtgt acacccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg 1080
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga aagcaatggg 1140
cagccggaga acaactacaa gaccacgcct cccgtgctgg actcogacgg ctcttcttc 1200
ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc 1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctctg 1320
ggt 1323

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<210> 48

<211> 1323

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 48

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cctgggtcaag gtcttgagtg gatgggtcgt gttaatcctt atcggggtag tactacctac      180
aaccagaaat tcgagggccg tgtcaccatg accacagaca catccacgag cacagccctac      240
atggagctgc gtgacctgcg ttctgacgac acggccgtgt attactgtgc gcgtgcgaac      300
attcttgact actggggcca gggcaccacc gtcaccgtct cctccgcctc caccaagggc      360
ccatcggtct tcccctagc gccctgctcc aggagcact cagagagcac agccgccctg      420
ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtgaa ctcaggcgcc      480
ctgaccagcg gcgtgcacac cttcccggt gtccctacagt cctcaggact ctactccctc      540
agcagcgtgg tgacctgccc ctccagcagc ttgggcaoga agacctacac ctgcaacgta      600
gatcacaagc ccagcaacac caaggtggac aagagagttg agtcaaata tgggtcccca      660
tgccaccct gccagcacc tgaggccccc gggggaccat cagtcttctt gttcccccca      720
aaaccaag acactctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac      780
gtgagccagg aagacccca ggtccagttc aactggtacg tggatggcgt ggaggtgcat      840
aatgccaaga caaagcccg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc      900
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgaac ggtctccaac      960
aaaggcctcc cgtcctccat cgagaaaacc atctccaaag ccaaggggca gcccggagag     1020

ccacaggtgt acaccctgcc cccatcccag gaggatga ccaagaacca ggtcagcctg     1080
acctgcctgg tcaaggett ctaccccagc gacatcgccg tggagtggga aagcaatggg     1140
cagccggaga acaactaaa gaccacgct cccgtgctgg actccgacgg ctcttcttc     1200
ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc     1260
tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctctg     1320
ggt                                             1323

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<210> 49

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 49

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Ser Val Ser Ser Ser Ile Ser Ser Thr Asn Leu His
1           5           10

```

<210> 50

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 50

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Gly Thr Ser Tyr Leu Ala Ser
1           5

```

<210> 51

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 51

Gln Gln Trp Ser Ser Tyr Pro Tyr Ser
 1 5

<210> 52

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 52

Gly Thr Ser Arg Leu Arg Ser
 1 5

<210> 53

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 53

Ser Val Ser Ser Ser Val Ser Ser Ile Tyr Leu His
 1 5 10

<210> 54

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 54

Ser Thr Ser Asn Leu Ala Ser
 1 5

<210> 55

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 55

Ile Gln Tyr Ser Gly Tyr Pro Leu Thr
 1 5

<210> 56

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 56

Gln Val Tyr Ser Gly Tyr Pro Leu Thr
 1 5

<210> 57

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 57

Ser	Val	Ser	Ser	Ser	Val	Arg	Ser	Ile	Tyr	Leu	His
1				5					10		

<210> 58

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 58

Gln	Val	Tyr	Arg	Gly	Tyr	Pro	Leu	Thr
1			5					

<210> 59

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 59

Gly	Tyr	Thr	Phe	Thr	Ser	Arg	Tyr	Ile	His
1			5					10	

<210> 60

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 60

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

Gly

<210> 61

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 61

Gly	Tyr	Gly	Ala	Phe	Tyr	Tyr
1			5			

<210> 62

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 62

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

Gly

<210> 63

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 63

Gly Tyr Gly Ala Phe Phe Tyr
1 5

<210> 64

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 64

Trp Ile Tyr Pro Val Thr Gly Asp Thr Tyr Tyr Arg Glu Pro Phe Lys
1 5 10 15

Gly

<210> 65

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 65

Gly Tyr Thr Phe Thr Asp Tyr Tyr Met His

1

5

10

<210> 66

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 66

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

Gly

<210> 67

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 67

Thr	Asn	Trp	Leu	Asp	Tyr
1			5		

<210> 68

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 68

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

Gly

<210> 69

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 69

Ala	Asn	Trp	Leu	Asp	Tyr
1				5	

<210> 70

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 70

Arg	Val	Asn	Pro	Tyr	Arg	Gly	Ser	Thr	Thr	Tyr	Asn	Gln	Lys	Phe	Glu
1				5					10					15	

Gly

<210> 71

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 71

Ala	Asn	Ile	Leu	Asp	Tyr
1				5	

<210> 72

<211> 1192

<212> PRT

<213> Homo sapiens

<400> 72

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
 1 5 10 15
 Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
 20 25 30
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
 35 40 45
 Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
 50 55 60
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
 65 70 75 80
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
 85 90 95
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
 100 105 110
 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
 115 120 125
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
 130 135 140
 Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
 145 150 155 160
 Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
 165 170 175
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
 180 185 190
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
 195 200 205
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
 210 215 220
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
 225 230 235 240
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
 245 250 255
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
 260 265 270
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
 275 280 285
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
 290 295 300
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
 305 310 315 320
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
 325 330 335
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
 340 345 350
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys

355 360 365
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
 370 375 380
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
 385 390 395 400
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
 405 410 415
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
 420 425 430
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
 435 440 445
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
 450 455 460
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
 465 470 475 480
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
 485 490 495
 Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
 500 505 510
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
 515 520 525
 Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
 530 535 540
 Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
 545 550 555 560
 Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu
 565 570 575
 Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
 580 585 590
 Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu
 595 600 605
 Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
 610 615 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
 625 630 635 640
 Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
 645 650 655
 Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
 660 665 670
 Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
 675 680 685
 His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
 690 695 700
 Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
 705 710 715 720
 Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
 725 730 735
 Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
 740 745 750
 Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn
 755 760 765
 Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg
 770 775 780
 Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
 785 790 795 800
 Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
 805 810 815
 Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
 820 825 830
 Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
 835 840 845
 Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
 850 855 860
 Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
 865 870 875 880

Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
 885 890 895
 Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
 900 905 910
 Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
 915 920 925
 Gln Asn Phe Thr Leu Glu Val Leu Phe Gln Gly Pro Asp Ile Glu Pro
 930 935 940
 Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 945 950 955 960
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 965 970 975
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 980 985 990
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 995 1000 1005
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 1010 1015 1020
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 1025 1030 1035
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 1040 1045 1050
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 1055 1060 1065
 Gln Pro Arg Glu Pro Gln Glu Tyr Thr Leu Pro Pro Ser Arg Glu
 1070 1075 1080
 Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 1085 1090 1095
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 1100 1105 1110
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 1115 1120 1125

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1130 1135 1140
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1145 1150 1155
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1160 1165 1170
 Lys Arg Ile Asp Tyr Lys Asp Asp Asp Asp Lys His Val His His
 1175 1180 1185
 His His His His
 1190
 <210> 73
 <211> 1192
 <212> PRT
 <213> Macaca mulatta
 <400> 73
 Met Lys Ala Pro Ala Val Leu Val Pro Gly Ile Leu Val Leu Leu Phe
 1 5 10 15
 Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
 20 25 30
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
 35 40 45
 Glu Thr Ala Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
 50 55 60
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
 65 70 75 80
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
 85 90 95
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
 100 105 110
 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
 115 120 125
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
 130 135 140
 Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
 145 150 155 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Asn Gln Cys Pro Asp Cys Val
 165 170 175
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
 180 185 190
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro His
 195 200 205
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
 210 215 220
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
 225 230 235 240
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Ile His Ala Phe Glu Ser Asn
 245 250 255
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asn Ala Gln
 260 265 270
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Leu Asn Ser Gly Leu
 275 280 285
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
 290 295 300
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
 305 310 315 320
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
 325 330 335
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
 340 345 350
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
 355 360 365
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
 370 375 380
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
 385 390 395 400
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
 405 410 415

Arg Ala Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
 420 425 430
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Val Lys Gly
 435 440 445
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
 450 455 460
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
 465 470 475 480
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Pro Leu
 485 490 495
 Asn Gln Asn Gly Tyr Thr Leu Val Val Thr Gly Lys Lys Ile Thr Lys
 500 505 510
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
 515 520 525
 Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
 530 535 540
 Cys Val Arg Ser Glu Glu Cys Pro Ser Gly Thr Trp Thr Gln Gln Ile
 545 550 555 560
 Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Thr Ser Ala Pro Leu Glu
 565 570 575
 Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
 580 585 590
 Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu
 595 600 605
 Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
 610 615 620
 Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
 625 630 635 640
 Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
 645 650 655
 Pro Ile Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
 660 665 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
 675 680 685
 His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
 690 695 700
 Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
 705 710 715 720
 Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
 725 730 735
 Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
 740 745 750
 Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu His
 755 760 765
 Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg
 770 775 780
 Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
 785 790 795 800
 Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
 805 810 815
 Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
 820 825 830
 Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
 835 840 845
 Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
 850 855 860
 Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
 865 870 875 880
 Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
 885 890 895
 Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
 900 905 910
 Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
 915 920 925
 Gln Asn Phe Thr Leu Glu Val Leu Phe Gln Gly Pro Asp Ile Glu Pro

930 935 940
 Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 945 950 955 960
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 965 970 975
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 980 985 990
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 995 1000 1005
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 1010 1015 1020
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 1025 1030 1035
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 1040 1045 1050
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 1055 1060 1065
 Gln Pro Arg Glu Pro Gln Glu Tyr Thr Leu Pro Pro Ser Arg Glu
 1070 1075 1080
 Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 1085 1090 1095
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 1100 1105 1110
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 1115 1120 1125
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1130 1135 1140
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1145 1150 1155
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1160 1165 1170
 Lys Arg Ile Asp Tyr Lys Asp Asp Asp Asp Lys His Val His His
 1175 1180 1185
 His His His His
 1190

<210> 74

<211> 1194

<212> PRT

<213> Rattus rattus

<400> 74

Met Lys Ala Pro Thr Ala Leu Ala Pro Gly Ile Leu Leu Leu Leu Leu
 1 5 10 15
 Thr Leu Ala Gln Arg Ser His Gly Glu Cys Lys Glu Ala Leu Val Lys
 20 25 30
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
 35 40 45
 Glu Thr Pro Ile His Asn Val Val Leu His Gly His His Ile Tyr Leu
 50 55 60
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Asp Lys Asp Leu Gln Lys
 65 70 75 80
 Val Ser Glu Phe Lys Thr Gly Pro Val Val Glu His Pro Asp Cys Phe
 85 90 95
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Val Ser Gly Gly Val Trp
 100 105 110
 Lys Asp Asn Val Asn Met Ala Leu Leu Val Asp Thr Tyr Tyr Asp Asp
 115 120 125
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
 130 135 140
 Val Leu Pro Pro Asp Asn Ala Ala Asp Ile Gln Ser Glu Val His Cys
 145 150 155 160
 Met Phe Ser Pro Leu Ala Glu Glu Glu Ser Gly Gln Cys Pro Asp Cys
 165 170 175
 Val Val Ser Ala Leu Gly Ala Lys Val Leu Leu Ser Glu Lys Asp Arg
 180 185 190
 Phe Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Pro Pro
 195 200 205

Asp Tyr Ser Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Gln
 210 215 220
 Asp Gly Phe Lys Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro
 225 230 235 240
 Glu Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Ile His Ala Phe Glu Ser
 245 250 255
 Asn His Phe Ile Tyr Phe Leu Thr Val Gln Lys Glu Thr Leu Asp Ala
 260 265 270
 Gln Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Val Asp Ser Gly
 275 280 285
 Leu His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys
 290 295 300
 Arg Arg Lys Arg Ser Thr Arg Glu Glu Val Phe Asn Ile Leu Gln Ala
 305 310 315 320
 Ala Tyr Val Ser Lys Pro Gly Ala Asn Leu Ala Lys Gln Ile Gly Ala
 325 330 335
 Ser Pro Tyr Asp Asp Ile Leu Tyr Gly Val Phe Ala Gln Ser Lys Pro
 340 345 350
 Asp Ser Ala Glu Pro Met Asn Arg Ser Ala Val Cys Ala Phe Pro Ile
 355 360 365
 Lys Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val
 370 375 380
 Arg Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn
 385 390 395 400
 Arg Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Val Arg Ser Asp Glu
 405 410 415
 Tyr Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met
 420 425 430
 Gly Arg Leu Asn His Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys
 435 440 445
 Gly Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met
 450 455 460
 Gln Val Val Leu Ser Arg Thr Ala His Phe Thr Pro His Val Asn Phe

465 470 475 480
 Leu Leu Asp Ser Tyr Pro Val Ser Pro Glu Val Ile Val Glu His Pro
 485 490 495
 Ser Asn Gln Asn Gly Tyr Thr Leu Val Val Thr Gly Lys Lys Ile Thr
 500 505 510
 Lys Ile Pro Leu Asn Gly Leu Gly Cys Gly His Phe Gln Ser Cys Ser
 515 520 525
 Gln Cys Leu Ser Ala Pro Tyr Phe Ile Gln Cys Gly Trp Cys His Asn
 530 535 540
 Arg Cys Val His Ser Asn Glu Cys Pro Ser Gly Thr Trp Thr Gln Glu
 545 550 555 560
 Ile Cys Leu Pro Ala Val Tyr Lys Val Phe Pro Thr Ser Ala Pro Leu
 565 570 575
 Glu Gly Gly Thr Met Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Lys
 580 585 590
 Lys Asn Asn Lys Phe Asp Leu Arg Lys Thr Lys Val Leu Leu Gly Asn
 595 600 605
 Glu Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Thr Asn Thr Leu Lys
 610 615 620
 Cys Thr Val Gly Pro Ala Met Ser Glu His Phe Asn Val Ser Val Ile
 625 630 635 640
 Val Ser Asn Ser Arg Glu Thr Thr Gln Tyr Ser Ala Phe Ser Tyr Val
 645 650 655
 Asp Pro Val Ile Thr Ser Ile Ser Pro Arg Tyr Gly Pro His Ala Gly
 660 665 670
 Gly Thr Leu Leu Thr Leu Thr Gly Lys Tyr Leu Asn Ser Gly Asn Ser
 675 680 685
 Arg His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser
 690 695 700
 Asp Ser Ile Leu Glu Cys Tyr Thr Pro Gly His Thr Val Ser Ala Glu
 705 710 715 720
 Phe Pro Val Lys Leu Lys Ile Asp Leu Ala Asp Arg Val Thr Ser Ser
 725 730 735

Phe Ser Tyr Arg Glu Asp Pro Val Val Ser Glu Ile His Pro Thr Lys
 740 745 750
 Ser Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Ile Gly Lys Asn Leu
 755 760 765
 Asn Ser Val Ser Thr Pro Lys Leu Val Ile Glu Val His Asp Val Gly
 770 775 780
 Val Asn Tyr Thr Val Ala Cys Gln His Arg Ser Ser Ser Glu Ile Ile
 785 790 795 800
 Cys Cys Thr Thr Pro Ser Leu Gln Gln Leu Asp Leu Gln Leu Pro Leu
 805 810 815
 Lys Thr Lys Ala Phe Phe Leu Leu Asp Gly Ile Leu Ser Lys His Phe
 820 825 830
 Asp Leu Thr Tyr Val His Asp Pro Met Phe Lys Pro Phe Glu Lys Pro
 835 840 845
 Val Met Ile Ser Met Gly Asn Glu Asn Val Val Glu Ile Lys Gly Asp
 850 855 860
 Asp Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn
 865 870 875 880
 Lys Ser Cys Glu Asn Leu His Trp His Ser Glu Ala Leu Leu Cys Thr
 885 890 895
 Val Pro Ser Asp Leu Leu Lys Leu Asn Gly Gly Glu Leu Asn Ile Glu
 900 905 910
 Trp Lys Gln Ala Val Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln
 915 920 925
 Pro Asp Gln Asn Phe Ala Leu Glu Val Leu Phe Gln Gly Pro Asp Ile
 930 935 940
 Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 945 950 955 960
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 965 970 975
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 980 985 990

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 995 1000 1005

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 1010 1015 1020

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 1025 1030 1035

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 1040 1045 1050

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 1055 1060 1065

Lys Gly Gln Pro Arg Glu Pro Gln Glu Tyr Thr Leu Pro Pro Ser
 1070 1075 1080

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 1085 1090 1095

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 1100 1105 1110

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 1115 1120 1125

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 1130 1135 1140

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 1145 1150 1155

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 1160 1165 1170

Pro Gly Lys Arg Ile Asp Tyr Lys Asp Asp Asp Asp Lys His Val
 1175 1180 1185

His His His His His His
 1190

<210> 75

<211> 932

<212> PRT

<213> Homo sapiens

<400> 75

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe

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

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
 275 280 285
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
 290 295 300
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
 305 310 315 320
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
 325 330 335
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
 340 345 350
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
 355 360 365
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
 370 375 380
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
 385 390 395 400
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
 405 410 415
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
 420 425 430
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
 435 440 445
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
 450 455 460
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
 465 470 475 480
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
 485 490 495
 Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
 500 505 510
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
 515 520 525

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

Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
785 790 795 800

Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
805 810 815

Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
820 825 830

Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
835 840 845

Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
850 855 860

Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
865 870 875 880

Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
885 890 895

Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
900 905 910

Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
915 920 925

Gln Asn Phe Thr
930

<210> 76

<211> 578

<212> PRT

<213> Homo sapiens

<400> 76

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
1 5 10 15

Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
20 25 30

Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
35 40 45

Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
50 55 60

Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65 70 75 80

Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
 85 90 95
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
 100 105 110
 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
 115 120 125
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
 130 135 140
 Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
 145 150 155 160
 Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
 165 170 175
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
 180 185 190
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
 195 200 205
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
 210 215 220
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
 225 230 235 240
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
 245 250 255
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
 260 265 270
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
 275 280 285
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
 290 295 300
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
 305 310 315 320
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
 325 330 335

Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
 340 345 350
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
 355 360 365
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
 370 375 380
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
 385 390 395 400
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
 405 410 415
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
 420 425 430
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
 435 440 445
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
 450 455 460
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
 465 470 475 480
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
 485 490 495
 Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
 500 505 510
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
 515 520 525
 Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
 530 535 540
 Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
 545 550 555 560
 Cys Leu Asp Tyr Lys Asp Asp Asp Asp Lys His Val His His His His
 565 570 575

His His

<210> 77

<211> 10

<212> PRT

<213> Homo sapiens

<400> 77

Val Val Asp Thr Tyr Tyr Asp Asp Gln Leu
 1 5 10

<210> 78

<211> 25

<212> PRT

<213> Homo sapiens

<400> 78

Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His Val Phe
 1 5 10 15

Pro His Asn His Thr Ala Asp Ile Gln
 20 25

<210> 79

<211> 18

<212> PRT

<213> Homo sapiens

<400> 79

Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe Ile Asn
1 5 10 15

Phe Phe

<210> 80

<211> 12

<212> PRT

<213> Homo sapiens

<400> 80

Val Arg Arg Leu Lys Glu Thr Lys Asp Gly Phe Met
1 5 10

<210> 81

<211> 6

<212> PRT

<213> Homo sapiens

<400> 81

Asp Thr Tyr Tyr Asp Asp
1 5

<210> 82

<211> 13

<212> PRT

<213> Homo sapiens

<400> 82

His Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser
1 5 10

<210> 83

<211> 4

<212> PRT

<213> Homo sapiens

<400> 83

Phe Ile Asn Phe

1

<210> 84

<211> 8

<212> PRT

<213> Homo sapiens

<400> 84

Lys Glu Thr Lys Asp Gly Phe Met
1 5

<210> 85

<211> 24

<212> PRT

<213> Homo sapiens

<400> 85

Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe Pro Cys Gln
1 5 10 15

Asp Cys Ser Ser Lys Ala Asn Leu
20

<210> 86

<211> 11

<212> PRT

<213> Homo sapiens

<400> 86

Cys Phe Pro Cys Gln Asp Cys Ser Ser Lys Ala
 1 5 10

<210> 87

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (4)..(4)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (6)..(6)

<223> Xaa can be any naturally occurring amino acid

<400> 87

Gly Thr Ser Xaa Leu Xaa Ser
 1 5

<210> 88

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa can be any naturally occurring amino acid

<400> 88

Ser Val Ser Ser Val Xaa Ser Ile Tyr Leu His
 1 5 10

<210> 89

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (1)..(2)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (4)..(4)

<223> Xaa can be any naturally occurring amino acid

<400> 89

Xaa Xaa Tyr Xaa Gly Tyr Pro Leu Thr
 1 5

<210> 90

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (12)..(12)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (14)..(14)

<223> Xaa can be any naturally occurring amino acid

<400> 90

Trp Ile Tyr Pro Val Thr Gly Asp Thr Tyr Tyr Xaa Glu Xaa Phe Lys
 1 5 10 15

Gly

<210> 91

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (6)..(6)

<223> Xaa can be any naturally occurring amino acid

<400> 91

Gly Tyr Gly Ala Phe Xaa Tyr
 1 5

<210> 92

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> misc_feature

<222> (5)..(5)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (7)..(8)

<223> Xaa can be any naturally occurring amino acid

<400> 92

Arg Val Asn Pro Xaa Arg Xaa Xaa Thr Thr Tyr Asn Gln Lys Phe Glu
 1 5 10 15
 Gly
 <210> 93
 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic Construct
 <220>
 <221> misc_feature
 <222> (1)..(1)
 <223> Xaa can be any naturally occurring amino acid
 <220>
 <221> misc_feature
 <222> (3)..(3)
 <223> Xaa can be any naturally occurring amino acid
 <400> 93
 Xaa Asn Xaa Leu Asp Tyr
 1 5
 <210> 94
 <211> 108
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic Construct
 <220>
 <221> misc_feature
 <222> (54)..(54)
 <223> Xaa can be any naturally occurring amino acid
 <220>
 <221> misc_feature
 <222> (56)..(56)
 <223> Xaa can be any naturally occurring amino acid
 <400> 94
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Ser Val Ser Ser Ser Ile Ser Ser Thr
 20 25 30
 Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Thr Ser Xaa Leu Xaa Ser Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
 85 90 95
 Tyr Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 95
 <211> 108
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic Construct

 <220>
 <221> misc_feature
 <222> (30)..(30)
 <223> Xaa can be any naturally occurring amino acid

 <220>
 <221> misc_feature
 <222> (90)..(91)
 <223> Xaa can be any naturally occurring amino acid

 <220>
 <221> misc_feature
 <222> (93)..(93)
 <223> Xaa can be any naturally occurring amino acid

 <400> 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 Ser Val Ser Ser Ser Val Xaa Ser Ile
 20 25 30

 Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
 35 40 45

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

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

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

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

<210> 96
 <211> 115
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic Construct

 <220>
 <221> misc_feature
 <222> (61)..(61)
 <223> Xaa can be any naturally occurring amino acid

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

Gly Trp Ile Tyr Pro Val Thr Gly Asp Thr Tyr Tyr Xaa Glu Xaa Phe
50 55 60

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

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

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. c-Met-monoklonalt antistof eller antigen-bindende fragment deraf omfattende tre komplementaritetsbestemmende regioner med let kæde (LCDRs) og tre komplementaritetsbestemmende regioner med tung kæde (HCDRs), hvor LCDR1 omfatter aminosyresekvensen SVSSSVSSIYLH (SEQ ID NO: 53), LCDR2 omfatter aminosyresekvensen STSNLAS (SEQ ID NO: 54), LCDR3 omfatter aminosyresekvensen QVYSGYPLT (SEQ ID NO: 56), HCDR1 omfatter aminosyresekvensen GYTFTDYMH (SEQ ID NO: 65), HCDR2 omfatter aminosyresekvensen RVNPNRRGTTYNQKFEG (SEQ ID NO: 68), og HCDR3 omfatter aminosyresekvensen ANWLDY (SEQ ID NO: 69).

2. Monoklonalt antistof eller antigen-bindende fragment deraf ifølge krav 1, som binder en epitop i α -kæden af human c-Met og inducerer internalisering af human c-Met af celleoverfladen.

3. Monoklonalt antistof eller antigen-bindende fragment deraf ifølge krav 1 eller krav 2, som inducerer hepatocyt-vækstfaktor (HGF)-afhængig internalisering af human c-Met af celleoverfladen.

4. Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 3, hvor det monoklonale antistof eller det antigen-bindende fragment deraf binder i en aminosyresekvens udvalgt fra:

- a) ¹²¹VVDTYDDQL₁₃₀ (SEQ ID NO:77),
- b) ¹³¹ISCGSVNRGTCQRHVFPNHHTADIQS₁₅₆ (SEQ ID NO:78),
- c) ¹⁷⁹ALGAKVLSSVKDRFINF₁₉₅ (SEQ ID NO:79) og
- d) ²¹⁶VRRLKETKDGFM₂₂₇ (SEQ ID NO:80).

5. Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 4, hvor antistoffet eller det antigen-bindende fragment deraf binder i en aminosyresekvens udvalgt fra:

- a. ¹²³DTYYDD₁₂₈ (SEQ ID NO:81),
- b. ¹⁴⁴HVFPNHHTADIQS₁₅₆ (SEQ ID NO: 82),
- c. ¹⁹²FINF₁₉₅ (SEQ ID NO:83) og

d. ²²⁰KETKDGFM₂₂₇ (SEQ ID NO:84).

- 5 **6.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 5, hvor det monoklonale antistof eller det antigen-bindende fragment deraf binder en aminosyresekvens i den konformationale epitop, **kendetegnet ved** ¹²³DTYYDD₁₂₈ (SEQ ID NO:81), ¹⁴⁴HVFPNHNTADIQS₁₅₆ (SEQ ID NO:82), ¹⁹²FINF₁₉₅ (SEQ ID NO:83) og ²²⁰KETKDGFM₂₂₇ (SEQ ID NO:84) indbefattet.
- 10 **7.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af de foregående krav, som omfatter en variabel region med let kæde (LCVR) og en variabel region med tung kæde (HCVR), hvor LCVR omfatter aminosyresekvensen af SEQ ID NO: 5, og HCVR omfatter aminosyresekvensen af
- 15 SEQ ID NO: 17.
- 8.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 7 omfattende en letkæde med en kappa-konstant region og en tungkæde med en konstant region med en IgG4-tung kæde.
- 20 **9.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 8 omfattende en letkæde, der er kodet af polynukleotidsekvensen af SEQ ID NO:35, og en tungkæde, der er kodet af polynukleotidsekvensen af SEQ ID NO:47.
- 25 **10.** Monoklonalt antistof ifølge et af kravene 1 til 9 omfattende to letkæder, der er kodet af polynukleotidsekvensen af SEQ ID NO:35, og to tungkæder, der er kodet af polynukleotidsekvensen af SEQ ID NO:47.
- 30 **11.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 8, hvor aminosyresekvensen af letkæden er identisk med aminosyresekvensen, der er kodet af polynukleotidsekvensen af SEQ ID NO:35; og aminosyresekvensen af tungkæden er identisk med aminosyresekvensen, der er kodet af polynukleotidsekvensen af SEQ ID NO:47.
- 35

- 5 **12.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 8 og 10 omfattende to letkæder, hvor aminosyresekvensen af letkæden er identisk med aminosyresekvensen, der er kodet af polynukleotidsekvensen af SEQ ID NO:35; og to tungkæder, hvor aminosyresekvensen af tungkæden er identisk med aminosyresekvensen, der er kodet af polynukleotidsekvensen af SEQ ID NO:47.
- 10 **13.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 8 omfattende en letkæde med aminosyresekvensen af SEQ ID NO:29 og en tungkæde med en konstant region med en IgG4-tungkæde.
- 15 **14.** Monoklonalt antistof ifølge et af kravene 1 til 8 og 13 omfattende to letkæder med aminosyresekvensen af SEQ ID NO:29 og to tungkæder med en konstant region med en IgG4-tungkæde.
- 20 **15.** Farmaceutisk sammensætning omfattende det monoklonale antistof eller det antigen-bindende fragment deraf ifølge et af de foregående krav og et farmaceutisk acceptabelt bærestof, fortyndingsmiddel eller hjælpestof.
- 25 **16.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 14 til anvendelse inden for terapi.
- 30 **17.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge et af kravene 1 til 14 til anvendelse ved behandling af kræft i et menneske.
- 30 **18.** Monoklonalt antistof eller antigen-bindende fragment deraf ifølge krav 17, hvor kræften er mavekræft, nyrekræft, tyktarmskræft, kolorektal kræft, hoved- og halskræft, prostatakkræft, melanom eller lungekræft.