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(54) Title: CMET MONOCLONAL BINDING AGENTS, DRUG CONJUGATES THEREOF AND USES THEREOF

(57) Abstract: Presented herein, in certain embodiments, are compositions comprising monoclonal binding agents that specifically bind to the extracellular domain of cMET and uses thereof.

Description

Title of Invention: CMET MONOCLONAL BINDING AGENTS, DRUG CONJUGATES THEREOF AND USES THEREOF

Technical Field

[0001] Embodiments of the invention relate to compositions comprising binding agents that specifically bind to cMET, and uses thereof.

Background Art

[0002] The protein cMET, sometimes called MET or hepatocyte growth factor receptor (HGFR), is a protein that in humans is encoded by the MET gene (MET proto-oncogene, receptor tyrosine kinase). cMET is a single-pass cell surface receptor that possesses tyrosine kinase activity. The primary single chain precursor protein of the MET translation product is post-translationally cleaved to produce an alpha and a beta subunit, which are disulfide linked to form a mature cell surface cMET receptor. cMET is expressed on cells of epithelial origin, as well as stem cells, progenitor cells and other cell types. Hepatocyte growth factor/Scatter Factor (HGF/SF) and its splicing isoforms (NK1, NK2) have been identified as ligands of cMET.

[0003] cMET is thought to be essential for normal embryonic development, organogenesis and wound healing. Abnormal cMET expression and/or activity is associated with certain neoplastic disorders and cancers (e.g., cancers of kidney, liver, stomach, breast, and brain) where cMET is implicated in tumor growth, angiogenesis, and metastasis. The overexpression of cMET as well as its autocrine activation by co-expression of its ligand are also implicated in oncogenesis.

Summary of Invention

[0004] Presented herein are novel binding agents, monoclonal antibodies and binding portions thereof, that bind specifically to cMET, pharmaceutical compositions thereof and methods of using the same.

[0005] In some aspects, presented herein is a binding agent that specifically binds to cMET, an extracellular domain of cMET or a portion thereof. In some embodiments a binding agent described herein binds specifically to a protein or polypeptide that comprises cMET, an extracellular domain of cMET or a portion thereof. In certain embodiments, a binding agent binds specifically to one or more mammalian cMETs selected from a human cMET, non-human primate cMET (e.g., a monkey cMET), a rat cMET, and a mouse cMET. In certain embodiments, a binding agent specifically binds to a variant of human cMET and/or to an extracellular domain of a human cMET comprising one or more naturally occurring variants. In certain embodiments, a binding agent specifically binds to a human cMET variant comprising an E168D and/or an N375S

variant.

[0006] In some aspects, a binding agent that specifically binds to cMET comprises a CDR-L1, a CDR-L2 and/or a CDR-L3 which are three polypeptide sequences of a light chain complementarity determining region (CDR-L), where the CDR-L1 is selected from Table 1, the CDR-L2 is selected from Table 2 and the CDR-L3 is selected from Table 3. In some aspects, a binding agent that specifically binds to cMET comprises a CDR-H1, a CDR-H2 and/or a CDR-H3 which are three polypeptide sequences of a heavy chain complementarity determining region (CDR-H), where the CDR-H1 is selected from Table 6, the CDR-H2 is selected from Table 7 and the CDR-H3 is selected from Table 8. In some aspects, a binding agent that specifically binds to cMET comprises a CDR-L1 selected from Table 1, a CDR-L2 selected from Table 2, a CDR-L3 selected from Table 3, a CDR-H1 selected from Table 6, a CDR-H2 selected from Table 7, and a CDR-H3 selected from Table 8. In some embodiments, a CDR-L1 is selected from SEQ ID NOs 2, 4, 6, 8, 10, 12 and 14. In some embodiments, a CDR-L2 is selected from SEQ ID NOs 17, 19, 21, 23 and 25. In some embodiments, a CDR-L3 is selected from SEQ ID NOs 27, 29, 31, 33 and 35. In some embodiments, a CDR-H1 is selected from SEQ ID NOs 51, 53, 55, 57 and 59. In some embodiments, a CDR-H2 selected from SEQ ID NOs 63, 65, 67, 69, 73 and 75. In some embodiments, a CDR-H3 is selected from Table 8 is selected from SEQ ID NOs 80, 82, 84, 86, 88, 91 and 93. In some embodiments, the binding agent is an antibody, or a cMET binding fragment thereof.

[0007] In certain embodiments a binding agent comprises a variable light chain region having an amino acid sequence selected from Table 4 or 5, and/or a variable heavy chain region having an amino acid sequence selected from Table 9 or 10. A variable light chain of Table 4 or 5, or a variable heavy chain of Table 9 or 10, may comprise one to twenty, or in some embodiments, one to ten amino acid modifications selected from an amino acid addition, an amino acid deletion and an amino acid substitution, where the binding agent retains specific binding to cMET.

[0008] In certain embodiments, a binding agent is a monoclonal antibody, or cMET binding fragment thereof. In some embodiments, the binding agent comprises a constant region of an IgG1, IgG2, IgG3, or IgG4. In some embodiments, the binding agent comprises a constant region of an IgD, IgE, IgA or IgM. In certain embodiments a binding agent is humanized and/or comprises at least one to four humanized or human framework regions. In certain embodiments, a binding agent comprises at least one to four mouse framework regions. In some embodiments, a binding agent is a Fab, Fab', F(ab')2, Fv or scFV fragment of an antibody.

[0009] In some aspects a binding agent described herein has one or more functional properties. In certain embodiments, a binding agent induces or promotes internalization

of cMET on a human cancer cell. In some embodiments, a binding agent induces or promotes degradation of cMET on a human cancer cell. In some embodiments, a binding agent does not have detectable cMET agonist activity. In some embodiments, a binding agent induces or promotes death of a cell to which it binds. In certain embodiments a binding agent is conjugated to an anti-neoplastic agent.

[0010] In some aspects, a binding agent described herein specifically binds to cMET, or a portion thereof. In some aspects, a binding agent described herein specifically binds to cMET, or a portion thereof with a KD of 10 nM or less, or 1 nM or less. In some aspects, an affinity of a binding agent for cMET, or a portion thereof, comprises a KD of 10 nM or less, or 1 nM or less

[0011] In some embodiments, a binding agent that specifically binds to cMET further comprises a second antigen binding portion that specifically binds to another antigen (e.g., an antigen that is not cMET, or a portion thereof). For example, in some embodiments, a binding agent comprises a first antigen binding domain that specifically binds to cMET and a second antigen binding domain that specifically binds to another polypeptide.

[0012] In certain aspects, presented herein are methods of treating a subject having or suspected of having a neoplastic disorder or cancer. In one embodiment, a method includes administering a therapeutically effective amount of a binding agent described herein to a subject. In some embodiments, a method comprises contacting a cell of the subject (e.g., a neoplastic or cancerous cell) with the binding agent. In certain embodiments, the binding agent is configured to specifically bind to the extracellular domain of cMET expressed on one or more cells of the subject. In certain embodiments, the binding agent decreases, inhibits or reduces mitosis of, and/or promotes or induces death of the one or more cells expressing cMET. In certain embodiments, the neoplastic disorder or cancer comprises a lung carcinoma, breast carcinoma, ovarian carcinoma, kidney carcinoma, colorectal carcinoma, gastric carcinoma, thyroid carcinoma, pancreas carcinoma, neuroblastoma, or a squamous cell carcinoma of the head and neck, cervical cancer, hepatocellular cancer, sarcomas, mesothelioma, glioblastoma, multiple myeloma, melanoma, prostate and esophageal carcinoma.

[0013] In some embodiments, a pharmaceutical composition which comprises the binding agent is provided. In some embodiments, a pharmaceutical composition comprises, in addition to the binding agent, a pharmaceutically acceptable excipient, diluent, additive and/or carrier. In some embodiments, a pharmaceutical composition is formulated as a sterile, lyophilized powder, that upon reconstitution, is suitable for intravenous administration to a mammal.

[0014] Certain aspects of the technology are described further in the following description, examples, claims and drawings.

[0015] The drawings illustrate embodiments of the technology and are not limiting. For clarity and ease of illustration, the drawings are not made to scale and, in some instances, various aspects may be shown exaggerated or enlarged to facilitate an understanding of particular embodiments.

Brief Description of Drawings

[0016] [fig.1]Fig. 1 shows a summary of the work flow used for generation of monoclonal antibodies (exemplary binding agents) that bind specifically to cMET. The lead monoclonal Ab P3D12 was generated from a mouse immunized with recombinant intact extracellular domain of cMET fused to human Fc.

[fig.2]Fig. 2 shows an immunization scheme used to generate monoclonal antibodies (exemplary binding agents) that bind specifically to cMET. Mice were initially immunized by intraperitoneal injection (i.p.) with 100 μg of a human cMET-Fc fusion protein (cMET-Fc), or 50 to 100 μg of a KLH conjugated cMET peptide in Freund's Complete Adjuvant (CFA) as indicated. cMET-Fc comprises the extracellular domain of human cMET fused to an Fc portion of an antibody. cMET peptides were strategically selected from a portion of the cMET extracellular domain. Immunized mice received one or more booster immunization comprising 25 or 50 μg of cMET-Fc or peptide in Incomplete Freund's adjuvant (IFA) as indicated. Some mice received repetitive immunizations at multiple sites (RIMMS). Immunizations included Met-Fc fusions, peptides, traditional and RIMMS. Spleens of immunized mice were obtained and fused to a suitable fusion partner. Over 20,000 hybridoma clones were obtained and screened.

[fig.3]Fig. 3 shows a 3D structure of the MET SEMA domain bound with a Fab of an agonist Met-mAb antibody (5D5 Fab) and HGF beta subunit (HGFb). The bottom arrow indicates the position of a portion of cMET used to design peptide 3.

[fig.4]Fig. 4 shows characterization results from an exemplary fusion (FUSION 6B1, plate 3). Anti-cMet hybridomas were selected, in part, for the presence of specific binding to cMet as assayed by ELISA (see column labeled "MET Binding ELISA OD450nm") and for ability to induce internalization of cMET on human cancer cell lines as measured by flow cytometry (see column labeled "FACS Geom. Mean"). A FACS Geo Mean value lower than a negative control indicates internalization of cMet. The arrow indicates a lead hybridoma F6B1P3D12.

[fig.5]Fig. 5 shows the results of a MET degradation assay. Anti-cMet antibodies isolated from the indicated wells (x-axis) were tested and selected for their ability to induce degradation of cMET on human cancer cell lines as measured by Mesoscale (MSD) cMet protein quantification. Relative values of Met degradation are indicated on the y-axis as % control (percent of control). Values lower than 100% control

(negative control level) indicate internalization and degradation of cMet. Degradation indicates not just internalization but lysosomal trafficking, an important property for an antibody drug conjugate. The arrow indicates the results for a lead hybridoma F6B1P3D12.

[fig.6]Fig. 6 shows the results of a phospho-ERK assay (P-ERK assay) that measures agonist activity of anti-cMET antibodies by indirectly measuring the phosphorylation of ERK induced by binding of an anti-cMET antibody to cMET on a cell surface. The amount of phosphorylated ERK (shown as % of control, y-axis) detected in cell lysates after treatment of viable cells with an anti-cMET antibody is shown. Anti-cMet antibodies produced from various anti-cMET hybridomas (x-axis) were tested at 6 ug/ml or 30 ug/ml (as indicated on x-axis), and selected according to their inability to induce significant phosphorylation of ERK (i.e., their ability not to induce proliferation, i.e., absence of agonist activity). A lead monoclonal antibody (mAb) P3D12 is indicated by the arrow.

[fig.7]Fig. 7 shows results of certain cMet mAbs that were assayed by ELISA for binding to human, monkey (Cynomolgus Macaque, "Cyno"), canine, rat, and mouse cMet. All monoclonal antibodies bound human and monkey cMet. P3D12 demonstrated significant cross-reactivity with rat cMet. Various concentrations of each antibody are indicated on the x-axis. Relative amounts bound are indicated on the y-axis (OD450nm).

[fig.8A]Fig. 8A shows an alignment of the amino acid sequences of the light chain variable regions of nine mouse monoclonal anti-cMET antibodies, the names of which are indicated to the left of each sequence. SEQ ID NOs are indicated to the right of each sequence. Amino acid sequences of the light chain variable regions of LC F6B1P1E2 and F6BP3E2 are 100% identical. Also, amino acid sequences of the light chain variable regions of LC F6B1P3D12 and F6B1P3E9 are 100% identical.

[fig.8B]Fig. 8B shows an alignment of the amino acid sequences of the heavy chain variable regions of nine mouse monoclonal anti-cMET antibodies, the names of which are indicated to the left of each sequence. SEQ ID NOs are indicated to the right of each sequence. Amino acid sequences of the heavy chain variable regions of F6B1P3D12H7913 and F6B1P3E9 are 100% identical. Also, amino acid sequences of the heavy chain variable regions of F6B1P1E2H7819 and F6BP3E2 are 100% identical.

[fig.9]Figs. 9A and 9B show the results of an in vivo xenograft mouse model evaluating the efficacy of the indicated anti-cMET antibody drug conjugates (ADC) using the MKN45 tumor model (a cMet+ gastric cancer model) in nude mice. Animals were treated once with ADCs at 2.5 mg/kg (9A) or 5.0 mg/kg (9B). The efficacy of each drug conjugated anti-cMET binding agent is compared to PBS or an unrelated

non-targeting monoclonal antibody (IgG-ADC). Tumor volume (y-axis) was measured at various time points after inoculation (y-axis, Days (post inoculation)). Inhibition of tumor growth indicates positive efficacy. Anti-cMET binding agents and the non-targeting monoclonal antibody (IgG) were conjugated to monomethyl auristatin F (MMAF).

[fig.10]Fig. 10 shows the results of a phospho-ERK assay (P-ERK assay) that measures agonist activity of anti-cMET antibodies by indirectly measuring the phosphorylation of ERK induced by binding of an anti-cMET antibody to cMET on a cell surface. The amount of phosphorylated ERK (shown as % of control, y-axis) detected in cell lysates after treatment of viable cells with an anti-cMET antibody is shown. The constant regions of the heavy and light chains of an isolated mouse monoclonal antibody designated as P3D12 were replaced with antibody constant regions of a human IgG1 (P3D12(hIgG1)), or a human IgG2 (P3D12(hIgG2)) as indicated on the x-axis. Each antibody was tested at 0.00064 ug/ml, 0.0032 ug/ml, 0.016 ug/ml, 0.08 ug/ml, 0.4 ug/ml, 2 ug/ml, 10 ug/ml and 50 ug/ml as indicated on the x-axis. "Control" indicates an untreated negative control. HGF(EC90) is a positive control and indicates cells treated with Hepatocyte Growth Factor (HGF), the natural ligand of cMet receptor. This data indicates that the human IgG2 isotype does not display detectable agonist activity.

[fig.11]Fig. 11 shows the results of a MET degradation assay. Degradation is a measure of internalization of the cMET receptor upon antibody binding. Chimeric anti-cMet antibodies were tested for their ability to induce degradation of cMET on human cancer cell lines as measured by Mesoscale (MSD) cMet protein quantification. Relative values of Met degradation are indicated on the y-axis as % control (percent of control). Values lower than 100% control indicate internalization and degradation of cMet. Chimeric antibodies were generated by replacing the constant regions of the heavy and light chains of an isolated mouse monoclonal antibody designated as P3D12 (P3D12(mouse)) with antibody constant regions of a human IgG1 (P3D12(hIgG1)), or a human IgG2 (P3D12(hIgG2)) as indicated on the x-axis. Each antibody was tested at 0.00064 ug/ml, 0.0032 ug/ml, 0.016 ug/ml, 0.08 ug/ml, 0.4 ug/ml, 2 ug/ml, 10 ug/ml and 50 ug/ml as indicated on the x-axis. Chimeric cMet antibodies of P3D12 showed similar internalization/degradation activity as the parental mouse P3D12 antibody.

[fig.12]Fig. 12 shows a flow chart of process development for testing and selection of lead anti-cMET monoclonal binding agents.

[fig.13]Fig. 13 shows an alignment of five humanized light chain variable regions of humanized versions of the murine anti-cMET clone P3D12, the names and SEQ ID NOs of which are indicated to the left of each sequence. Five independent methods were used to humanize the murine anti-cMET mAbs. Two of the methods gave the

same result, therefore there are 4 different light chains shown.

[fig.14]Fig. 14 shows an alignment of five humanized heavy chain variable regions of humanized versions of the murine clone P3D12, the names and SEQ ID NOs of which are indicated to the left of each sequence. Five independent methods were used to humanize the murine anti-cMET mAb. Two of the methods gave the same result, therefore there are 4 different light chains (see Fig. 13) and 4 different heavy chains which can make a combination of 16 different binding agents.

[fig.15]Fig. 15 shows the results of an in vivo xenograft mouse model testing the efficacy of the indicated humanized anti-cMET antibody drug conjugates (ADC) at 2.5 mg/kg (2.5 mpk), or at 5 mg/kg (5 mpk) as demonstrated using an MKN45 tumor model (a cMet+ gastric cancer model). Animals were treated once with the indicated ADCs at 2.5 or 5.0 mg/kg. The efficacy of each anti-cMET binding agent is compared to PBS or the non-targeting monoclonal antibody Rituximab (Retux), which is an anti-cancer monoclonal antibody that targets CD20, which is primarily found on the surface of immune system B cells. Tumor volume (y-axis) was measured at various time points (y-axis) after inoculation. Inhibition of tumor growth indicates positive efficacy. Anti-cMET binding agents were conjugated to monomethyl auristatin F (MMAF).

[fig.16]Fig. 16 shows binding of anti-cMET monoclonal binding agents hD12 and MET IgG2 to cMET-Fc and mutant cMET (E168D) Fc recombinant fusion proteins. The E168D mutation is a somatic mutation found in small cell lung cancer (SCLC). The mutation is located in the Sema domain and leads to constitutive activation of the cMet receptor. Abundance of somatic mutations of cMet are very low. E168D occurs in 0.8% to 3% of SCLC patients. A binding ELISA was performed with human cMET or E168D cMET extracellular domains fused to human IgG1 Fc. cMET proteins were coated on a plate overnight and the samples titrated and detected with a goat anti-human IgG (H+L)-HRP. EC50s were determined using sigmoidal dose response fit.

Description of Embodiments

[0017] Presented herein, in some embodiments, are monoclonal binding agents that bind cMET, or a portion thereof, as well as compositions and uses thereof. The proto-oncogene MET translation product comprises the mesenchymal epithelial transition factor (MET). MET is used synonymously herein with the term "cMET". cMET is also known as hepatocyte growth factor receptor (HGFR). Human cMET (e.g., SEQ ID NO:109) comprises an immature polypeptide sequence of 1390 amino acids and includes an N-terminal single sequence from amino acids 1-24, an extracellular domain of human cMET from about amino acid 24-932, a transmembrane domain from about amino acid 933 to 955 and a cytoplasmic domain at about amino acid 956 to 1390, numbered from the N-terminus to the C-terminus. Methods of identifying leader

sequences, extracellular domains, transmembrane domains, and cytoplasmic domains of a cMET receptor are known and any suitable method can be used to identify such domains or regions within a cMET polypeptide sequence derived from a suitable mammalian species. A human cMET polypeptide may comprise several known variants (e.g., see URL:http://www.uniprot.org/uniprot/P08581, as accessed on May 5, 2016, which cMET variants and alternative sequences disclosed therein are incorporated herein by reference). Non-limiting examples of naturally occurring variants of a human cMET include amino acid substitutions at 143, 150, 156, 168, 238, 316, 320, 375, 385, 773, 970, 991, and/or 992 of human cMET (SEQ ID NO: 109). In some embodiments cMET or a cMET extracellular domain comprises an E to D substitution at position 168 of human cMET, referred to herein as E168D. In some embodiments cMET or a cMET extracellular domain comprises an N to S substitution at position 375 of human cMET, referred to herein as N375S.

[0018] In some embodiments cMET is a mammalian cMET. In some embodiments cMET is a primate cMET. In some embodiments cMET is a human cMET. In some embodiments cMET is a monkey cMET. In some embodiments cMET is a rodent cMET (e.g., rat and/or mouse). In some embodiments cMET is a canine cMET (e.g., a dog cMET). Non-limiting examples of a mammalian cMET are provided in Example 5 and/or in a sequence listing of this application. In certain embodiments, an extracellular domain of cMET comprises an N-terminal portion of a cMET polypeptide that is typically expressed on the cell surface of an intact mammalian cell. An extracellular domain of cMET may comprise two or more polypeptide chains derived from a MET translation product. In certain embodiments an extracellular domain of cMET can be expressed in a soluble and/or a non-membrane bound form that lacks a cytoplasmic and/or transmembrane domain. In certain embodiments an extracellular domain of cMET is expressed, isolated and/or purified as a fusion protein. For example, the extracellular domain of a mammalian cMET can be engineered and expressed as a fusion protein comprising an Fc portion of an immunoglobulin (e.g., cMET-Fc). In certain embodiments cMET and/or the extracellular domain of cMET comprises one or more amino acid additions, deletions or substitutions. A cMET polypeptide may be at least 80%, at least 85%, at least 90% or at least 95% to a cMET polypeptide disclosed herein. In certain embodiments, a cMET polypeptide comprises a portion of (e.g., a sub-sequence of) a cMET protein. In some embodiments a portion of a cMET comprises an extracellular domain of cMET, or a portion thereof.

[0019] Presented herein, in some embodiments, are compositions (e.g., pharmaceutical compositions) comprising one or more binding agents that bind specifically to cMET or a portion thereof. In some embodiments a binding agent presented herein is used for the treatment, prevention and/or diagnosis of a neoplastic disorder and/or a cancer in a

subject.

[0020] The term "subject" refers to a mammal. Any suitable mammal can be treated by a method or composition described herein. Non-limiting examples of mammals include humans, non-human primates (e.g., apes, gibbons, chimpanzees, orangutans, monkeys, macaques, and the like), domestic animals (e.g., dogs and cats), farm animals (e.g., horses, cows, goats, sheep, pigs) and experimental animals (e.g., mouse, rat, rabbit, guinea pig). In some embodiments a mammal is a human. A mammal can be any age or at any stage of development (e.g., an adult, teen, child, infant, or a mammal in utero). A mammal can be male or female. A mammal can be a pregnant female.

[0021] In some embodiments a subject is in need of a treatment or composition described herein. In certain embodiments a subject has or is suspected of having a neoplastic disorder or a cancer. In some embodiments a subject in need of a treatment or composition described herein has or is suspected of having a neoplastic disorder or a cancer. In certain embodiments a binding agent or composition described herein is used to treat a subject having, or suspected of having, a neoplastic disorder or cancer.

[0022] In certain embodiments, a binding agent comprises or consists of one or more polypeptides or one or more proteins that bind specifically to at least one antigen (e.g., cMET or a portion thereof). A binding agent often comprises at least one antigen binding portion (i.e. a binding portion). An antigen binding portion of a binding agent is that portion that binds specifically to an antigen. In certain embodiments a binding portion of a binding agent comprises or consists of a single polypeptide (e.g., single chain antibody). In some embodiments a binding portion of a binding agent comprises or consists of two polypeptides. In some embodiments a binding portion of a binding agent comprises or consists of 2, 3, 4 or more polypeptides. In some embodiments a binding agent comprises one or more structural portions (e.g., scaffolds, structural polypeptides, constant regions and/or framework regions). In some embodiments a binding agent, or binding portion thereof is attached to a substrate (e.g., a polymer, a non-organic material, silicon, a bead, and the like).

[0023] A binding agent may comprise one antigen binding portion or multiple antigen binding portions. For example, a binding agent that comprises one binding portion is sometimes referred to as monovalent. A binding agent that comprises two binding portions is sometimes referred as divalent. In some embodiments a binding agent comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more binding portions. In certain embodiments, all of the binding portions of a multivalent binding agent bind to the same antigen. In certain embodiments, all of the binding portions of a multivalent binding agent comprise one or more polypeptide sequences that are at least 90%, at least 95%, at least 99% or 100% identical.

[0024] In certain embodiments, two or more binding portions of a binding agent bind to

different antigens. Such binding agents are sometimes referred to as bi-specific or multi-specific binding agents (e.g., antibodies). Thus, in certain embodiments a binding agent comprises a first antigen binding portion that specifically binds cMET, or a portion thereof, and a second antigen binding portion that specifically binds another antigen (e.g., a polypeptide that is not cMET, or a portion thereof). A binding agent that specifically binds cMET, in some embodiments, is covalently or non-covalently attached to another binding agent that does not bind specifically to cMET, or a portion thereof. In certain embodiments, a binding agent that specifically binds cMET comprises a second binding agent the specifically binds to another antigen.

[0025] In some embodiments a binding agent comprises an antibody, or a portion thereof (e.g., a binding portion thereof). In certain embodiments, a binding agent comprises or consists of a suitable antibody, an antibody fragment and/or an antigen binding portion of an antibody (e.g., a binding fragment, i.e., a binding portion thereof). In some embodiments a binding agent is an antibody (e.g., a monoclonal antibody and/or a recombinant antibody). A binding agent or antibody can be generated, manufactured or produced by a suitable method. In some embodiments a binding agent is monoclonal. In some embodiments a binding agent is a monoclonal antibody derived from a suitable species. Certain non-limiting examples of a binding agent include monoclonal antibodies, chimeric antibodies, antibody binding fragments (e.g., an antigen binding portion of an antibody), a CDR-grafted antibody, a humanized antibody, a human antibody, or portions thereof. Human antibodies can be obtained by any suitable method. For example, human antibodies can be obtained from trans-chromosomal animals engineered to produce fully human antibodies. In certain embodiments, a binding agent is not polyclonal, is not a polyclonal antibody and the term "binding agent" does not refer to polyclonal antibodies.

[0026] In some embodiments a binding agent is derived, produced, obtained, isolated, and/or purified from a suitable species. In some embodiments a binding agent is derived, produced, obtained, isolated, and/or purified from a rabbit, goat, horse, cow, rat, mouse, fish, bird, or llama, for example. In some embodiments a binding agent is derived, produced, obtained, isolated, and/or purified from a bird (e.g., a chicken, or a bird egg). In some embodiments a binding agent is derived, produced, obtained, isolated, and/or purified from a plant (e.g., a recombinant binding agent produced by a genetically engineered plant). In some embodiments a binding agent is derived, produced, obtained, isolated, and/or purified from a suitable mammal. In certain embodiments a suitable mammal is a genetically altered mammal (e.g., a trans-chromosomal or transgenic mammal) engineered to produce antibodies comprising human heavy chains and/or human light chains or portions thereof. In some embodiments a binding agent is produced, obtained, isolated, or purified from a

prokaryotic or eukaryotic cell (e.g., a recombinant binding agent produced by a genetically engineered cell). In some embodiments a binding agent is produced, obtained, isolated, or purified from a virus (e.g., a recombinant binding agent produced by a genetically engineered virus). A binding agent can be expressed, isolated from and/or purified from a suitable expression system non-limiting examples of which include a suitable bacteria, phage, insect, virus, plant or mammalian expression system. For example, a nucleic acid encoding a binding agent can be introduced into a suitable mammalian cell line that expresses and secretes the binding agent into the cell culture media.

[0027] In certain embodiments, a binding agent is not found in nature and is not naturally occurring. For example, in certain embodiments, a binding agent is generated artificially in an animal by administering an emulsified cocktail that includes a foreign recombinant antigen, a powerful adjuvant, and often a mineral oil and/or a detergent, thereby inducing an artificial immune response to the foreign recombinant antigen (e.g., cMET, cMET-Fc).

[0028] In certain embodiments, a monoclonal antibody or a monoclonal binding agent is a substantially homogeneous population of binding agents, or binding fragments thereof, where each individual binding agent in the population is substantially identical and/or binds to the same epitope, with the exception of possible variants that may arise during production of a monoclonal binding agent. In some embodiments such variants generally are absent or may be present in minor amounts. In contrast to polyclonal antibody preparations which typically include a population of different antibodies directed against different determinants (epitopes), each binding agent of a population of monoclonal binding agents often binds to a single determinant of an antigen. Monoclonal binding agents are often not contaminated by other immunoglobulins. One or more different monoclonal binding agents may be purposely added to a composition to form a mixture.

[0029] The modifier "monoclonal" is not to be construed as requiring production of a binding agent by any particular method. A monoclonal binding agent can be produced by any suitable method. For example, in certain embodiments, a monoclonal antibody is made by the hybridoma method (e.g., as described by Kohler et al, Nature, 256:495 (1975)), or a variation thereof. In some embodiments a monoclonal binding agent is made by a recombinant DNA method. For example, a monoclonal binding agent can be made by screening a recombinant library using a suitable expression system (e.g., a phage display expression system). In some embodiments a monoclonal binding agent is isolated from a phage library of binding agents, for example by using a technique described in Clackson et al, Nature, 352:624-628 (1991) and/or Marks et al, J. Mol Biol, 222:581-597 (1991), or a variation thereof.

[0030] In certain embodiments, a binding agent comprises one or more structural or backbone portions, sometimes referred to as scaffolds. A binding agent may comprise a scaffold, non-limiting examples of which include a scaffold derived from an antibody, a Z domain of Protein A, gamma-B crystalline, ubiquitin, cystatin, Sac7d, a triple helix coiled coil, a lipocalin, an ankyrin repeat motif, an SH3 domain of Fyn, a Kunitz domain of a suitable protease inhibitor, a fibronectin domain, a nucleic acid polymer, and the like, portions thereof or combinations thereof. In some embodiments a binding agent does not comprise a scaffold. In certain embodiments, a binding agent comprises one or more structural portions of a mammalian antibody.

[0031] In certain embodiments a binding agent comprises one or more constant regions (e.g., constant regions derived from an antibody, e.g., a mammalian antibody). In certain embodiments a binding agent comprises a constant region of an antibody light chain and/or a constant region of an antibody heavy chain. In a mammalian antibody at least two types of immunoglobulin light chains exist which are referred to as lambda (λ) and kappa (κ). A binding agent may comprise any suitable constant region of an antibody, or one or more portions thereof. In some embodiments a binding agent comprises a lambda light chain constant region or a portion thereof. In some embodiments a binding agent comprises a kappa light chain constant region or a portion thereof. In some embodiments a binding agent comprises a polypeptide that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to a polypeptide sequence of a constant region, or portion thereof, of a light chain of a mammalian antibody. In some embodiments a binding agent comprises a polypeptide that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to a polypeptide sequence of a constant region of an antibody light chain of a human antibody. In some embodiments a binding agent does not include a light chain constant region.

[0032] In certain embodiments a binding agent comprises a constant region of an antibody heavy chain. In mammals, an antibody can have at least five types/classes of Ig heavy chains denoted as IgA, IgD, IgE, IgG, and IgM, which are determined by the presence of distinct heavy chain constant regions, or portion thereof (e.g., CH1, CL, CH2, CH3 domains). A binding agent can include any suitable heavy chain constant region, or portion thereof. In some embodiments a binding agent comprises a heavy chain constant region of an IgG1, IgG2, IgG3 or IgG4, or one or more portions thereof. In some embodiments a binding agent comprises one or more heavy chain constant regions of an IgM, IgD, IgA, or IgE isotype, or a portion thereof. In some embodiments a binding agent comprises a polypeptide that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical, or 100% identical to a polypeptide sequence of a constant region, or portion thereof, of a heavy chain of a

mammalian antibody. In some embodiments a binding agent comprises a polypeptide that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% identical or 100% identical to a polypeptide sequence of a constant region of an antibody heavy chain of a human antibody. In some embodiments a binding agent comprises one or more additions, deletions and/or modification to a constant region. A binding agent is sometimes modified to change the antibody class, or isotype of a binding agent. In some embodiments a binding agent comprises one or more additions, deletions and/or modification (one or more amino acid substitutions, deletions or additions) to modify one or more functions of a binding agent, for example to abolish, enhance or decrease serum half-life, Fc receptor binding, complement binding (e.g., C1q binding), glycosylation, sialylation, cellular toxicity, antibody-dependent cell-mediated phagocytosis (ADCP), antibody dependent cellular cytotoxicity (ADCC), and the like. In some embodiments a binding agent does not include one or more portions of a heavy chain constant region or light chain constant region. In some embodiments a binding agent does not include a heavy chain constant region.

[0033] In some embodiments a binding agent comprises or consists of one or more variable regions of an antibody, or a portion thereof. In some embodiments a binding agent comprises one or more light chain variable regions, or a portion thereof. In some embodiments a binding agent comprises one or more heavy chain variable regions, or a portion thereof. In certain embodiments a binding agent comprises at least one light chain variable region and at least one heavy chain variable region. A light chain variable region and heavy chain variable region can be on the same or different polypeptides. In certain embodiments, an antigen binding portion of a binding agent consists of one or more heavy chain variable regions. In certain embodiments, an antigen binding portion of a binding agent consists of one or more light chain variable regions. In certain embodiments, an antigen binding portion of a binding agent consists of one or more light chain variable regions and one or more heavy chain variable regions.

[0034] In some embodiments a binding agent comprises or consists of a Fab, Fab', F(ab')2, Fv fragment, single-chain Fv (scFv), diabody (Dab), synbody, the like and/or a combination or portion thereof. In some embodiments a binding agent is a Fab, Fab', F(ab')2, Fv fragment, single-chain Fv (scFv), diabody (Dab), synbody, the like and/or a combination, or portion thereof (see, e.g., U.S. Patent Nos. 6,099,842 and 5,990,296). In some embodiments a binding agent comprises a single-chain polypeptide comprising one or more antigen binding portions. For example, a single-chain binding agent can be constructed by joining a heavy chain variable region, or antigen binding portion thereof, with a light chain variable region, or antigen binding portion thereof, with a linker (e.g., an amino acid, a polypeptide linker) using recombinant molecular

biology processes. Such single chain binding agents often exhibit specificities and affinities for an antigen similar to a parent two-chain monoclonal binding agent. Binding agents often comprise engineered regions such as CDR-grafted or humanized portions. In certain embodiments a binding agent is an intact two-chain immunoglobulin, and in other embodiments a binding agent is a Fab monomer or a Fab dimer.

[0035] Nucleic acids, or portions thereof, that encode a polypeptide of a binding agent may be cloned, subcloned, rearranged or modified for recombinant expression by a suitable cloning procedure and subsequently expressed using a suitable expression system by a method known to those skilled in the art (e.g., see Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, 1982; Antibody Engineering: Methods and Protocols, Vol. 248 of Methods in molecular biology, edited by Benny K. C. Lo, Springer Science & Business Media, 2004; Antibody Engineering, Vol. 1, Roland E. Kontermann, Stefan Duebel, Edition 2, Publisher Springer Science & Business Media, 2010; Antibody Phage Display: Methods and Protocols, Biomed Protocols, Vol. 178 of Methods in molecular biology, Editors Philippa M. O'Brien, Robert Aitken, Springer Science & Business Media, 2004).

[0036] In mammals, the heavy chain variable region and light chain variable region of an antibody each contribute three CDRs (complementarity determining regions) commonly referred to as CDR1, CDR2 and CDR3, that are separated and/or flanked by framework regions (e.g., FR1, FR2, FR3 and FR4). The term "CDR" as used herein refers to an amino acid sequence of a polypeptide identified as a complementarity determining region. In certain embodiments, definitive delineation of a CDR polypeptide sequence and identification of residues comprising the binding site of a binding agent is accomplished by solving the structure of a binding agent and/or solving the structure of a binding agent-antigen complex. In certain embodiments, this can be accomplished by any suitable method, such as X-ray crystallography and/or computer modeling. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR sequences of a binding agent or antibody. For example, the amino acid sequence and/or location of CDRs in a polypeptide sequence of a binding agent, an antibody, a binding portion thereof or variable region thereof, can be identified using a suitable method, non-limiting examples of which include the Kabat system (e.g., see Kabat, E. A., et al., 1991; Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication No. 91-3242, as well as Johnson, G. and Wu, T. T. 2000, Nucleic Acids Research), and/or the Chothia Numbering Scheme (e.g., Chothia & Lesk, (1987) J. Mol. Biol, 196:901-917; Chothia et al, Nature, (1989) 342:878-883; and Al-Lazikani et al., (1997) JMB 273,927-948). In some embodiments the amino sequence and/or location of CDRs of an antibody can be identified using the AbM

method and/or contact method. The "AbM" definition uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure (see e.g., Martin et al, Proc. Natl. Acad. Sci. (USA), 86:9268-9272 (1989); "AbM™, A Computer Program for Modeling Variable Regions of Antibodies," Oxford, UK; Oxford Molecular, Ltd.). The AbM definition models the tertiary structure of an antibody from primary sequence using a combination of knowledge databases and ab initio methods, such as those described by Samudrala et al., "Ab Initio Protein Structure Prediction Using a Combined Hierarchical Approach," in PROTEINS, Structure, Function and Genetics Suppl, 3:194-198 (1999). In certain embodiments, a contact definition is based on an analysis of the available complex crystal structures (see e.g., MacCallum et ah, J. Mol. Biol, 5:732-45 (1996)).

[0037] In some embodiments a binding agent and/or an antigen binding portion of a binding agent comprises at least 2, at least 3, at least 4, at least 5 or at least 6 CDRs. In some embodiments a binding agent comprises 3 to 60 CDRs (e.g., for binding agents having multiple antigen binding portions). In some embodiments a binding agent comprises 3 to 12 CDRs. In some embodiments an antigen binding portion of a binding agent comprises 1 to 6 CDR polypeptide sequences.

[0038] In certain embodiments, a binding agent and/or an antigen binding portion of a binding agent comprises one, two or three CDRs of a light chain variable region. In some embodiments a light chain variable region of a binding agent comprises one or more CDRs (e.g., one, two, three, or more CDRs). The amino acid sequences representing a CDR in a light chain variable region of an antibody or binding agent is referred to as CDR-L1, CDR-L2, and CDR-L3 which are numbered sequentially (i.e., L1, L2 and L3) in the direction from the amino terminus (N-terminus) to the carboxy terminus (C-terminus) of a light chain variable region. For example, in a polypeptide representing a light chain variable region of a binding agent, CDR-L1,when present, is the most N-terminal light chain CDR; CDR-L3, when present, is the most C-terminal light chain CDR; and CDR-L2, when present, is located (i) between CDR-L1 and CDR-L3, (ii) on the N-terminal side of CDR-L3 or (iii) on the C-terminal side of CDR-L1, of a light chain variable region or binding portion of a binding agent. The terms "CDR-L1", "CDR-L2" and "CDR-L3" refer to, in part, an amino acid sequence of a polypeptide identified as, or disclosed herein as, a complementarity determining region of a binding agent (e.g., a CDR of a light chain variable region). Non-limiting examples of amino acid sequences of a CDR-L1, CDR-L2 and CDR-L3 are provided in Tables 1-3, respectively. A light chain variable region or antigen binding portion of a binding agent described herein may comprise any combination of a CDR-L1, a CDR-L2, and a CDR-L3 disclosed herein, wherein the binding agent retains specific binding to cMET, or a portion thereof. In certain embodiments, a light chain variable region or

antigen binding portion of a binding agent described herein comprises a single light chain CDR comprising an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3. In certain embodiments, a light chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3, and any other suitable CDR-L2 and/or CDR-L1 polypeptide sequence, where the binding agent retains specific binding to cMET, or a portion thereof. In certain embodiments, the light chain CDRs of a light chain variable region or antigen binding portion of a binding agent consists of a CDR-L3 and a CDR-L2, where the CDR-L3 comprises an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3 and the CDR-L2 comprises an amino acid sequence at least 70% identical to a CDR-L2 selected from Table 2. In certain embodiments, a light chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3 and an amino acid sequence at least 70% identical to a CDR-L2 selected from Table 2, and any other suitable CDR-L1 polypeptide sequence, where the binding agent retains specific binding to cMET, or a portion thereof. In certain embodiments, a light chain variable region or antigen binding portion of a binding agent described herein comprises three light chain CDRs consisting of an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3, an amino acid sequence at least 70% identical to a CDR-L2 selected from Table 2 and an amino acid sequence selected at least 70% identical to a CDR-L1 of Table 1. In certain embodiments, a light chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-L3 selected from Table 3, an amino acid sequence at least 70% identical to a CDR-L2 selected from Table 2 and an amino acid sequence at least 70% identical to a CDR-L1 selected from Table 1, where the binding agent retains specific binding to cMET, or a portion thereof.

[0039] In some embodiments a binding agent comprises one or more light chain CDRs that are at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the CDR sequences listed in Tables 1, 2 or 3. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L1 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 1. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L1 of any one of the sequences shown in Table 1.

[0040] CDR-L1 Sequences

[Table 1]

ID	Clone	Amino Acid Sequence
SEQ ID NO:1	F5_P5_B9_L	RSSQTIVHGTGNTYLE
SEQ ID NO:2	F5_P5_B9_L	QTIVHGTGNTY
SEQ ID NO:3	F6A_P8_E2_L	KASENVGTYVS
SEQ ID NO:4	F6A_P8_E2_L	ENVGTY
SEQ ID NO:5	F6AP12F12_L	RSSQSLLYSINQKNYLA
SEQ ID NO:6	F6AP12F12_L	QSLLYSINQKNY
SEQ ID NO:7	F6B_P1_B5_L	KASENIYNYLA
SEQ ID NO:8	F6B_P1_B5_L	ENIYNY
SEQ ID NO:9	F6B1_P3_D12_L / F6B1_P3_E9_L	SASSSVTSNYLY
SEQ ID NO:10	F6B1_P3_D12_L / F6B1_P3_E9_L	SSVTSNY
SEQ ID NO:11	F6B_P2_D4_L / F6B1_P1_E2_L/ F6B_P3_E2_L	SASSSVSSNYLY
SEQ ID NO:12	F6B_P2_D4_L / F6B1_P1_E2_L/ F6B_P3_E2_L	SSVSSNY
SEQ ID NO:13	Consensus	SASSSV(S/T)SNYLY
SEQ ID NO:14	P3D12 VL-abb/sdr	QSVTSNY
SEQ ID NO:15	P3D12 VL-abb/sdr	RASQSVTSNYLY

[0041] Clone names referenced in Tables 1-10 indicate the Fusion number ("F"), Plate number ("P") and well number (A1 to H12) of a 96-well plate from which the clone was derived. Accordingly, clone F6AP12F12 was derived from Fusion 6A, Plate 12, Well F12, for example. Fusion numbers of each clone correspond to the Fusions indicated in Fig. 2.

[0042] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L2 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 2. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L2 of any one of the sequences shown in Table 2.

[0043] CDR-L2 Sequences

[Table 2]

ID	Clone	Amino Acid Sequence
SEQ ID NO:16	F5_P5_B9_L	KVSNRFS
SEQ ID NO:17	F5_P5_B9_L	KVS
SEQ ID NO:18	F6A_P8_E2_L	GASNKYT
SEQ ID NO:19	F6A_P8_E2_L	GAS
SEQ ID NO:20	F6AP12F12_L	WASTRES
SEQ ID NO:21	F6AP12F12_L	WAS
SEQ ID NO:22	F6B_P1_H5_L	AATNLAD
SEQ ID NO:23	F6B_P1_H5_L	AAT
SEQ ID NO:24	F6B1_P3_D12_L / F6B1_P3_E9_L / F6B_P2_D4_L / F6B1_P1_E2_L / F6B_P3_E2_L	STSNLAS
SEQ ID NO:25	F6B1_P3_D12_L / F6B1_P3_E9_L / F6B_P2_D4_L / F6B1_P1_E2_L / F6B_P3_E2_L	STS

[0044] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L3 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 3. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-L3 of any one of the sequences shown in Table 3.

[0045] CDR-L3 Sequences

[Table 3]

ID	Clone	Amino Acid Sequence
SEQ ID NO:26	F5_P5_B9_L	FQGSHVPYTFGGGTKLEIRR
SEQ ID NO:27	F5_P5_B9_L	FQGSHVPYT
SEQ ID NO:28	F6A_P8_E2_L	GQSYSYPLTFGAGTKLELKR
SEQ ID NO:29	F6A_P8_E2_L	GQSYSYPLT
SEQ ID NO:30	F6AP12F12_L	QQYYTYPLTFGAGTKLELK
SEQ ID NO:31	F6AP12F12_L	QQYYTYPLT
SEQ ID NO:32		QHFWGTPYTFGGGTKLEIR
SEQ ID NO:33		QHFWGTPYT
SEQ ID NO:34	F6B_P1_H5_L / F6B1_P3_D12_L / F6B1_P3_E9_L / F6B_P2_D4_L / F6B1_P1_E2_L / F6B_P3_E2_L	HQWSSYPPTFGSGTKLEIK
SEQ ID NO:35	F6B_P1_H5_L / F6B1_P3_D12_L / F6B1_P3_E9_L / F6B_P2_D4_L / F6B1_P1_E2_L/ F6B_P3_E2_L	HQWSSYPPT
SEQ ID NO:36	Consensus	$(X_1)Q(X_2)(X_3)(X_4)YP(X_5)T$ where X_1 is H, Q, or G; X_2 is W, S or Y; X_3 is S or Y; X_4 is S or T; and X_5 is P or L.

[0046] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a light chain variable region having at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to an amino acid sequence of Table 4. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a light chain variable region sequence of Table 4.

[0047] VARIABLE LIGHT CHAIN SEQUENCES

[Table 4]

ID	Clone	Amino Acid Sequence
SEQ ID NO:37	F5_F6_B9_L	DVLMTQTPLSLPVSLGDQASISCRSSQTIV HGTGNTYLEWYLQKPGQSPKLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDLGV YYCFQGSHVPYTFGGGTKLEIKR
SEQ ID NO:38	F6A_F8_E2_L	DIVMTQSPKSMSMSVGERVTLSCKASENVG TYVSWYQQKPDQSPKLLIYGASNRYTGVPD RFTGSGSATDFTLTISSVQAEDLADYHCGQ SYSYPLTFGAGTKLELKR
SEQ ID NO:39	F6AF12F12_L	DIVMSQSPSSLAVSVGEKVTMSCRSSQSLL YSTNQKNYLAWYQQIPGQSPKLLIYWASTR ESGVPDRFTGSGSGTDFTLTISSVKAEDLA LYYCQQYYFYPLTFGAGTKLELKR
SEQ ID NO:40	F6B_F1_H5_L	RCDIQMTQSPASLSVSVGETVTITCRASEN IYNTLAWYLQKQGKSPQLLVYAATNLADGV PSRFSGSGSGTQYSLKINSLQSEDFGSYYC QHFWGTPYTFGGGTKLEIKR
SEQ ID NO:41	F6B1_F3_D12_L & F6B1_F3_E9_L	QIVLTQSPAIMSASPGEKVTLTCSASSSVT SNYLYWYQQKPGSSPKLWIYSTSNLASGVP ARFSGSGSGTSYSLTISSMEAEDAASYFCH QWSSYPFTFGSGTKLEIKR
SEQ ID NO:42	F6B_F2_D4_L	QIVLTQSPAIMSASPGEKVTLTCSASSSVS SNYLYWYQQKPGSSPKLWIYSTSNLASGVP VRFSGSGSGTSYSLTISSMEAEDAASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:43	F6B1_F1_E2_L& F6B_F3_E2_L	QIVLTQSPAIMSASPGEKVTLTCSASSSVS SNYLYWYHQKPGSSPKLWIYSTSNLASGVP VRFSGSGSGTSYSLTISSMEAEDAASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:44	Consensus	QIVLTQSPAIMSASPGEKVTLTCSASSSVS SNYLYWY(H/Q)QKPGSSPKLWIYSTSNLA SGVP(A/R)FSGSGSGTSYSLTISSMEAED AASYFCHQWSSYPPTFGSGTKLEIKR

[0048] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a humanized light chain variable region having at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to a sequence of Table 5. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a humanized light chain variable region sequence of Table 5.

[0049] Humanized P3D12 Light Chains

[Table 5]

ID	Clone	Amino Acid Sequence
SEQ ID NO:45	P3D12 VL	QIVLTQSPAIMSASPGEKVTLTCSASSSVT SNYLYWYQQKPGSSPKLWIYSTSNLASGVP ARFSGSGSGTSYSLTISSMEAEDAASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:46	P3D12 VL-ven	QIVLTQSPATMSASPGERVTLSCSASSSVT SNYLYWYQQKPGSSPRLWIYSTSNLASGVP ARFSGSGSGTSYTLTISRMEPEDAASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:47	P3D12 VL-fra	QIVLTQSPAILSLSPGERATLSCSASSSVT SNYLYWYQQKPGSSPKLLIYSTSNLASGVP ARFSGSGSGTSYTLTISSLEAEDAASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:48	P3D12 VL-abb/sdr	QIVLTQSPATLSLSPGERATLSCRASQSVT SNYLYWYQQKPGSSPRLLIYSTSNLASGVP ARFSGSGSGTDYTLTISRLEPEDFASYFCH QWSSYPPTFGSGTKLEIKR
SEQ ID NO:49	P3D12 VL-cdr	QIVLTQSPATLSLSPGERATLSCSASSSVT SNYLYWYQQKPGSSPRLLIYSTSNLASGVP ARFSGSGSGTSYTLTISRLEPEDFASYFCH QWSSYPPTFGSGTKLEIKR

[0050] In certain embodiments, a binding agent and/or an antigen binding portion of a binding agent comprises one, two or three CDRs of a heavy chain variable region. In some embodiments a heavy chain variable region comprises one or more CDRs (e.g., one, two, three, or more CDRs). The amino acid sequences representing a CDR in a heavy chain variable region of an antibody or binding agent is referred to as CDR-H1, CDR-H2, and CDR-H3, which are numbered sequentially (i.e., H1, H2 and H3) in the direction from the amino terminus (N-terminus) to the carboxy terminus (C-terminus) of a heavy chain variable region. For example, in a polypeptide representing a heavy chain variable region of a binding agent, CDR-H1,when present, is the most N-terminal CDR; CDR-H3, when present, is the most C-terminal CDR; and CDR-H2, when present, is located (i) between CDR-H1 and CDR-H3, (ii) on the N-terminal side of CDR-H3 or (iii) on the C-terminal side of CDR-H, of a heavy chain variable region. The terms "CDR-H1", "CDR-H2" and "CDR-H3" refer to, in part, an amino acid sequence of a polypeptide identified as, or disclosed herein as, a complementarity determining region of a binding agent (e.g., a CDR of a heavy chain variable region of a binding agent). Non-limiting examples of amino acid sequences of a CDR-H1, CDR-H2 and CDR-H3 are provided in Tables 6-8, respectively. A heavy chain variable region or antigen binding portion of a binding agent described herein may comprise any combination of a CDR-H1, a CDR-H2, and a CDR-H3 disclosed herein where the binding agent retains specific binding to cMET, or a portion thereof. In certain embodiments, a heavy chain variable region or antigen binding portion of a binding agent described herein comprises a single heavy chain CDR consisting of an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8. In certain em-

bodiments, a heavy chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8, and any other suitable CDR-H2 and/or CDR-H1 polypeptide sequence, where the binding agent retains specific binding to cMET, or a portion thereof. In certain embodiments, the heavy chain CDRs of a heavy chain variable region or antigen binding portion of a binding agent consists of a CDR-H3 and a CDR-H2, where the CDR-H3 comprises an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8 and the CDR-H2 comprises an amino acid sequence at least 70% identical to a CDR-H2 selected from Table 7. In certain embodiments, a heavy chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8 and an amino acid sequence at least 70% identical to a CDR-H2 selected from Table 7, and any other suitable CDR-H1 polypeptide sequence, where the binding agent retains specific binding to cMET or a portion thereof. In certain embodiments, a heavy chain variable region or antigen binding portion of a binding agent described herein comprises three heavy chain CDRs consisting of an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8, an amino acid sequence at least 70% identical to a CDR-H2 selected from Table 7 and an amino acid sequence selected at least 70% identical to a CDR-H1 of Table 6. In certain embodiments, a heavy chain variable region or antigen binding portion of a binding agent described herein comprises an amino acid sequence at least 70% identical to a CDR-H3 selected from Table 8, an amino acid sequence at least 70% identical to a CDR-H2 selected from Table 7 and an amino acid sequence at least 70% identical to a CDR-H1 selected from Table 6, where the binding agent retains specific binding to cMET, or a portion thereof.

[0051] In some embodiments a binding agent comprises one or more heavy chain CDRs with at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to any one of the CDRs of Tables 6, 7 or 8. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H1 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 6. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H1 of any one of the sequences shown in Table 6.

[0052] CDR-H1 Sequences

[Table 6]

ID	Clone	Amino Acid Sequence
SEQ ID NO:50	F5_P5_B9_H	GFSLTNYGVN
SEQ ID NO:51	F5_P5_B9_H	GFSLTNYG
SEQ ID NO:52	F6A_P8_E2_H	GFNINDYFMH
SEQ ID NO:53	F6A_P8_E2_H	FNINDYF
SEQ ID NO:54	F6A_P12_F12_H	GFTFTDYYMS
SEQ ID NO:55	F6A_P12_F12_H	GFTFTDYY
SEQ ID NO:56	F6B_P1_H5_H	GYTFTDYNMD
SEQ ID NO:57	F6B_P1_H5_H	YTFTDYN
SEQ ID NO:58	F6B1_P3_D12_H / F6B1P3E9_H / F6_B1_P1_E2_H/ F6B_P3_E2_H / F6B_P2_D4_H	GYTFTSYWMH
SEQ ID NO:59	F6B1_P3_D12_H / F6B1P3E9_H / F6_B1_P1_E2_H / F6B_P3_E2_H / F6B_P2_D4_H	YTFTSYW
SEQ ID NO:60	Consensus	GYTFT(D/S)Y(N/W)
SEQ ID NO:61	Consensus	G(Y/F)TFT(D/S)Y(N/W/Y)M(H/S)

[0053] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H2 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 7. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H2 of any one of the sequences shown in Table 7.

[0054] CDR-H2 Sequences

[Table 7]

ID	Clone	Amino Acid Sequence
SEQ ID NO:62	F5_P5_B9_H	LIWGGGDTDYNSALKS
SEQ ID NO:63	F5_P5_B9_H	IWGGGDT
SEQ ID NO:64	F6A_P8_E2_H	WIDPENGNTIYDPKFQG
SEQ ID NO:65	F6A_P8_E2_H	IDPENGNT
SEQ ID NO:66	F6A_P12_F12_H	FIRNKANGYTTKYSASVKG
SEQ ID NO:67	F6A_P12_F12_H	IRNKANGYTT
SEQ ID NO:68	F6B_P1_H5_H	DINPNNGGTIYNQKFKG
SEQ ID NO:69	F6B_P1_H5_H	INPNNGGT
SEQ ID NO:70	F6B1_P3_D12_H / F6B1P3E9_H	YIKPSTDNTEYNQKFKD
SEQ ID NO:71	F6B1_P3_D12_H / F6B1P3E9_H	IKPSTDNT
SEQ ID NO:72	F6_B1_P1_E2_H / F6B_P3_E2_H	YINPSTDYIEYNQKFKD
SEQ ID NO:73	F6_B1_P1_E2_H / F6B_P3_E2_H	INPSTDYT
SEQ ID NO:74	F6B_P2_D4_H	YINPSTDYIEYNQKFKD
SEQ ID NO:75	F6B_P2_D4_H	INPSTDYI
SEQ ID NO:76	Consensus	INPSTDY(I/T)
SEQ ID NO:77	Consensus	(Y/D)I(K/N)PSTD(N/Y)(T/I)EY(A/N)QKF(Q/K)(G/D)
SEQ ID NO:78	P3D12 VH-abb/sdr	YIKPSTDNTEYAQKFQG

[0055] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H3 that is at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identical to any one of the sequences shown in Table 8. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a CDR-H3 of any one of the sequences shown in Table 8.

[0056] CDR-H3 Sequences

[Table 8]

ID	Clone	Amino Acid Sequence
SEQ ID NO:79	F5_P5_B9_H	CARDYYGFDY
SEQ ID NO:80	F5_P5_B9_H	DYYGFDY
SEQ ID NO:81	F6A_P8_E2_H	CARGGNYLRESYYYAMDY
SEQ ID NO:82	F6A_P8_E2_H	RGGNYLRESYYYAMDY
SEQ ID NO:83	F6A_P12_F12_H	CSKDRGYFDY
SEQ ID NO:84	F6A_P12_F12_H	DRGYFDY
SEQ ID NO:85	F6B_P1_B5_H	RARGDYYGSSRYYYAMDY
SEQ ID NO:86	F6B_P1_B5_H	RGDYYGSSRYYYAMDY
SEQ ID NO:87	F6B1_P3_D12_H / F6B1P3E9_H	CARSYGNYPLMDY
SEQ ID NO:88	F6B1_P3_D12_H / F6B1P3E9_H & F6_B1_P1_E2_H / F6B_P3_E2_H	SYGNYPLMDY
SEQ ID NO:89	F6_B1_P1_E2_H / F6B_P3_E2_H	CVRSYGNYPLMDY
SEQ ID NO:90	F6B_P2_D4_H	CARSYGNFPLMDY
SEQ ID NO:91	F6B_P2_D4_H	RSYGNFPLMDY
SEQ ID NO:92	Consensus	C(A/V)RSYGN(F/Y)PLMDY
SEQ ID NO:93	Consensus	RSYGN(F/Y)PLMDY

[0057] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a heavy chain variable region having at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to a sequence of Table 9. In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a heavy chain variable region sequence of Table 9.

[0058] VARIABLE HEAVY CHAIN SEQUENCES

[Table 9]

ID	Clone	Amino Acid Sequence
SEQ ID NO:94	F5_P5_B9_H	QVQLKESGPGLVAPSQSLSITCTVSGFSL TNYGVNWVRQPPGKGLEWLGLIWGGGDTD YNSALKSRLSISKDNSKSQVFLKMETNSL QTDDTARYYCARDYYGFDYWGQGTTLTVS S
SEQ ID NO:95	F6A_P12_F12_H	EVKLVESGGGLVQPGGSLRLSCATSGFTF TDYYMSWVRQPPGKALEWLGFIRNKANGY TTEYSASVKGRFTISRDNSQSILYLQMNT LRAEDSATYYCSKDRGYFDYWGQGTTLTV SS
SEQ ID NO:96	F6A_P8E2_H	VNSEVQLQQSGAELVRPGALVKLSCKASG FNINDYFMHWVKQRPEQGLEWIGWIDPEN GNTIYDPRFQGKASITADTSSNTAYLQLS SLTSEDTAVYYCAPGGNYLRESYYYAMDY WGQGTSVTVSS
SEQ ID NO:97	F6B_P1_H5_H	VLSEVLLQQSGPELVKPGASVKIPCKASG YTFTDYNMDWVKQSHGKSLEWIGDINPNN GGTIYNQKFKGKATLTVDKSSSTAYMELR SLTSEDTAVYYRARGDYYGSSRYYYAMDY WGQGTSVTVSS
SEQ ID NO:98	F6B1_P3_D12_H	QVQLQQSGAELAKPGASVKMSCPASGYTF TSYWMHWVKQRPGQGLDWIGYIKPSTDNT EYNQKFKDKATLTADKSSSTAYMQLSSLT SEDSAVYYCARSYGNYPLMDYWGQGTSVT VSS
SEQ ID NO:99	F6B1P3E9_H	QVQLQQSGAELAKPGASVKMSCRASGYTF TSYWMHWVKQRPGQGLDWIGYIKPSTDNT EYNQKFKDKATLTADKSSSTAYMQLSSLT SEDSAVYYCARSYGNYPLMDYWGQGTSVT VSS
SEQ ID NO:100	F6B1_P1_E2_H	QVQLQQSGAELAKPGASVKMSCKASGYTF TSYWMSWVKQRPGQGLEWIGYINPSTDYT EYNQKFKDKATLTADKSSTTAYMQLSSLT SEDSAVYYCVRSYGNYPLMDYWGQGTSVT VSS
SEQ ID NO:101	F6B_P3_E2_H	QVQLQQSGAELAKPGASVKMSCKASGYTF TSYWMHWVKQRPGQGLEWIGYINPSTDYT EYNQKFKDKATLTADKSSTTAYMQLSSLT SEDSAVYYCVRSYGNYPLMDYWGQGTSVT VSS
SEQ ID NO:102	F6B_P2_D4_H	QVQLQQSGAELAKPGASVKMSCKASGYTF TSYWMHWVKQRPGQGLEWIGYINPSTDYI EYNQKFKDKATLTAGKSSSTAYMQLSSLT SEDSAVYYCARSYGNFPLMDYWGQGTSVT VSS
SEQ ID NO:103	Consensus	QVQLQQSGAELAKPGASVKMSC(K/P)AS GYTFTSYWMHWVKQRPGQGL(E/D)WIGY I(K/N)PSTD(Y/N)(T/I)EYNQKFKDK ATLTADKSS(S/T)TAYMQLSSLTSEDSA VYYC(A/V)RSYGN(Y/F)PLMDYWGQGT SVTVSS

[0059] In some embodiments a binding agent or the antigen binding portion of a binding agent comprises a humanized heavy chain variable region having at least 70%, 75%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to a sequence of Table 10. In some embodiments a binding agent or

the antigen binding portion of a binding agent comprises a humanized heavy chain variable region sequence of Table 10.

[0060] Humanized P3D12 Heavy Chains

[Table 10]

ID	Clone	Amino Acid Sequence
SEQ ID NO:104	P3D12 VH	QVQLQQSGAELAKPGASVKMSCKASGYTF TSYWMHWVKQRPGQGLDWIGY IKPSTDN TEYNQKFKDKATLTADKSSSTAYMQLSSL TSEDSAVYYCARSYGNYPLMDYWGQGTSV TVSS
SEQ ID NO:105	P3D12 VH-fra	QVQLQQSGAEVKKPGASVKVSCKASGYTF TSYWMHWVKQRPGQGLDWIGY IKPSTDN TEYNQKFKDRVTLTADKSTSTAYMQLSNL ISEDTAVYYCARSYGNYPLMDYWGQGTSV TVSS
SEQ ID NO:106	P3D12 VH-ven	QVQLVQSGAEVAKPGASVKMSCKASGYTF TSYWMHWVKQAPGQGLDWIGYIKPSTDNT EYNQKFKDKATLTADKSTSTAYMQLSSLR SEDTAVYYCARSYGNYPLMDYWGQGTTVT VSS
SEQ ID NO:107	P3D12 VH-abb/sdr	QVQLVQSGAEVKKPGASVKVSCKASGYTF TSYWMHWVKQAPGQGLDWMGYIKPSTDNT EYAQKFQGRVTLTADKSTSTAYMELSSLR SEDTAVYYCARSYGNYPLMDYWGQGTTVT VSS
SEQ ID NO:108	P3D12 VH-cdr	QVQLVQSGAEVKKPGASVKVSCKASGYTF TSYWMHWVKQAPGQGLDWIGYIKPSTDNT EYNQKFKDKATLTADKSTSTAYMELSSLR SEDTAVYYCARSYGNYPLMDYWGQGTTVT VSS

[0061] In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 75%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to any one of the amino acid sequences of SEQ ID Nos 26 to 36 (e.g., a CDR-L3 sequence selected from Table 3) and a CDR-H3 comprising an amino acid sequence at least 70%, at least 75%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to any one of the amino acid sequences of SEQ ID Nos 79 to 93 (e.g., a CDR-H3 sequence selected from Table 8). In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 90%, at least 95%, at least 98%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 34 or 35, and a CDR-H3 comprising an amino acid sequence at least 70%, at least 90%, at least 95%, at least 98%, at least 99% or 100% identical to the amino acid sequence of SEQ ID NO: 87, 88, 92 or 93.

[0062] In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 26 to 36 (e.g., a CDR-L3 sequence selected from Table 3), a CDR-L2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 16 to 25 (e.g., a CDR-L2 sequence selected from Table 2), a CDR-H3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 79 to 93 (e.g., a CDR-H3 sequence selected from Table 8) and a CDR-H2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 62 to 78 (e.g., a CDR-H2 sequence selected from Table 7). In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 34 or 35, a CDR-L2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 24 or 25, a CDR-H3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 87, 88, 92 or 93 and a CDR-H2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 70, 71 or 78.

[0063] In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 26 to 36 (e.g., a CDR-L3 sequence selected from Table 3), a CDR-L2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 16 to 25 (e.g., a CDR-L2 sequence selected from Table 2), a CDR-L1 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 1 to 15 (e.g., a CDR-L1 sequence selected from Table 1), a CDR-H3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 79 to 93 (e.g., a CDR-H3 sequence selected from Table 8), a CDR-H2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 62 to 78 (e.g., a CDR-H2 sequence selected from Table 7), and a CDR-H1 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to any one of the amino acid sequences of SEQ ID Nos 50 to 61 (e.g., a CDR-H1 sequence selected from Table 6). In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a CDR-L3 comprising an amino acid sequence at least 70%, at least 90%, or 100%

identical to the amino acid sequence of SEQ ID Nos 34 or 35, a CDR-L2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 24 or 25, a CDR-L1 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 9, 10 or 15, a CDR-H3 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 87 or 88, a CDR-H2 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 70, 71 or 78, and a CDR-H1 comprising an amino acid sequence at least 70%, at least 90%, or 100% identical to the amino acid sequence of SEQ ID NO: 58 or 59.

[0064] In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a heavy chain variable region comprising an amino acid sequence at least 70%, at least 75%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to any one of the amino acid sequences of SEQ ID Nos 94 to 108 (e.g., a heavy chain variable region selected from Tables 9 and 10), and a light chain variable region comprising an amino acid sequence at least 70%, at least 75%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to any one of the amino acid sequences of SEQ ID Nos 37 to 49 (e.g., a light chain variable region selected from Tables 4 and 5). In some embodiments a binding agent, or an antigen binding portion of a binding agent, comprises a heavy chain variable region comprising an amino acid sequence at least 90% identical to any one of the amino acid sequences of SEQ ID Nos 104 to 108 (e.g., a heavy chain variable region selected from Table 10), and a light chain variable region comprising an amino acid sequence at least 90% identical to any one of the amino acid sequences of SEQ ID Nos 45 to 49 (e.g., a light chain variable region selected from Table 5).

[0065] The abbreviations of "abb", "sdr", "fra", "ven. "and "cdr" as used herein are explained below. The abbreviation "cdr" or "CDR" refer to a Complementarity-Determining Region. The abbreviation "abb" refers to abbreviated CDR according to Padlan et al. (1995) "Identification of specificity-determining residues in antibodies" FASEB J 9:133-139. In some embodiments, abbreviated CDRs are defined as residues 27D-34, 50-55, and 89-96 in the light chain, and 31-35B, 50-58, and 95-101 in the heavy chain, which are grafted onto an appropriate human scaffold. The critical framework residues are often preserved. The abbreviation "sdr" refers to "specificity determining residues" according to Padlan et al. (1995) which are residues thought to be involved in antigen binding. The abbreviation "fra" refers to the "Frankenstein

approach" based on the suggestion of Wu and Kabat (1992) "Possible use of similar framework region amino acid sequences between human and mouse immunoglobulins for humanizing mouse antibodies" Mol Immunol 29:1141-1146. The abbreviation "ven" refers to "Veneering" according to Padlan (1991), "A possible procedure for reducing the immunogenicity of antibody variable domains while preserving their ligand-binding properties" Mol Immunol 28:489-498.

[0066] The term "percent identical" or "percent identity" refers to sequence identity between two amino acid sequences. Identity can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When an equivalent position in the compared sequences is occupied by the same amino acid, then the molecules are identical at that position. When the equivalent site is occupied by the same or a similar amino acid residue (e.g., similar in steric and/or electronic nature), then the molecules can be referred to as homologous (similar) at that position. Expression as a percentage of homology, similarity, or identity refers to a function of the number of identical or similar amino acids at positions shared by the compared sequences. Expression as a percentage of homology, similarity, or identity refers to a function of the number of identical or similar amino acids at positions shared by the compared sequences. Various alignment algorithms and/or programs may be used, including FASTA, BLAST, or ENTREZ. FASTA and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.), and can be used with, e.g., default settings. ENTREZ is available through the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Md. In one embodiment, the percent identity of two sequences can be determined by the GCG program with a gap weight of 1, e.g., each amino acid gap is weighted as if it were a single amino acid or nucleotide mismatch between the two sequences.

[0067] Other techniques for alignment are described in Methods in Enzymology, vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. In some embodiments an alignment program that permits gaps in the sequence is utilized to align the sequences. The Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. See Meth. Mol. Biol. 70:173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. An alternative search strategy uses MPSRCH software, which runs on a MASPAR computer. MPSRCH uses a Smith-Waterman algorithm to score sequences on a massively parallel computer. This approach improves ability to pick up distantly related matches, and is especially tolerant of small gaps and nucleotide sequence errors. Nucleic acid-encoded amino acid sequences can be used to search both protein

and DNA databases.

[0068] In some embodiments a binding agent, or antigen binding portion of a binding agent comprises one or more CDRs selected from a light chain variable region of Tables 4 and 5. In some embodiments a binding agent, or antigen binding portion of a binding agent comprises one or more CDRs selected from a heavy chain variable region of Tables 9 and 10. In some embodiments a binding agent, or antigen binding portion of a binding agent comprises one or more CDRs selected from a light chain variable region of Tables 4 and 5 and one or more CDRs selected from a heavy chain variable region of Tables 9 and 10. In certain embodiments, a binding agent, or antigen binding portion of a binding agent, comprises a CDR-L1, a CDR-L2, and a CDR-L3, each selected from any one of the light chain variable regions of Tables 4 and 5, and a CDR-H1, a CDR-H2, and a CDR-H3, each selected from any one of the heavy chain variable regions of Tables 9 and 10. An amino acid sequence of a CDR (e.g., a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3) can be identified within a heavy chain or light chain variable region disclosed herein by any suitable method described herein or known to those skilled in the art.

[0069] In some embodiments a binding agent comprises one or more suitable sequences selected from Tables 1-10 wherein the selected polypeptide sequence comprises 0 to 5, 1 to 5, 0 to 10, 1 to 10, 0 to 15, or 1 to 15 amino acid modifications where an amino acid modification can be an amino acid addition, an amino acid deletion and/or an amino acid substitution. In some embodiments, a binding agent disclosed herein comprises one or more amino acid analogues, non-native amino acids or amino acid derivatives.

[0070] In certain embodiments, a binding agent, or antigen binding portion of a binding agent comprises one or more framework regions (FR). Framework regions are often located between CDRs and/or flank CDR sequences of a heavy or light chain variable region of an antibody or binding agent. In mammals, a heavy chain variable region often comprises four framework regions and a light chain variable region often comprises four framework regions. Any suitable method can be used to identify one or more framework regions in an antibody, in a variable region of an antibody or in a binding agent. A binding agent may comprise synthetic or naturally occurring framework regions which are unmodified or modified (e.g., optimized) as discussed below.

[0071] In some embodiments a binding agent, or antigen binding portion thereof is chimeric, grafted and/or humanized. Chimeric, grafted and or humanized binding agents often comprise modified or substituted constant regions and/or framework regions while maintaining binding specificity to cMET, or a portion thereof. In some embodiments a binding agent, or antigen binding portion thereof, comprises constant regions,

framework regions, or portions thereof, derived from a human antibody. In some embodiments a binding agent, or antigen binding portion thereof, comprises fully synthetic portions, one or more amino acids, or sequences of amino acids that are not found in native antibody molecules.

[0072] Naturally occurring framework regions, or portions thereof may be obtained from any suitable species. In certain embodiments the complementarity determining regions (CDRs) of the light and heavy chain variable regions of a binding agent, or an antigen binding portion thereof, is grafted into framework regions from the same, or another, species. For example, one or more framework regions of a binding agent may be derived from a rodent species (e.g., a mouse or rat) or a primate species (e.g., a human).

[0073] In certain embodiments, the CDRs of the light and/or heavy chain variable regions of a binding agent, or an antigen binding portion thereof, can be grafted to consensus human framework regions. To create consensus human framework regions, in certain embodiments, framework regions from several human heavy chain or light chain amino acid sequences can be aligned to identify a consensus sequence. In certain embodiments, the heavy chain or light chain framework regions of an antibody or binding agent are replaced with one or more framework regions, or portions thereof, from a different heavy chain or light chain variable region. In some embodiments a binding agent, or antigen binding portion thereof, comprises one or more human framework regions. In certain embodiments a binding agent, or antigen binding portion thereof, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 human framework regions. In some embodiments a binding agent, or antigen binding portion thereof, comprises one or more mouse framework regions. In certain embodiments a binding agent, or antigen binding portion thereof, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mouse framework regions. In certain embodiments a binding agent, or antigen binding portion thereof, comprises one or more human framework regions and one or more mouse framework regions.

[0074] Methods of generating chimeric, humanized and/or optimized antibodies or binding agents, for example by modifying, substituting or deleting framework regions, or portions thereof, are known. Non-limiting examples of CDR grafting are described, e.g., in U.S. Patent Nos. 6, 180,370, 6,054,297, 5,693,762, 5,859,205, 5,693,761, 5,565,332, 5,585,089, and 5,530, 101, and in Jones et al, Nature, 321 :522-525 (1986); Verhoeyen et al, Science, 239:1534-1536 (1988), and Winter, FEBS Letts., 430:92-94 (1998). Additional non-limiting examples of generating chimeric, grafted and/or humanized binding agents include U.S. patent No. 5,530,101; U.S. patent No. 5,707,622; U.S. patent No. 5,994,524; U.S. patent No. 6,245,894; Queen et al., (1988) PNAS 86:10029-10033; Riechmann et al., Nature (1988) 332:323-327; Antibody En-

gineering: Methods and Protocols, Vol. 248 of Methods in molecular biology, edited by Benny K. C. Lo, Springer Science & Business Media, (2004); and Antibody Engineering, Vol. 1, Roland E. Kontermann, Stefan Duebel, Edition 2, Publisher Springer Science & Business Media, (2010). In some embodiments a binding agent can be humanized by exchanging one or more framework regions, or portions thereof (e.g., one or more amino acids), with one or more framework regions, or portions thereof from a human antibody. In certain embodiments, an antibody or binding agent can be humanized or grafted by transferring one or more CDRs (e.g., 1, 2, 3, 4, 5 or all 6 CDRs) from a donor binding agent (e.g., a mouse monoclonal antibody) to an acceptor binding agent (e.g., a human antibody) while retaining the binding specificity of the donor binding agent. In certain embodiments, the process of making a chimeric, grafted or humanized binding agent comprises making one or more amino acid substitutions, additions or deletions in a constant region or framework region of a binding agent. In certain embodiments, techniques such as "reshaping", "hyperchimerization," or "veneering/resurfacing" can be used to produce humanized binding agents. (e.g., see Vaswami et al, Annals of Allergy, Asthma, & Immunol. 81 :105 (1998); Roguska et al, Prot. Engin., 9:895-904 (1996); and U.S. Patent No. 6,072,035). In some aspects, a binding agent is modified by a method discussed above, or by another suitable method, to reduce immunogenicity (e.g., see Gilliland et al, J. Immunol, 62(6):3663-71 (1999)).

[0075] In certain embodiments, an amino acid sequence of a binding agent is modified to optimize binding affinity for a target (e.g., cMET), species cross-reactivity, solubility and/or function (e.g., agonist activity, or lack thereof). In some embodiments a specific combination of CDRs disclosed herein can be optimized for binding to cMET, and/or to optimize a function or characteristic of a binding agent disclosed herein. For example, a characterized light chain variable region disclosed herein (e.g., a light chain variable region of SEQ ID NO:48) can be co-expressed, using a suitable expression system, with a library of heavy chain variable regions comprising a CDR-H1 and CDR-H2 of a characterized heavy chain variable region (e.g., a heavy chain variable region of SEQ ID NO:107), where the CDR-H3 is replaced with a library of CDR-H3 sequences, which may include one or more CDR-H3 regions of Table 8, for example. The resulting light chain/heavy chain binding agents can be screened for binding to cMET and/or for a specific function. Optimized binding agents can be identified and the amino acid sequence of the CDR-H3 can be identified by a suitable method. The above screening method can be used to identify binding agents comprising specific combinations of CDRs, or specific optimized CDR sequences (e.g., CDR sequences comprising amino acid substitutions, additions or deletions) that provide a binding agent with improved binding specificity, binding affinity and/or function. Such methods of screening and optimizing binding agents are known (e.g., see Portolano et

al., (1993) Journal of Immunology 150:880-887; and Clarkson et al., (1991) Nature 352:624-628). Such references teach methods of producing antibodies that bind a specific antigen by using known variable light chain, known variable heavy chains, or portion thereof (e.g., CDRs thereof) by screening a library of complementary variable regions.

[0076] In certain embodiments, a binding agent is modified to eliminate or add glycosylation sites in order to optimize affinity and/or function of a binding agent (e.g., see Co et al, Mol. Immunol, 30:1361-1367 (1993)). In some embodiments the number and/or type of glycosylation sites in a binding agent is modified or altered. An N-linked glycosylation site is often characterized by the sequence Asn-X-Ser or Asn-X-Thr, where the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided in certain embodiments is a rearrangement of N-linked carbohydrate chains where one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. In some embodiments a binding agent is modified by deleting one or more cysteine residues or substituting one or more cysteine residues for another amino acid (e.g., serine) as compared to an unmodified binding agent. In certain embodiments cysteine variants can be useful for optimizing expression, secretion, and/or solubility.

[0077] In certain embodiments a binding agent is modified to include certain amino acid additions, substitutions, or deletions designed or intended, for example, to reduce susceptibility of a binding agent to proteolysis, reduce susceptibility of a binding agent to oxidation, increase serum half-life and/or confer or modify other physicochemical, pharmacokinetic or functional properties of a binding agent.

[0078] In some embodiments a binding agent specifically binds to a mammalian cMET, or portion thereof. In some embodiments a binding agent specifically binds to an extracellular domain or extracellular regions of a mammalian cMET, or a portion thereof. In certain aspects, a binding agent specifically binds to a wild-type cMET produced by a cell of an unaltered (non-genetically modified) mammal found in nature. In certain aspects a binding agent specifically binds to a naturally occurring cMET variant. In certain aspects a binding agent specifically binds to a cMET comprising one or more amino acid substitutions, additions or deletions. In certain embodiments a binding agent specifically binds to a cMET produced and/or expressed on the surface of a cell of a human, non-human primate, dog, cat, or rodent (e.g., a mouse or rat). In certain embodiments, a binding agent specifically binds to one or more cMET polypeptides, or a portion thereof, having an amino acid sequence of any one of SEQ ID Nos 109 to

113. In certain embodiments, a binding agent specifically binds to a human cMET. In certain embodiments, a binding agent specifically binds to an extracellular domain of human cMET. In certain embodiments, a binding agent specifically binds to a human cMET, and/or an extracellular domain thereof, wherein the human cMET comprises an E168 to D168 substitution (i.e., an E168D variant of cMET). In certain embodiments, a binding agent specifically binds to a human cMET, and/or an extracellular domain thereof, wherein the human cMET comprises an N375 to S375 substitution (i.e., an N375S variant of human cMET).

[0079] The term "specifically binds" refers to a binding agent that binds a target peptide in preference to binding other molecules or other peptides as determined by, for example, as determined by a suitable in vitro assay (e.g., an Elisa, Immunoblot, Flow cytometry, and the like). A specific binding interaction discriminates over non-specific binding interactions by about 2-fold or more, often about 10-fold or more, and sometimes about 100-fold or more, 1000-fold or more, 10,000-fold or more, 100,000-fold or more, or 1,000,000-fold or more.

[0080] In some embodiments a binding agent that specifically binds to cMET, or a portion thereof, is a binding agent that binds cMET, or a portion thereof (e.g., an extracellular domain of cMET), with a binding affinity constant (KD) equal to or less than 100 nM, equal to or less than 50 nM, equal to or less than 25 nM, equal to or less than 10 nM, equal to or less than 5 nM, equal to or less than 1 nM, equal to or less than 900 pM, equal to or less than 800 pM, equal to or less than 750 pM, equal to or less than 700 pM, equal to or less than 600 pM, equal to or less than 500 pM, equal to or less than 400 pM, equal to or less than 300 pM, equal to or less than 200 pM, or equal to or less than 100 pM. In some embodiments a binding agent that specifically binds to cMET, or a portion thereof, is a binding agent that binds human cMET, or a portion thereof (e.g., an extracellular domain of human cMET), with a binding affinity constant (KD) equal to or less than 100 nM, equal to or less than 50 nM, equal to or less than 25 nM, equal to or less than 10 nM, equal to or less than 5 nM, equal to or less than 1 nM, equal to or less than 900 pM, equal to or less than 800 pM, equal to or less than 750 pM, equal to or less than 700 pM, equal to or less than 600 pM, equal to or less than 500 pM, equal to or less than 400 pM, equal to or less than 300 pM, equal to or less than 200 pM, or equal to or less than 100 pM. In some embodiments a binding agent that specifically binds to cMET, or a portion thereof, is a binding agent that binds specifically to cMET, or a portion thereof, derived from a non-human species (e.g., a non-human primate, or rodent; e.g., a mouse or rat), with a binding affinity constant (KD) equal to or less than 100 nM, equal to or less than 50 nM, equal to or less than 25 nM, equal to or less than 10 nM, equal to or less than 5 nM, equal to or less than 1 nM, equal to or less than 900 pM, equal to or less than 800 pM, equal to or less than 750

pM, equal to or less than 700 pM, equal to or less than 600 pM, equal to or less than 500 pM, equal to or less than 400 pM, equal to or less than 300 pM, equal to or less than 200 pM, or equal to or less than 100 pM. In certain embodiments, a binding agent disclosed herein specifically binds human cMET, or a portion thereof, and specifically binds to cMET, or a portion thereof, derived from a non-human primate. In certain embodiments, a binding agent disclosed herein specifically binds human cMET, or a portion thereof, and specifically binds to cMET, or a portion thereof, derived from a rodent (e.g., a mouse or rat). In certain embodiments, a binding agent (i) specifically binds to a human cMET, or portion thereof (e.g., an extracellular domain of human cMET) with a KD of 10nM or less, or 1 nM or less, and (ii) specifically binds to a rat or mouse cMET, or portion thereof (e.g., an extracellular domain of rat or mouse cMET) with a KD of 100 nM or less, 90 nM or less, 80 nM or less, 70 nM or less, 60 nM or less, 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less or 10 nM or less.

[0081] In some embodiments a binding agent comprises a label. As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, e.g., by incorporation of a labeled amino acid or attachment to a polypeptide of biotin moieties that can be detected by labeled avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain embodiments, a label or marker can be attached to a binding agent to generate a therapeutic or diagnostic agent. A binding agent can be attached covalently or non-covalently to any suitable label or marker. Various methods of labeling polypeptides and glycoproteins are known to those skilled in the art and can be used. Non-limiting examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{125}I, ^{131}I), fluorescent labels, enzymatic labels (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent labels, a metallic label, a chromophore, an electro-chemiluminescent label, a phosphorescent label, a quencher (e.g., a fluorophore quencher), a fluorescence resonance energy transfer (FRET) pair (e.g., donor and acceptor), a dye, an enzyme substrate, a small molecule, a mass tag, quantum dots, nanoparticles, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), the like or combinations thereof.

[0082] In some embodiments a binding agent comprises a suitable carrier. A binding agent can be attached covalently or non-covalently to a suitable carrier. Non-limiting examples of a carrier include agents or molecules that alter or extend the in vivo half-life of a binding agent, polyethylene glycol, glycogen (e.g., by glycosylation of a binding agent), a dextran, a carrier or vehicle described in U.S. Patent No. 6,660,843,

the like or combinations thereof.

[0083] In some embodiments a binding agent comprises a suitable therapeutic agent. A binding agent can be attached covalently or non-covalently to any suitable therapeutic agent. Non-limiting examples of a therapeutic agent include a medication, toxin, radioisotope, ligand, receptor, cytokine, antibody, anti-neoplastic agent, inhibitor (e.g., a receptor antagonist, an enzyme inhibitor), a cytokine or an agent disclosed in U.S. Patent No. 6,660,843, which is incorporated herein by reference, the like or combinations thereof. Non-limiting examples of anti-neoplastic agents include an auristatin (e.g., monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), and the like), a dolastatin, a maytansine, a tubulysin, an irinotecan or derivative or metabolite thereof (e.g., SN38), a calicheamicin, a pyrrolobenzodiazepine (PBD), a duocarmycin, a doxorubicin, a pseudomonas exotoxin A (e.g., PE38), derivatives thereof, the like or combinations thereof. Accordingly, in certain embodiments, a binding agent disclosed herein comprises an anti-neoplastic agent.

[0084] In some embodiments a label, therapeutic agent or carrier is bound to a binding agent by use of a suitable linker. Non-limiting examples of a suitable linker include silanes, thiols, phosphonic acid, polyethylene glycol (PEG), amino acids and peptides, polymers thereof, derivatives thereof, the like and combinations thereof. Methods of attaching two or more molecules using a linker are to those skilled in the art and are sometimes referred to as "crosslinking."

[0085] In some embodiments a label, therapeutic agent, carrier or linker is attached to a suitable thiol group of a binding agent (e.g., a thiol group of a cysteine residue). Any suitable amino acid residue of a constant region or framework region of a binding agent can be substituted with an amino acid residue containing a thiol group (e.g., a cysteine) for the purpose of attaching a label, therapeutic agent, carrier or linker. Non-limiting examples of amino acids that can be substituted with a thiol containing amino acid residue include A118, S119, S239, V282, T289, N361, and V422 of an IgG2, S115, S252, V289, T306, and N384 of an IgG1, or a corresponding position in an IgG1, IgG2, IgG3 or IgG4. Other non-limiting examples of attaching a label, therapeutic agent, carrier and/or linker to a binding agent include reacting an amine with an N-hydroxysuccinimide (NHS) ester, an imidoester, a pentafluorophenyl (PFP) ester, a hydroxymethyl phosphine, an oxirane or any other carbonyl compound; reacting a carboxyl with a carbodiimide; reacting a sulfhydryl with a maleimide, a haloacetyl, a pyridyldisulfide, and/or a vinyl sulfone; reacting an aldehyde with a hydrazine; reacting any non-selective group with diazirine and/or aryl azide; reacting a hydroxyl with isocyanate; reacting a hydroxylamine with a carbonyl compound; the like and combinations thereof.

[0086] In certain embodiments, a binding agent comprises one or more functional charac-

teristics. Accordingly, a binding agent can be described structurally and functionally (e.g., by what it does, or by what it is capable of doing). Binding agents disclosed herein can bind specifically to an extracellular portion of cMET, for example, an extracellular portion of cMET present on the surface of a cell. In some embodiments a cell is a human cancer cell or human neoplastic cell that expresses cMET. In certain embodiments, upon binding cMET on the surface of a cell, certain binding agents disclosed herein induce internalization of cMET. In some embodiments, a binding agent binds specifically to cMET, or a portion thereof, and induces degradation of cMET on a cell (e.g., on a cancer cell). Internalization and/or degradation of cell surface bound receptors induced by binding of a ligand or binding agent is a known biological process. The ability of a binding agent to induce cMET internalization and/or degradation is easily observed, without undue experimentation, by use of a suitable experimental assay. Accordingly, in some embodiments, a binding agent binds specifically to cMET, or a portion thereof, on a cell surface and induces internalization and/or degradation of cMET.

[0087] In some embodiments, a binding agent binds specifically to cMET, or a portion thereof, and induces or promotes signaling (e.g., tyrosine kinase activity). In certain embodiments a binding agent binds specifically to cMET on a cell surface and does not detectably induce or promote signaling (e.g., tyrosine kinase activity). Accordingly, in certain embodiments, an anti-cMET binding agent disclosed herein does not have detectable cMET agonist activity. In certain embodiments, an anti-cMET binding agent lacks agonistic activity upon binding cMET on a cell surface and/or fails to induce or promote detectable tyrosine kinase activity upon binding to cMET on a cell surface. In some embodiments, an anti-cMET binding agent is a cMET antagonist. In certain embodiments, an anti-cMET binding agent decreases, inhibits, reduces, blocks or prevents signaling through a cMET receptor and/or decreases, inhibits, reduces, blocks or prevents a cMET receptor from inducing or promoting detectable tyrosine kinase activity. In some embodiments, an anti-cMET binding agent disclosed herein decreases, inhibits, reduces, prevents or blocks cMET from binding to its native cognate ligand (e.g., hepatocyte growth factor, or an isoform thereof).

[0088] In certain embodiments, contacting a cell of a subject with a binding agent disclosed herein induces or promotes death of the cell. In certain embodiments, contacting a cell of a subject with a binding agent disclosed herein induces or promotes cell-death by apoptosis or necrosis of a cell expressing cMET. In certain embodiments, contacting a cell of a subject with a binding agent disclosed herein induces or promotes death of the cell by an ADCC, ADCP or complement-dependent cellular cytotoxicity (CDCC) process.

[0089] In certain embodiments, contacting a cell of a subject with a binding agent disclosed

herein decreases, inhibits, or reduces mitosis of the cell. In certain embodiments, contacting a cell of a subject with a binding agent disclosed herein decreases, inhibits, or reduces metastasis of the cell.

[0090] In some embodiments, presented herein is a composition or pharmaceutical composition comprising one or more binding agents that binds specifically to cMET, or a portion thereof (e.g., an extracellular domain of cMET, or a portion thereof).

[0091] A pharmaceutical composition can be formulated for a suitable route of administration. In some embodiments a pharmaceutical composition is formulated for subcutaneous (s.c.), intradermal, intramuscular, intraperitoneal and/or intravenous (i.v.) administration. In certain embodiments, a pharmaceutical composition can contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates (e.g., phosphate buffered saline) or suitable organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta- cyclodextrin); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counter ions (such as sodium); solvents (such as glycerin, propylene glycol or polyethylene glycol); diluents; excipients and/or pharmaceutical adjuvants (Remington's Pharmaceutical Sciences, 18th Ed., A.R. Gennaro, ed., Mack Publishing Company (1995)).

[0092] In certain embodiments, a pharmaceutical composition comprises a suitable excipient, non-limiting example of which include anti-adherents (e.g., magnesium stearate), a binder, fillers, monosaccharides, disaccharides, other carbohydrates (e.g., glucose, mannose or dextrins), sugar alcohols (e.g., mannitol or sorbitol), coatings (e.g., cellulose, hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose, synthetic polymers, shellac, gelatin, corn protein zein, enterics or other polysaccharides), starch (e.g., potato, maize or wheat starch), silica, colors, disintegrants, flavors, lubricants, preservatives, sorbents, sweeteners, vehicles, suspending agents, surfactants and/or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal), stability enhancing agents (such as sucrose or sorbitol), and tonicity enhancing agents (such as alkali metal halides, sodium or potassium chloride,

mannitol, sorbitol), and/or any excipient disclosed in Remington's Pharmaceutical Sciences, 18th Ed., A.R. Gennaro, ed., Mack Publishing Company (1995). The term "binder" as used herein refers to a compound or ingredient that helps keeps a pharmaceutical mixture combined. Suitable binders for making pharmaceutical formulations and are often used in the preparation of pharmaceutical tablets, capsules and granules are known to those skilled in the art. For clarification, the term "binding agent" as used herein does not refer to a "binder" that is used in certain pharmaceutical formulations. Although a pharmaceutical composition, in certain embodiments, may comprise a binding agent that specifically binds cMET as well as a binder.

[0093] In some embodiments a pharmaceutical composition comprises a suitable pharmaceutically acceptable additive and/or carrier. Non-limiting examples of suitable additives include a suitable pH adjuster, a soothing agent, a buffer, a sulfur-containing reducing agent, an antioxidant and the like. Non-limiting examples of a sulfur-containing reducing agent includes those having a sulfhydryl group such as N-acetylcysteine, N-acetylhomocysteine, thioctic acid, thiodiglycol, thioethanolamine, thioglycerol, thiosorbitol, thioglycolic acid and a salt thereof, sodium thiosulfate, glutathione, and a C1-C7 thioalkanoic acid. Non-limiting examples of an antioxidant include erythorbic acid, dibutylhydroxytoluene, butylhydroxyanisole, alpha - tocopherol, tocopherol acetate, L-ascorbic acid and a salt thereof, L-ascorbyl palmitate, L-ascorbyl stearate, sodium bisulfite, sodium sulfite, triamyl gallate and propyl gallate, as well as chelating agents such as disodium ethylenediaminetetraacetate (EDTA), sodium pyrophosphate and sodium metaphosphate. Furthermore, diluents, additives and excipients may comprise other commonly used ingredients, for example, inorganic salts such as sodium chloride, potassium chloride, calcium chloride, sodium phosphate, potassium phosphate and sodium bicarbonate, as well as organic salts such as sodium citrate, potassium citrate and sodium acetate.

[0094] The pharmaceutical compositions used herein can be stable over an extended period of time, for example on the order of months or years. In some embodiments a pharmaceutical composition comprises one or more suitable preservatives. Non limiting examples of preservatives include benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, hydrogen peroxide, the like and/or combinations thereof. A preservative can comprise a quaternary ammonium compound, such as benzalkonium chloride, benzoxonium chloride, benzethonium chloride, cetrimide, sepazonium chloride, cetylpyridinium chloride, or domiphen bromide (BRADOSOL(R)). A preservative can comprise an alkyl-mercury salt of thiosalicylic acid, such as thimerosal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate. A preservative can comprise a paraben, such as methylparaben or propylparaben. A

preservative can comprise an alcohol, such as chlorobutanol, benzyl alcohol or phenyl ethyl alcohol. A preservative can comprise a biguanide derivative, such as chlorohexidine or polyhexamethylene biguanide. A preservative can comprise sodium perborate, imidazolidinyl urea, and/or sorbic acid. A preservative can comprise stabilized oxychloro complexes, such as known and commercially available under the trade name PURITE(R). A preservative can comprise polyglycol-polyamine condensation resins, such as known and commercially available under the trade name POLYQUART(R) from Henkel KGaA. A preservative can comprise stabilized hydrogen peroxide. A preservative can be benzalkonium chloride. In some embodiments a pharmaceutical composition is free of preservatives.

[0095] In some embodiments a composition, pharmaceutical composition or binding agent is substantially free of blood, or a blood product contaminant (e.g., blood cells, platelets, polypeptides, minerals, blood borne compounds or chemicals, and the like). In some embodiments a composition, pharmaceutical composition or binding agent is substantially free of serum and serum contaminants (e.g., serum proteins, serum lipids, serum carbohydrates, serum antigens and the like). In some embodiments a composition, pharmaceutical composition or binding agent is substantially free a pathogen (e.g., a virus, parasite or bacteria). In some embodiments a composition, pharmaceutical composition or binding agent is substantially free of endotoxin. In some embodiments a composition, pharmaceutical composition or binding agent is sterile. In certain embodiments, a composition or pharmaceutical composition comprises a binding agent that specifically binds an extracellular domain of cMET and a diluent (e.g., phosphate buffered saline). In certain embodiments, a composition or pharmaceutical composition comprises a binding agent that specifically binds an extracellular domain of cMET and an excipient, (e.g., sodium citrate dehydrate, or polyoxyethylene-sorbitan-20 mono-oleate (polysorbate 80)).

[0096] The pharmaceutical compositions described herein may be configured for administration to a subject in any suitable form and/or amount according to the therapy in which they are employed. For example, a pharmaceutical composition configured for parenteral administration (e.g., by injection or infusion), may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulation agents, excipients, additives and/or diluents such as aqueous or non-aqueous solvents, co-solvents, suspending solutions, preservatives, stabilizing agents and or dispersing agents. In some embodiments a pharmaceutical composition suitable for parental administration may contain one or more excipients. In some embodiments a pharmaceutical composition is lyophilized to a dry powder form. In some embodiments a pharmaceutical composition is lyophilized to a dry powder form, which is suitable for reconstitution with a suitable pharmaceutical solvent (e.g., water, saline, an

isotonic buffer solution (e.g., PBS), and the like). In certain embodiments, reconstituted forms of a lyophilized pharmaceutical composition are suitable for parental administration (e.g., intravenous administration) to a mammal.

[0097] In some embodiments a pharmaceutical compositions described herein may be configured for topical administration and may include one or more of a binding and/or lubricating agent, polymeric glycols, gelatins, cocoa-butter or other suitable waxes or fats. In some embodiments a pharmaceutical composition described herein is incorporated into a topical formulation containing a topical carrier that is generally suited to topical drug administration and comprising any suitable material known to those skilled in the art. In certain embodiments, a topical formulation of a pharmaceutical composition is formulated for administration of a binding agent from a topical patch.

[0098] In certain embodiments, an optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage (see e.g., Remington's Pharmaceutical Sciences, supra). In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antibodies of the invention.

[0099] In some embodiments a composition, pharmaceutical composition or binding agent described herein is used to treat a subject having or suspected of having a neoplastic disorder or cancer. In certain embodiments, a binding agent or pharmaceutical composition described herein is used in treating a neoplastic disorder or cancer in a subject, wherein the binding agent specifically binds to an extracellular domain of human cMET. Is some embodiments, presented herein is a method of treating a subject having or suspected of having a neoplastic disorder or cancer. In certain embodiments, a method of treating a subject having or suspected of having a neoplastic disorder or cancer comprises administering a therapeutically effective amount of a composition, pharmaceutical composition or binding agent described herein to the subject. In certain embodiments, a method of treatment comprises contacting a cell (e.g., one or more cells) of a subject with a therapeutically effective amount of a composition, pharmaceutical composition or binding agent described herein. In certain embodiments, a method of treatment comprises contacting a cell (e.g., one or more cells) of a subject with a therapeutically effective amount of a binding agent that specifically binding to an extracellular portion of human cMET, or variant thereof. The cell of a subject is often a cell that expresses an extracellular portion of cMET. A cell of a subject may be found inside a subject (e.g., in vivo) or outside the subject (e.g., in vitro or ex vivo).

[0100] A composition, pharmaceutical composition or binding agent disclosed herein can be used to treat a suitable neoplastic order or cancer involving a cell type that expresses cMET. Non-limiting examples of a neoplastic disorder or cancer that can be treated by

a method herein includes a lung carcinoma, breast carcinoma, ovarian carcinoma, kidney carcinoma, colorectal carcinoma, gastric carcinoma, thyroid carcinoma, pancreas carcinoma, neuroblastoma, or a squamous cell carcinoma of the head and neck, cervical cancer, hepatocellular cancer, sarcomas, mesothelioma, glioblastoma, multiple myeloma, melanoma, prostate and esophageal carcinoma. In certain embodiments a neoplastic cell of a cancer or neoplastic order can be quickly assayed for expression of cMET using a suitable anti-cMET binding agent, or a novel binding agent described herein by using a suitable method (e.g., whole cell ELISA, FACs, any suitable immunoassay, and the like).

[0101] Any suitable method of administering a composition, pharmaceutical composition or binding agent to a subject can be used. The exact formulation and route of administration for a composition for use according to the methods of the invention described herein can be chosen by the individual physician in view of the patient's condition. See, e.g., Fingl et al. 1975, in "The Pharmacological Basis of Therapeutics," Ch. 1, p. 1; which is incorporated herein by reference in its entirety. Any suitable route of administration can be used for administration of a pharmaceutical composition or a binding agent described herein. Non-limiting examples of routes of administration include topical or local (e.g., transdermally or cutaneously, (e.g., on the skin or epidermis), in or on the eye, intranasally, transmucosally, in the ear, inside the ear (e.g., behind the ear drum)), enteral (e.g., delivered through the gastrointestinal tract, e.g., orally (e.g., as a tablet, capsule, granule, liquid, emulsification, lozenge, or combination thereof), sublingual, by gastric feeding tube, rectally, and the like), by parenteral administration (e.g., parenterally, e.g., intravenously, intra-arterially, intramuscularly, intraperitoneally, intradermally, subcutaneously, intracavity, intracranial, intra-articular, into a joint space, intracardiac (into the heart), intracavernous injection, intralesional (into a skin lesion), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intrauterine, intravaginal, intravesical infusion, intravitreal), the like or combinations thereof.

[0102] In some embodiments a composition herein is provided to a subject. A composition that is provided to a subject is sometimes provided to a subject for self-administration or for administration to a subject by another (e.g., a non-medical professional). For example a composition described herein can be provided as an instruction written by a medical practitioner that authorizes a patient to be provided a composition or treatment described herein (e.g., a prescription). In another example, a composition can be provided to a subject where the subject self-administers a composition orally, intravenously or by way of an inhaler, for example.

[0103] Alternately, one can administer compositions for use according to the methods of the invention in a local rather than systemic manner, for example, via direct application to

the skin, mucous membrane or region of interest for treating, including using a depot or sustained release formulation.

[0104] In some embodiments a pharmaceutical composition comprising a binding agent can be administered alone (e.g., as a single active ingredient (AI or e.g., as a single active pharmaceutical ingredient (API)). In other embodiments, a pharmaceutical composition comprising a binding agent can be administered in combination with one or more additional AIs/APIs, for example, as two separate compositions or as a single composition where the one or more additional AIs/APIs are mixed or formulated together with the binding agent in a pharmaceutical composition.

[0105] A pharmaceutical composition can be manufactured by any suitable manner, including, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0106] In some embodiments a pharmaceutical composition comprising a binding agent is administered at a suitable frequency or interval as needed to obtain an effective therapeutic outcome. An effective therapeutic outcome can be determined by monitoring the number, viability, growth, mitosis, or metastasis of neoplastic or cancerous cells in a subject affected with a neoplastic disorder or cancer. Accordingly, in certain embodiments, a decrease in the number, viability, growth, mitosis, or metastasis of neoplastic or cancerous cells in a subject is considered an effective therapeutic outcome. In some embodiments, a pharmaceutical composition comprising a binding agent can be administered hourly, once a day, twice a day, three times a day, four times a day, five times a day, and/or at regular intervals, for example, every day, every other day, three times a week, weekly, every other week, once a month and/or simply at a frequency or interval as needed or recommended by a medical professional.

[0107] In some embodiments, an amount of a binding agent in a composition is an amount needed to obtain an effective therapeutic outcome. In certain embodiments, the amount of a binding agent in a composition (e.g., a pharmaceutical composition) is an amount sufficient to prevent, treat, reduce the severity of, delay the onset of, and/or alleviate a symptom of a neoplastic disorder or cancer, as contemplated herein.

[0108] A "therapeutically effective amount" means an amount sufficient to obtain an effective therapeutic outcome and/or an amount necessary sufficient to prevent, treat, reduce the severity of, delay the onset of, and/or alleviate a symptom of a neoplastic disorder or cancer. In certain embodiments, a "therapeutically effective amount" means an amount sufficient to terminate the grow of, and/or slow the growth of a neoplasm or cancer. In certain embodiments, a "therapeutically effective amount" means an amount sufficient to inhibit the replication of, and/or induce the death of one or more neoplastic cells. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure

provided herein.

[0109] In some embodiments, an amount of a binding agent in a composition is an amount that is at least a therapeutically effective amount and an amount low enough to minimize unwanted adverse reactions. The exact amount of a binding agent or combinations of active agents required will vary from subject to subject, depending on age, weight, and general condition of a subject, the severity of the condition being treated, and the particular combination of drugs administered. Thus, it is not always possible to specify an exact therapeutically effective amount to treat a neoplastic disorder in a diverse group of subjects. As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures. Thus, a therapeutically effective amount of a binding agent used to treat a neoplastic disorder may be determined by one of ordinary skill in the art using routine experimentation.

[0110] In certain embodiments, an amount of a binding agent in a composition is administered at a suitable therapeutically effective amount or a dose (e.g., at a suitable volume and concentration, which sometimes depends, in part, on a particular route of administration). Within certain embodiments, a binding agent (e.g., a binding agent in a composition) can be administered at a dose from about .01 mg/kg (e.g., per kg body weight of a subject) to 500 mg/kg, 0.1 mg/kg to 500 mg/kg, 0.1 mg/kg to 400 mg/kg, 0.1 mg/kg to 300 mg/kg, 0.1 mg/kg to 200 mg/kg, 0.1 mg/kg to 150 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 75 mg/kg, 0.1 mg/kg to 50 mg/kg, 0.1 mg/kg to 25 mg/kg, 0.1 mg/kg to 10 mg/kg, 0.1 mg/kg to 5 mg/kg or 0.1 mg/kg to 1 mg/kg. In some aspects the amount of a binding agent can be about 10 mg/kg, 9 mg/kg, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, 1 mg/kg, 0.9 mg/kg, 0.8 mg/kg, 0.7 mg/kg, 0.6 mg/kg, 0.5 mg/kg, 0.4 mg/kg, 0.3 mg/kg, 0.2 mg/kg, or 0.1 mg/kg. In some embodiments a therapeutically effective amount of a binding agent is between about 0.1 mg/kg to 500 mg/kg, or between about 1 mg/kg and about 300 mg/kg. Volumes suitable for intravenous administration are well known.

[0111] In some embodiments a binding agent is used to detect cMET, in vitro or in vivo. In some embodiments a binding agent is used to detect cMET on a cell surface and/or to determine the presence or absence of a neoplastic cell (e.g., a malignant cell), where the cell expresses cMET. In some embodiments a binding agent is used to determine if a subject has a neoplastic disorder or cancer. In some embodiments a method of detecting cMET comprises determining the presence or absence of cMET on a cell in a sample, (e.g., a sample obtained directly or indirectly from a subject).

[0112] Any suitable method can be used to detect and/or quantitate the presence, absence and/or amount of a binding agent specifically bound to cMET, or a portion thereof,

non-limiting examples of such methods can be found in Immunology, Werner Luttmann; Academic Press, 2006 and/or Medical Detection and Quantification of Antibodies to Biopharmaceuticals: Practical and Applied Considerations, Michael G. Tovey; John Wiley & Sons, July 12, 2011. Additional non-limiting examples of methods that can be used to detect and/or quantitate the presence, absence and/or amount of a binding agent specifically bound to cMET, or a portion thereof, include use of a competitive immunoassay, a non-competitive immuno assay, western blots, a radioimmunoassay, an ELISA (enzyme linked immunosorbent assay), a competition or sandwich ELISA, a sandwich immunoassay, an immunoprecipitation assay, an immunoradiometric assay, a fluorescent immunoassay, a protein A immunoassay, a precipitin reaction, a gel diffusion precipitin reaction, an immunodiffusion assay, an agglutination assay, a complement fixation assay, an immunohistochemical assay, a Western blot assay, an immunohistological assay, an immunocytochemical assay, a dot blot assay, a fluorescence polarization assay, a scintillation proximity assay, a homogeneous time resolved fluorescence assay, an IAsys analysis, a BIAcore analysis, the like or a combination thereof.

[0113] A pharmaceutical composition comprising an amount or dose of a binding agent can, if desired, be provided in a kit, pack or dispensing device, which can contain one or more doses of a binding agent. The pack can for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration. The pack or dispenser can also be accompanied with a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, can be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert.

[0114] In some embodiments a kit or pack comprises an amount of a binding agent sufficient to treat a patient for 1 day to 1 year, 1 day to 180 days, 1 day to 120 days, 1 day to 90 days, 1 day to 60 days, 1 day to 30 days, or any day or number of days there between, 1-4 hours, 1-12 hours, or 1-24 hours.

[0115] A kit optionally includes a product label or packaging inserts including a description of the components or instructions for use in vitro, in vivo, or ex vivo, of the components therein. Exemplary instructions include instructions for a diagnostic method, treatment protocol or therapeutic regimen. In certain embodiments, a kit comprises packaging material, which refers to a physical structure housing components of the kit. The packaging material can maintain the components sterilely, and can be made of material commonly used for such purposes (e.g., paper, corrugated fiber, glass, plastic, foil, ampules, vials, tubes, etc.). Product labels or inserts include "printed

matter," e.g., paper or cardboard, or separate or affixed to a component, a kit or packing material (e.g., a box), or attached to an ampule, tube or vial containing a kit component. Labels or inserts can additionally include a computer readable medium, optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/ optical storage media, FLASH media or memory type cards. Product labels or inserts can include identifying information of one or more components therein, dose amounts, clinical pharmacology of the active ingredient(s) including mechanism of action, pharmacokinetics (PK) and pharmacodynamics (PD). Product labels or inserts can include information identifying manufacturer information, lot numbers, manufacturer location, date, information on an indicated condition, disorder, disease or symptom for which a kit component may be used. Product labels or inserts can include instructions for the clinician or for a subject for using one or more of the kit components in a method, treatment protocol or therapeutic regimen. Instructions can include dosage amounts, frequency or duration, and instructions for practicing any of the methods, treatment protocols or therapeutic regimes set forth herein. Kits of the invention therefore can additionally include labels or instructions for practicing any of the methods and uses of the invention described herein. Product labels or inserts can include information on potential adverse side effects and/or warnings.

[0116] In certain embodiments, a kit comprises one or more controls having a known amount of cMET. In some embodiments, a kit comprises cells expressing cMET. The cells in the kit can be maintained under appropriate storage conditions until the cells are ready to be used.

[0117] In some embodiments, a kit is a diagnostic kits comprising a binding agent. A binding agent comprised in a diagnostic kit can take any suitable form. In some embodiments, a diagnostic comprises a binding agent and a detectable label. In certain embodiments, for example, a diagnostic kit comprises or consists of a stick test, including necessary reagents to perform the method of the invention and to produce, for example, a colorimetric result which can be compared against a color chart or standard curve. A diagnostic kit can also comprise components necessary for detecting a binding agent that specifically binds to cMET, for example a secondary antibody.

Example 1

[0118] Antibody Generation

To induce an antibody response against cMET, mice were immunized with cMET-Fc or cMET peptide as described in Figures 1 and 2. In some embodiments peptide derived from strategic regions were selected for immunization. Figure 3 illustrates an example of a structural loop on MET that inspired the design of peptide 3. Spleens

from immunized mice were obtained and splenocytes were fused to a suitable fusion partner to produce hybridomas using a standard protocol. Hybridoma clones were isolated and hybridoma media was tested for binding to MET and/or for the ability to induce internalization of cMET on human cancer cell lines as measured by flow cytometry (Figure 4). Selected hybridoma antibodies were selected for their ability to induce MET degradation (Figure 5) or inability to induce phosphorylation of ERK (Figure 6).

[0119] Additional assays were performed to select ideal anti-cMET antibody candidates. For example, anti-cMET antibodies were tested for species cross-reactivity by determining the ability of an antibody to bind to human cMET, monkey cMET (e.g., Macaca fascicularis, i.e., Cynomolgus Macaque), rat cMET and mouse cMET as measured by ELISA (Figures 7 & Table 1). In vivo half-life and other pharmacokinetic characteristics were also evaluated (data not shown). Potency and specificity of antibody drug conjugates (ADC) was also determined on high, medium and negative cMET expressing cell lines using anti-cMET antibodies that were conjugated to MMAF)(Figure 9 and 15, Tables 11 and 12). ADCs were tested for efficacy in vivo using an MKN45 Xenograft model.

[0120] [Table 11]

In Vitro Ranking	Antibody	Avg. Cytotoxicity EC50, pM SNU16 cells (Met medium)	Avg. Cytotoxicity EC50, pM SNU620 cells (Met high)	Met Binding KD (pM) SPR w/hMet-Fc	Met Degradation (pM) MSD	Cell Proliferation (Agonism) ERK Phospho Assay	Cross-reactivity		
							NHP	Rat	Mouse
	5D5			800		Yes/Strong	Yes	No	No
	A8F45	850	87	700	10,000	NO	Yes	No	No
1	F68LP3D12	25	60	350	140	NO	Yes	Yes	No
2	F68P2D8	60	33	480	3,000	NO	Yes	No	No
2	F68LP3E2	70	55	880	1,920	Very low	Yes	Low	No
3	F6AP12F12	180	97	110	450	NO	Not tested	Not tested	Not tested
3	F5P5B5	20	3	80	255	Very low	Yes	No	No
3	F6AP8E2	351	192	160	7,000	Very low at high concentrations	Yes	No	No
3	F68P1H5/N6	80	68	340	3,000	Maybe at high concentrations	Yes	No	No

SPR=Surface Plasmon Resonance

MSD=Meso Scale Discovery Platform

NHP=Non-human Primate (i.e., Cynomolgus Macaque)

5D5=agonist positive control

ABF46=MET ADC, positive control

Example 2

[0121] Summary of Characteristics of Selected Humanized Monoclonal Binding Agents

Humanized and isotype switched monoclonal binding agents were generated which comprise the heavy chain CDRs and light chain CDRs of the mouse monoclonal antibody P3D12. Sixteen different heavy chain (HC) and light chain (LC) combinations were tested for solubility in PBS, binding to human cMET, binding to rat cMET, binding affinity to human and rat cMET as determined by surface plasmon resonance (SPR), the presence of agonistic activity and cMET degradation reported as Meso Scale Discovery platform (MSD). The results are summarized in Table 12 below.

[0122]

[Table 12]

Rank	HC	LC	Clone	%identity to WT	ELISA rMET vs parental	ELISA rMET vs parental	sc-MKN45 Adc, ICS2, pH6, SKD-16 (n=3)	SPR kD, nM, rMET-Fc	SPR kD nM, rMET-Fc	pERK (MET agonism, MKN)	MET degradation equal to parental (MKN)
	VH-abbybat	VL-abbybat	G2aka		0.3	2.1	392	0.9	26	negative	yes
		VL-fra	G2akf		1.0	8.5	388	0.8	22	negative	yes
		VL-ven	G2akv	insoluble	1.6	1.3				negative	yes
		VL-cdr	G2akc		1.3	0.7	382	0.7	38	negative	yes
	VH-fra	VL-abbybat	G2fva		1.8	3.8				negative	yes
3		VL-fra	G2fkf		1.7	1.4	266	0.4	30	negative	yes
		VL-ven	G2fkv	insoluble	1.7	1.2				negative	yes
		VL-cdr	G2fkc		1.7	2.3				negative	yes
	VH-ven	VL-abbybat	G2vva		0.9	2.7				negative	yes
2		VL-fra	G2vkf		2.1	2.8	382	0.3	8	negative	yes
		VL-ven	G2vkv	insoluble	1.6	1.6				negative	yes
		VL-cdr	G2vkc		1.1	1.9				negative	yes
4	VH-cdr	VL-abbybat	G2cka		1.3	2.7	238	0.3	29	negative	yes
		VL-fra	G2ckf		0.7	0.9	392	0.3	7	negative	yes
1		VL-ven	G2ckv	insoluble	1.1	1.0				negative	yes
		VL-cdr	G2ckc		1.8	2.0	289	0.9	31	negative	yes
	Chimeric H2D12						266	0.7	38		
	Mouse H2D12						32	0.9	16		

Example 3

[0123] A human subject presents with multiple metastatic carcinomas of 2 cm or larger, present in liver and lung. A biopsy is performed to determine if the cells of the carcinoma express cMET on their cell surface. The presence of cell surface cMET expression is confirmed from the biopsy results.

[0124] The human subject is administered a binding agent that specifically binds to the extracellular domain of human cMET. The binding agent optionally comprises human kappa and IgG1 heavy-chain constant regions, the light chain variable region of SEQ

ID NO: 41 and the heavy chain variable regions of SEQ ID NO:98. The binding agent can be administered at a dose of 30 mg/kg, intravenously, in a volume of 300 ml over a period of 2 hours, once a day for six weeks. The presence, size and viability of the tumor is determined by follow-up biopsy and ultrasound. The subject is determined to be in remission after six weeks of treatment.

Example 4

[0125] A human subject presents with multiple metastatic carcinomas of 2 cm or larger, present in liver and lung. A biopsy is performed to determine if the cells of the carcinoma express cMET on their cell surface. The presence of cell surface cMET expression is confirmed from the biopsy results.

[0126] The human subject is administered a binding agent that specifically binds to the extracellular domain of human cMET. The binding agent optionally comprises human kappa and IgG2a heavy-chain constant regions, the humanized light chain variable region of SEQ ID NO: 48 and the humanized heavy chain variable region of SEQ ID NO: 107. The binding agent is optionally conjugated to MMAF. The binding agent is administered at a dose of 1 mg/kg, intravenously, in a volume of 300 ml over a period of 2 hours, once a day for six weeks. The presence, size and viability of the tumor is determined by follow-up biopsy and ultrasound. The subject is determined to be in remission after six weeks of treatment.

Example 5

[0127] cMET Sequences

SEQ ID NO: 109 (Human cMET - UniProtKB - P08581 (MET_HUMAN)) *Residue E168 and N375 are bolded and underlined.

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPI
QNVILHEHHIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPCQDCSSKA
NLSGGVWKDNINMALVVDTYYDDQLISCGSVNRGTCQRHVFPHNHTADIQSE
VHCIFSPQIE**E**PSQCPDCVVSALGAKVLSSVKDRFINFFVGNTINSSYFPDHPLHS
ISVRRLKETKDGFMFLTDQSYIDVLPEFRDSYPIKYVHAFESNNFIYFLTVQRET
LDAQTFHTRIIRFCSINSGLHSYMEMPLECILTEKRKKRSTKKEVFNILQAAYVS
KPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDFF**N**KI
VNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEARRDEYRTEFTTALQRVDL
FMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLLDSH
PVSPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCG
WCHDKCVRSEECLSGTWTQQICLPAIYKVFPNSAPLEGGTRLTICGWDFGFRR
NNKFDLKKTRVLLGNESCTLTLSESTMNTLKCTVGPAMNKHFNMSIIISNGHG
TTQYSTFSYVDPVITSISPKYGPMAGGTLLTLTGNYLNSGNSRHISIGGKTCTLK
SVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFSYREDPIVYEIHPTKSFISGG

STITGVGKNLNSVSVPRMVINVHEAGRNFTVACQHRSNSEIICCTTPSLQQLNL
QLPLKTKAFFMLDGILSKYFDLIYVHNPVFKPFEKPVMISMGNENVLEIKGNDI
DPEAVKGEVLKVGNKSCENIHLHSEAVLCTVPNDLLKLNSELNIEWKQAISST
VLGKVIVQPDQNFTGLIAGVVSISTALLLLLGFFLWLKKRKQIKDLGSELVRYD
ARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGSCRQVQ
YPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVVIGPSSLIVHFN
EVIGRGHFGCVYHGTLLDNDGKKIHCAVKSLNRITDIGEVSQFLTEGIIMKDFS
HPNVLSLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIGFGLQVA
KGMKYLASKKFVHRDLAARNCMLDEKFTVKVADFGLARDMYDKEYYSVHN
KTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNTF
DITVYLLQGRRLLQPEYCPDPLYEVMLKCWHPKAEMRPSFSELVSRISAIFSTFI
GEHYVHVNATYVNVKCVAPYPSLLSSEDNADDEVDTRPASFWETS

[0128] SEQ ID NO: 110 (Rat cMET-UniProtKB - P97523 (MET_RAT))

MKAPTALAPGILLLLLTLAQRSHGECKEALVKSEMNVNMKYQLPNFTAETPI
HNVVLPGHHIYLGATNYIYVLNDKDLQKVSEFKTGPVVEHPDCFPCQDCSSKA
NVSGGVWKDNVNMALLVDTYYDDQLISCGSVNRGTCQRHVLPPDNAADIQS
EVHCMFSPLAEEESGQCPDCVVSALGAKVLLSEKDRFINFFVGNTINSSYPPDY
SLHSISVRRLKETQDGFKFLTDQSYIDVLPEFRDSYPIKYIHAFESNHFIYFLTVQ
KETLDAQTFHTRIIRFCSVDSGLHSYMEMPLECILTEKRRKRSTREEVFNILQAA
YVSKPGANLAKQIGASPYDDILYGVFAQSKPDSAEPMNRSAVCAFPIKYVNDF
FNKIVNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEVRSDEYRTEFTTALQR
VDLFMGRLNHVLLTSISTFIKGDLTIANLGTSEGRFMQVVLSRTAHFTPHVNFL
LDSYPVSPEVIVEHPSNQNGYTLVVTGKKITKIPLNGLGCGHFQSCSQCLSPPYF
IQCGWCHNRCVHSNECPSGTWTQEICLPAVYKVFPTSAPLEGGTMLTICGWDF
GFKKNNKFDLRKTKVLLGNESCTLTLSESTTNTLKCTVGPAMSEHFNVSVIVS
NSRETTQYSAFSYVDPVITSISPRYGPHAGGTLLTLTGKYLNSGNSRHISIGGKT
CTLKSVSDSILECYTPGHTVSAEFPVKLKIDLADRVTSSFSYREDPVVSEIHPTK
SFISGGSTITGIGKNLNSVSTPKLVIEVHDVGVNYTVACQHRSSSEIICCTTPSLR
QLDLQLPLKTKAFFLLDGILSKHFDLTYVHDPMFKPFEKPVMISMGNENVVEI
KGDDIDPEAVKGEVLKVGNKSCENLHWHSEALLCTVPSDLLKLNGGELNIEW
KQAVSSTVLGKVIVQPDQNFAGLIIGAVSISVVVLLVSGLFLWLRKRKHKDLG
SELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQN
GACRQVQYLLTDLSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVPHVVIGP
SSLIVHFNEVIGRGHFGCVYHGTLLDSDGKKIHCAVKSLNRITDIEEVSQFLTEG
IIMKDFSHPNVLSLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIG
FGLQVAKGMKYLVSKKFVHRDLAARNCMLDEKFTVKVADFGLARDMYDKE
YYSVHNKTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAPPY
PDVNTFDITIYLLQGRRLLQPEYCPDALYEVMLKCWHPKAEMRPSVSELVSRIS

SIFSTFIGEHYVHVNATYVNVKCVAPYPSLLPSQDNIDGEANT

[0129] SEQ ID NO: 111 (Mouse cMET- UniProtKB - P16056 (MET_MOUSE))

MKAPTVLAPGILVLLLSLVQRSHGECKEALVKSEMNVNMKYQLPNFTAETPI
QNVVLHGHHIYLGATNYIYVLNDKDLQKVSEFKTGPVLEHPDCLPCRDCSSKA
NSSGGVWKDNINMALLVDTYYDDQLISCGSVNRGTCQRHVLPPDNSADIQSE
VHCMFSPEEESGQCPDCVVSALGAKVLLSEKDRFINFFVGNTINSSYPPGYSLH
SISVRRLKETQDGFKFLTDQSYIDVLPEFLDSYPIKYIHAFESNHFIYFLTVQKET
LDAQTFHTRIIRFCSVDSGLHSYMEMPLECILTEKRRKRSTREEVFNILQAAYVS
KPGANLAKQIGASPSDDILFGVFAQSKPDSAEPVNRSAVCAFPIKYVNDFFNKI
VNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEARSDEYRTEFTTALQRVDLF
MGRLNQVLLTSISTFIKGDLTIANLGTSEGRFMQVVLSRTAHLTPHVNFLLDSH
PVSPEVIVEHPSNQNGYTLVVTGKKITKIPLNGLGCGHFQSCSQCLSAPYFIQCG
WCHNQCVRFDECPSGTWTQEICLPAVYKVFPTSAPLEGGTVLTICGWDFGFRK
NNKFDLRKTKVLLGNESCTLTLSESTTNTLKCTVGPAMSEHFNVSVIISNSRET
TQYSAFSYVDPVITSISPRYGPQAGGTLLTLTGKYLNSGNSRHISIGGKTCTLKS
VSDSILECYTPAQTTSDEFPVKLKIDLANRETSSFSYREDPVVYEIHPTKSFISGG
STITGIGKTLNSVSLPKLVIDVHEVGVNYTVACQHRSNSEIICCTTPSLKQLGLQ
LPLKTKAFFLLDGILSKHFDLTYVHNPVFEPFEKPVMISMGNENVVEIKGNNID
PEAVKGEVLKVGNQSCESLHWHSGAVLCTVPSDLLKLNSELNIEWKQAVSST
VLGKVIVQPDQNFAGLIIGAVSISVVVLLLSGLFLWMRKRKHKDLGSELVRYD
ARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGACRQVQ
YPLTDLSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVVIGPSSLIVHFN
EVIGRGHFGCVYHGTLLDNDGKKIHCAVKSLNRITDIEEVSQFLTEGIIMKDFS
HPNVLSLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIGFGLQVA
KGMKYLASKKFVHRDLAARNCMLDEKFTVKVADFGLARDMYDKEYYSVHN
KTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNTF
DITIYLLQGRRLLQPEYCPDALYEVMLKCWHPKAEMRPSFSELVSRISSIFSTFI
GEHYVHVNATYVNVKCVAPYPSLLPSQDNIDGEGNT

[0130] SEQ ID NO: 112 (Dog cMET)

MKAPAVLAPGILVLLFTLVQKSYGECKEALVKSEMNVNMKYQLPNFTAETP
IQNVVLHKHHIYLGAVNYIYVLNDKDLQKVAEYKTGPVLEHPDCSPCQDCSH
KANLSGGVWEDNINMALLVDTYYDDQLISCGSVHRGTCQRHILPPSNIADIQS
EVHCMYSSQADEEPSQCPDCVVSALGTKVLISEKDRFINFFVGNTINSSDHPDH
SLHSISVRRLKETQDGFKFLTDQSYIDVLPEFRDSYPIKYVHAFESNHFIYFLTV
QRETLDAQTFHTRIIRFCSVDSGLHSYMEMPLECILTEKRRKRSTREEVFNILQA
AYVSKPGAHLAKQIGANLNDDILYGVFAQSKPDSAEPMNRSAVCAFPIKYVNE
FFNKIVNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEARNDEYRTEFTTALQ
RVDLFMGQFNQVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSGLSTPHVNF

RLDSHPVSPEAIVEHPLNQNGYTLVVTGKKITRIPLNGLGCEHFQSCSQCLSAPP
FVQCGWCHDRCVHLEECPTGAWTQEVCLPAIYEVFPTSAPLEGGTVLTVCGW
DFGFRRNNKFDLKKTKVFLGNESCTLTLSESTTNMLKCTVGPAVNEHFNISIIIS
NGRGTAQYSTFSYVDPIITSISPSYGPKNGGTLLTLTGKYLNSGNSRHISMGGKT
CTLKSVSDSILECYTPAQATATEFPIKLKIDLANREMNSFSYQEDPIVYAIHPTK
SFISGGSTITAVGKNLNSVSVLRMVIDVHETRRNFTVACQHRSNSEIICCTTPSL
QQLNLQLPLKTKAFFMLDGIHSKYFDLIYVHNPVFKPFEKPVMISIGNENVLEI
KGNDIDPEAVKGEVLKVGNKSCETIYSDSKAVLCKVPNDLLKLNNELNIEWK
QAVSSTVLGKVIVQPDQNFTGLIAGVISISTIVLLLLGLFLWLKRKKQIKDLGSE
LVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGS
CRQVQYPLTDLSPMLTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVVIGPS
SLIVHFNEVIGRGHFGCVYHGTLLDNDDKKIHCAVKSLNRITDIGEVSQFLTEGI
IMKDFSHPNVLSLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIG
FGLQVAKGMKYLASKKFVHRDLAARNCMLDEKFTVKVADFGLARDMYDKE
YYSVHNKTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAPPY
PDVNTFDITVYLLQGRRLLQPEYCPDPLYEVMLKCWHPRAELRPSFSELVSRIS
AIFSTFIGEHYVHVNATYVNVKCVAPYPSLLSSQDNIDGEGDT

[0131] SEQ ID NO: 113 (Macaca mulatta, Rhesus cMET - NCBI Reference Sequence: NP_001162100.1)

MKAPAVLVPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETA
IQNVILHEHHIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPCQDCSSKA
NLSGGVWKDNINMALVVDTYYDDQLISCGSVNRGTCQRHVFPHNHTADIQSE
VHCIFSPQIEEPNQCPDCVVSALGAKVLSSVKDRFINFFVGNTINSSYFPHHPLH
SISVRRLKETKDGFMFLTDQSYIDVLPEFRDSYPIKYIHAFESNNFIYFLTVQRET
LNAQTFHTRIIRFCSLNSGLHSYMEMPLECILTEKRKKRSTKKEVFNILQAAYV
SKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDFFN
KIVNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEARRDEYRAEFTTALQRV
DLFMGQFSEVLLTSISTFVKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFLL
DSHPVSPEVIVEHPLNQNGYTLVVTGKKITKIPLNGLGCRHFQSCSQCLSAPPF
VQCGWCHDKCVRSEECPSGTWTQQICLPAIYKVFPTSAPLEGGTRLTICGWDF
GFRRNNKFDLKKTRVLLGNESCTLTLSESTMNTLKCTVGPAMNKHFNMSIIISN
GHGTTQYSTFSYVDPIITSISPKYGPMAGGTLLTLTGNYLNSGNSRHISIGGKTC
TLKSVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFSYREDPIVYEIHPTKSFIS
GGSTITGVGKNLHSVSVPRMVINVHEAGRNFTVACQHRSNSEIICCTTPSLQQL
NLQLPLKTKAFFMLDGILSKYFDLIYVHNPVFKPFEKPVMISMGNENVLEIKGN
DIDPEAVKGEVLKVGNKSCENIHLHSEAVLCTVPNDLLKLNSELNIEWKQAISS
TVLGKVIVQPDQNFTGLIAGVVSISIALLLLLGLFLWLKKRKQIKDLGSELVRY
DARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGSCRQV

QYPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVVIGPSSLIVHF
NEVIGRGHFGCVYHGTLLDNDGKKIHCAVKSLNRITDIGEVSQFLTEGIIMKDF
SHPNVLSLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIGFGLQV
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NKTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNT
FDITVYLLQGRRLLQPEYCPDPLYEVMLKCWHPKAEMRPSFSELVSRISAIFSTF
IGEHYVHVNATYVNVKCVAPYPSLLSSEDNADDEVDT

Example 6

[0132] Embodiments

A1. A binding agent that specifically binds to cMET, or a portion thereof, wherein the binding agent comprises a CDR-L1, CDR-L2 and a CDR-L3, each independently selected from a light chain variable domain selected from Table 4 or Table 5.

[0133] A2. A binding agent that specifically binds to cMET, or a portion thereof, wherein the binding agent comprises a CDR-H1, CDR-H2 and a CDR-H3, each independently selected from a heavy chain variable domain selected from Table 9 or Table 10.

[0134] A3. A binding agent that specifically binds to cMET, or a portion thereof, wherein the binding agent comprises (i) a CDR-L1, CDR-L2 and a CDR-L3, each independently selected from a light chain variable domain selected from Table 4 or Table 5 and (ii) a CDR-H1, CDR-H2 and a CDR-H3, each independently selected from a heavy chain variable domain selected from Table 9 or Table 10.

[0135] A4. A binding agent that specifically binds to CMET, or a portion thereof, wherein the binding agent comprises three CDRs of a light chain variable domain selected from the CDRs of Tables 1, 2 and 3, and three CDRs of a heavy chain variable domain selected from the CDRs of Tables 4, 5 and 6.

[0136] A5. A binding agent that specifically binds to CMET, or a portion thereof, wherein the binding agent comprises a CDR-L1 selected from Table 1, a CDR-L2 selected from Table 2, a CDR-L3 selected from Table 3, a CDR-H1 selected from Table 4, a CDR-H2 selected from Table 5 and a CDR-H3 selected from Table 6.

[0137] A6. A binding agent that specifically binds to CMET, or a portion thereof, wherein the binding agent comprises a CDR-L1 that is at least 80% identical to a CDR selected from Table 1, a CDR-L2 that is at least 80% identical to a CDR selected from Table 2, a CDR-L3 that is at least 80% identical to a CDR selected from Table 3, a CDR-H1 that is at least 80% identical to a CDR selected from Table 4, a CDR-H2 that is at least 80% identical to a CDR selected from Table 5 and a CDR-H3 that is at least 80% identical to a CDR selected from Table 6.

[0138] A7. The binding agent of any one of embodiments A1 to A6, wherein the binding agent is a recombinant monoclonal antibody.

[0139] A8. A pharmaceutical composition comprising:
a binding agent of any one of embodiments A1 to A7; and
a pharmaceutical acceptable excipient, diluent, additive or carrier.

[0140] A9. The pharmaceutical composition of embodiment A8, wherein the binding agent comprises a constant region of an IgG_1, IgG_2, IgG_3, or IgG_4.

[0141] A10. The pharmaceutical composition of embodiment A8 or A9, wherein the binding agent comprises a constant region of an IgD, IgE, IgA or IgM.

[0142] A11. The pharmaceutical composition of any one of embodiments A8 to A10, wherein the binding agent is humanized.

[0143] B1. A recombinant monoclonal antibody comprising:
a CDR-L1 that is at least 80% identical to a CDR selected from Table 1, a CDR-L2 that is at least 80% identical to a CDR selected from Table 2, a CDR-L3 that is at least 80% identical to a CDR selected from Table 3, a CDR-H1 that is at least 80% identical to a CDR selected from Table 4, a CDR-H2 that is at least 80% identical to a CDR selected from Table 5 and a CDR-H3 that is at least 80% identical to a CDR selected from Table 6, wherein the antibody specifically binds to an extracellular domain of human cMET.

[0144] B2. The antibody of embodiment B1, wherein the antibody is humanized, chimeric or CDR grafted.

[0145] C1. An antibody binding agent, pharmaceutical composition or antibody of any one of embodiments A1 to A11, B1, and B2, for use in treating a neoplastic disorder or cancer in a subject.

[0146] The entirety of each patent, patent application, publication or any other reference or document cited herein hereby is incorporated by reference. In case of conflict, the specification, including definitions, will control.

[0147] Citation of any patent, patent application, publication or any other document is not an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

[0148] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

[0149] All of the features disclosed herein may be combined in any combination. Each feature disclosed in the specification may be replaced by an alternative feature serving a same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, disclosed features (e.g., antibodies) are an example of a genus of equivalent or similar features.

[0150] As used herein, all numerical values or numerical ranges include integers within such ranges and fractions of the values or the integers within ranges unless the context clearly indicates otherwise. Further, when a listing of values is described herein (e.g., about 50%, 60%, 70%, 80%, 85% or 86%) the listing includes all intermediate and fractional values thereof (e.g., 54%, 85.4%). Thus, to illustrate, reference to 80% or more identity, includes 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94% etc., as well as 81.1%, 81.2%, 81.3%, 81.4%, 81.5%, etc., 82.1%, 82.2%, 82.3%, 82.4%, 82.5%, etc., and so forth.

[0151] Reference to an integer with more (greater) or less than includes any number greater or less than the reference number, respectively. Thus, for example, a reference to less than 100, includes 99, 98, 97, etc. all the way down to the number one (1); and less than 10, includes 9, 8, 7, etc. all the way down to the number one (1).

[0152] As used herein, all numerical values or ranges include fractions of the values and integers within such ranges and fractions of the integers within such ranges unless the context clearly indicates otherwise. Thus, to illustrate, reference to a numerical range, such as 1-10 includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, as well as 1.1, 1.2, 1.3, 1.4, 1.5, etc., and so forth. Reference to a range of 1-50 therefore includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc., up to and including 50, as well as 1.1, 1.2, 1.3, 1.4, 1.5, etc., 2.1, 2.2, 2.3, 2.4, 2.5, etc., and so forth.

[0153] Reference to a series of ranges includes ranges which combine the values of the boundaries of different ranges within the series. Thus, to illustrate reference to a series of ranges, for example, of 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-75, 75-100, 100-150, 150-200, 200-250, 250-300, 300-400, 400-500, 500-750, 750-1,000, 1,000-1,500, 1,500-2,000, 2,000-2,500, 2,500-3,000, 3,000-3,500, 3,500-4,000, 4,000-4,500, 4,500-5,000, 5,500-6,000, 6,000-7,000, 7,000-8,000, or 8,000-9,000, includes ranges of 10-50, 50-100, 100-1,000, 1,000-3,000, 2,000-4,000, etc.

[0154] Modifications can be made to the foregoing without departing from the basic aspects of the technology. Although the technology has been described in substantial detail with reference to one or more specific embodiments, those of ordinary skill in the art will recognize that changes can be made to the embodiments specifically disclosed in this application, yet these modifications and improvements are within the scope and spirit of the technology.

[0155] The invention is generally disclosed herein using affirmative language to describe the numerous embodiments and aspects. The invention also specifically includes embodiments in which particular subject matter is excluded, in full or in part, such as substances or materials, method steps and conditions, protocols, or procedures. For example, in certain embodiments or aspects of the invention, materials and/or method steps are excluded. Thus, even though the invention is generally not expressed herein

in terms of what the invention does not include aspects that are not expressly excluded in the invention are nevertheless disclosed herein.

[0156] The technology illustratively described herein suitably can be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising," "consisting essentially of," and "consisting of" can be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and use of such terms and expressions do not exclude any equivalents of the features shown and described or segments thereof, and various modifications are possible within the scope of the technology claimed. The term "a" or "an" can refer to one of or a plurality of the elements it modifies (e.g., "a reagent" can mean one or more reagents) unless it is contextually clear either one of the elements or more than one of the elements is described. The term "about" as used herein refers to a value within 10% of the underlying parameter (i.e., plus or minus 10%), and use of the term "about" at the beginning of a string of values modifies each of the values (i.e., "about 1, 2 and 3" refers to about 1, about 2 and about 3). For example, a weight of "about 100 grams" can include weights between 90 grams and 110 grams. The term, "substantially" as used herein refers to a value modifier meaning "at least 95%", "at least 96%","at least 97%","at least 98%", or "at least 99%" and may include 100%. For example, a composition that is substantially free of X, may include less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% of X, and/or X may be absent or undetectable in the composition.

[0157] Thus, it should be understood that although the present technology has been specifically disclosed by representative embodiments and optional features, modification and variation of the concepts herein disclosed can be resorted to by those skilled in the art, and such modifications and variations are considered within the scope of this technology.

Claims

[Claim 1] A binding agent comprising:
a CDR-L1, a CDR-L2 and a CDR-L3 which are three polypeptide sequences of a light chain complementarity determining region (CDR-L),
wherein the CDR-L1 is selected from SEQ ID Nos 1-15, the CDR-L2 is selected from SEQ ID Nos 16-25 and the CDR-L3 is selected from SEQ ID Nos 26-36, and
wherein the binding agent specifically binds to an extracellular domain of mesenchymal epithelial transition factor (cMET).

[Claim 2] A binding agent comprising:
a CDR-H1, a CDR-H2 and a CDR-H3 which are three polypeptide sequences of a heavy chain complementarity determining region (CDR-H),
wherein the CDR-H1 is selected from SEQ ID Nos 50-61, the CDR-H2 is selected from SEQ ID Nos 62-78 and the CDR-H3 is selected from SEQ ID Nos 79-93, and
wherein the binding agent specifically binds to an extracellular domain of mesenchymal epithelial transition factor (cMET).

[Claim 3] A binding agent comprising:
a CDR-L1 selected from SEQ ID NOs. 1-15, a CDR-L2 selected from SEQ ID NOs. 16-25, a CDR-L3 selected from SEQ ID NOs. 26-36, a CDR-H1 selected from SEQ ID Nos 50-61, a CDR-H2 selected from SEQ ID Nos 62-78, and a CDR-H3 selected from SEQ ID Nos 79-93
wherein the binding agent specifically binds to an extracellular domain of mesenchymal epithelial transition factor (cMET).

[Claim 4] The binding agent of claim 1 or 3, wherein the CDR-L1 is selected from SEQ ID NOs 2, 4, 6, 8, 10, 12 and 14.

[Claim 5] The binding agent of claim 1, 3 or 4, wherein the CDR-L2 is selected from SEQ ID NOs 17, 19, 21, 23 and 25.

[Claim 6] The binding agent of claim 1, 3, 4 or 5, wherein the CDR-L3 is selected from SEQ ID NOs 27, 29, 31, 33 and 35.

[Claim 7] The binding agent of claim 2 or 3, wherein the CDR-H1is selected from SEQ ID NOs 51, 53, 55, 57 and 59.

[Claim 8] The binding agent of claim 2, 3 or 7, wherein the CDR-H2 selected from SEQ ID Nos 62-78 is selected from SEQ ID NOs 63, 65, 67, 69, 73 and 75.

[Claim 9] The binding agent of claim 2, 3 or 8, wherein the CDR-H3 is selected from SEQ ID NOs 80, 82, 84, 86, 88, 91 and 93.

[Claim 10] The binding agent of any one of claims 1 to 9, wherein the binding agent is an antibody, or a binding fragment thereof.

[Claim 11] The binding agent of claim 10, wherein the binding agent is a monoclonal antibody, or binding fragment thereof.

[Claim 12] The binding agent of any one of claims 1 to 11, wherein the binding agent comprises a constant region of an IgG_1, IgG_2, IgG_3, or IgG_4.

[Claim 13] The binding agent of any one of claims 1 to 11, wherein the binding agent comprises a constant region of an IgD, IgE, IgA or IgM.

[Claim 14] The binding agent of any one of claims 1 to 13, wherein the binding agent is humanized.

[Claim 15] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises at least one humanized or human framework region.

[Claim 16] The binding agent of claim 15, wherein the binding agent comprises at least three humanized or human framework regions.

[Claim 17] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises at least one mouse framework region.

[Claim 18] The binding agent of claim 17, wherein the binding agent comprises at least three mouse framework regions.

[Claim 19] The binding agent of any one of claims 1 to 18, wherein the binding agent is a Fab, Fab', F(ab')2, Fv or scFV fragment of an antibody.

[Claim 20] The binding agent of any one of claims 1 to 19, wherein the binding agent consists of a single chain polypeptide.

[Claim 21] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises a variable light chain region having an amino acid sequence selected from SEQ ID NOS 37-44.

[Claim 22] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises a variable heavy chain region having an amino acid sequence selected from SEQ ID NOS 94-103.

[Claim 23] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises a light chain sequence selected from SEQ ID NOS 45-49.

[Claim 24] The binding agent of any one of claims 1 to 13, wherein the binding agent comprises a heavy chain sequence selected from SEQ ID NOS 104-108.

[Claim 25] The binding agent of claim 23 or 24, wherein the light chain sequence selected from SEQ ID NOS 45-49 and/or the heavy chain sequence

selected from SEQ ID NOS 104-108 comprises one to five amino acid modifications selected from an amino acid addition, an amino acid deletion and an amino acid substitution.

[Claim 26] The binding agent of any one of claims 1 to 25, wherein the binding agent induces internalization of cMET on a human cancer cell.

[Claim 27] The binding agent of any one of claims 1 to 25, wherein the binding agent induces degradation of cMET on a human cancer cell.

[Claim 28] The binding agent of any one of claims 1 to 25, wherein the binding agent is not a cMET agonist.

[Claim 29] The binding agent of any one of claims 1 to 28, wherein the binding agent binds specifically to a mammalian cMET.

[Claim 30] The binding agent of claim 29, wherein the mammalian cMET is a human cMET, monkey cMET or rat cMET.

[Claim 31] The binding agent of claim 30, wherein the binding agent binds specifically to a human cMET, monkey cMET and rat cMET.

[Claim 32] The binding agent of claim 30, wherein the binding agent binds specifically to human cMET.

[Claim 33] The binding agent of any one of claims 1 to 32, wherein the binding agent specifically binds to the extracellular domain of a wild type cMET.

[Claim 34] The binding agent of any one of claims 1 to 32, wherein the binding agent specifically binds to the extracellular domain of a cMET variant.

[Claim 35] The binding agent of claim 34, wherein the cMET variant comprises an E168D or an N375S variant of cMET.

[Claim 36] The binding agent of any one of claims 1 to 34, wherein the binding agent specifically binds the extracellular domain of human cMET with a KD of 10 nM or less.

[Claim 37] The binding agent of claim 36, wherein the binding agent specifically binds the extracellular domain of human cMET with a KD of 1 nM or less.

[Claim 38] The binding agent of any one of claims 1 to 37, wherein the binding agent comprises an anti-neoplastic agent.

[Claim 39] A composition comprising a first binding agent that is the binding agent of any one of claims 1 to 38, and a second binding agent that does not bind specifically to cMET.

[Claim 40] The composition of claim 39, wherein a first binding agent is the binding agent that specifically binds to the extracellular domain of cMET and the second binding agent is conjugated to the first binding

agent.

[Claim 41] A method of treating a subject having a neoplastic disorder or cancer comprising:
a) providing a subject having, or suspected of having, a neoplastic disorder; and
b) administering a therapeutically effective amount of the binding agent of any one of claims 1 to 38 or the composition of any one of claims 39 to 40 to the subject.

[Claim 42] The method of claim 41, wherein the binding agent specifically binds to the extracellular domain of cMET expressed on one or more cells of the subject.

[Claim 43] The method of claim 41 or 42, wherein the binding agent inhibits mitosis of, and/or induces death of the one or more cells expressing cMET.

[Claim 44] The method of any one of claims 41 to 43, wherein the neoplastic disorder or cancer comprises a lung carcinoma, breast carcinoma, ovarian carcinoma, kidney carcinoma, colorectal carcinoma, gastric carcinoma, thyroid carcinoma, pancreas carcinoma, neuroblastoma, or a squamous cell carcinoma of the head and neck, cervical cancer, hepato-cellular cancer, sarcomas, mesothelioma, glioblastoma, multiple myeloma, melanoma, prostate and esophageal carcinoma.

[Claim 45] A pharmaceutical composition comprising the binding agent of any one of claims 1 to 38, and a pharmaceutically acceptable excipient, diluent, additive or carrier.

[Claim 46] The pharmaceutical composition of claim 45, wherein the additive comprises a preservative.

[Claim 47] The pharmaceutical composition of claim 45 or 46, wherein the diluent comprises phosphate buffered saline.

[Claim 48] The pharmaceutical composition of any one of claims 45 to 47, wherein the excipient comprises sodium citrate dehydrate or polyoxyethylene-sorbitan-20 mono-oleate (polysorbate 80).

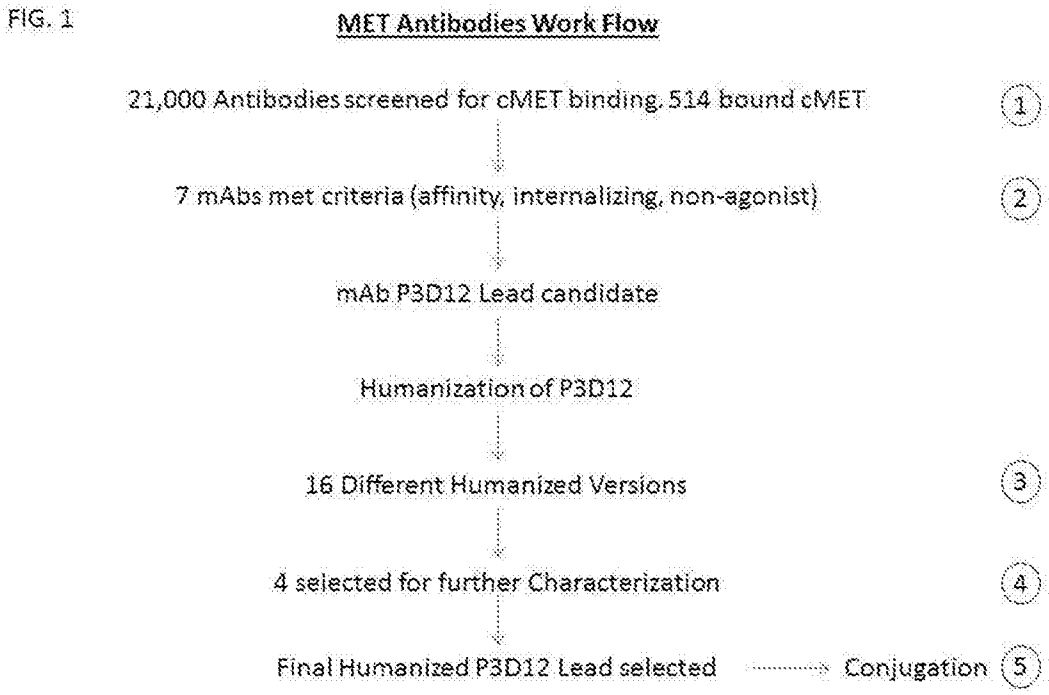
[Claim 49] The pharmaceutical composition any one of claims 45 to 48, wherein the carrier comprises a recombinant protein.

[Claim 50] The pharmaceutical composition of any one of claims 45 to 49, wherein the composition is sterile.

[Claim 51] The pharmaceutical composition of any one of claims 45 to 50, wherein the composition is formulated as a sterile, lyophilized powder suitable for intravenous administration to a mammal.

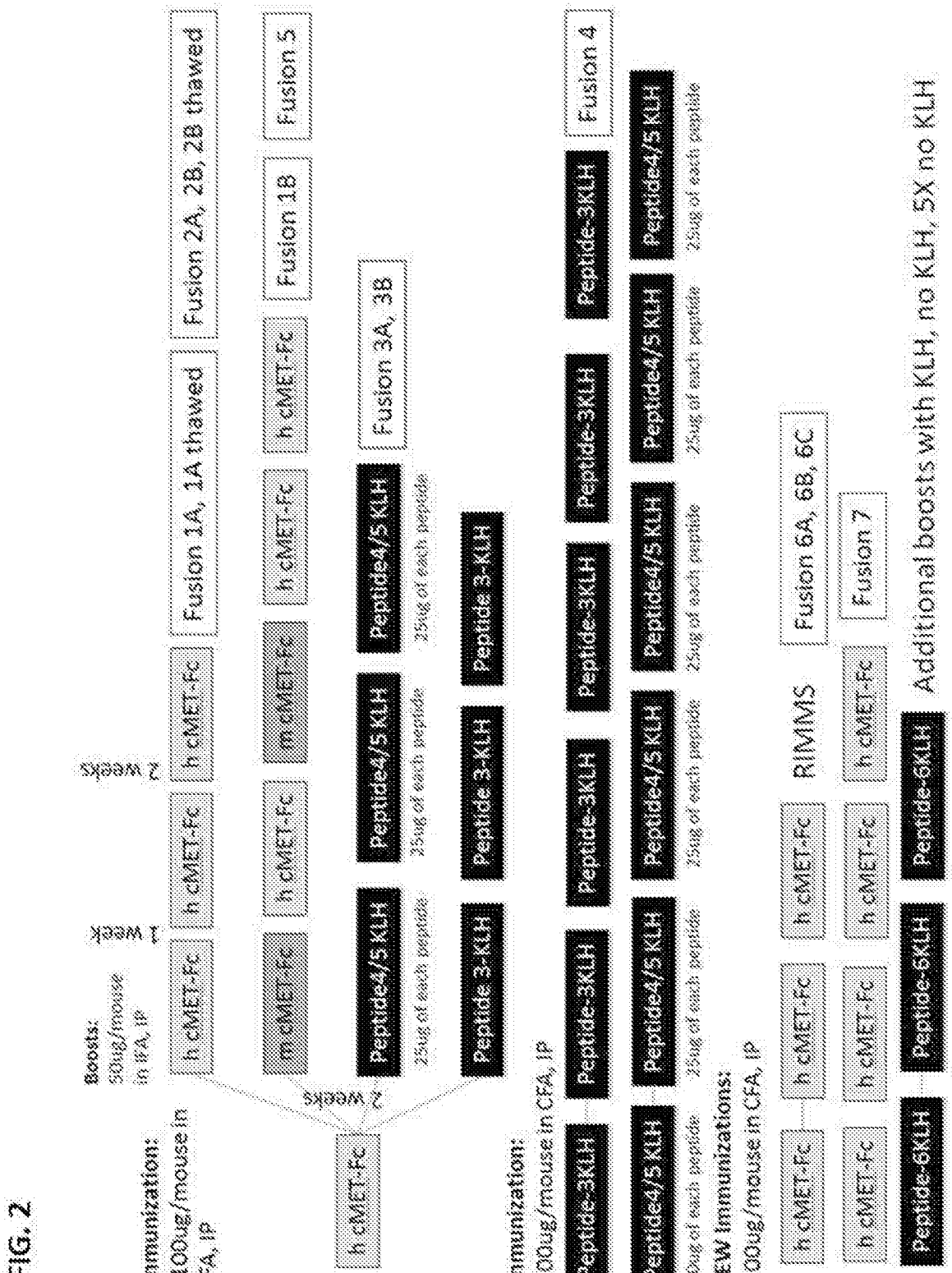
[Fig. 1]

FIG. 1


MET Antibodies Work Flow
21,000 Antibodies screened for cMET binding. 514 bound cMET
1
7 mAbs met criteria (affinity, internalizing, non-agonist)
2
mAb P3D12 Lead candidate
Humanization of P3D12
16 Different Humanized Versions
3
4 selected for further Characterization
4
Final Humanized P3D12 Lead selected
Conjugation
5

[Fig. 2]

FIG. 2


Immunization:
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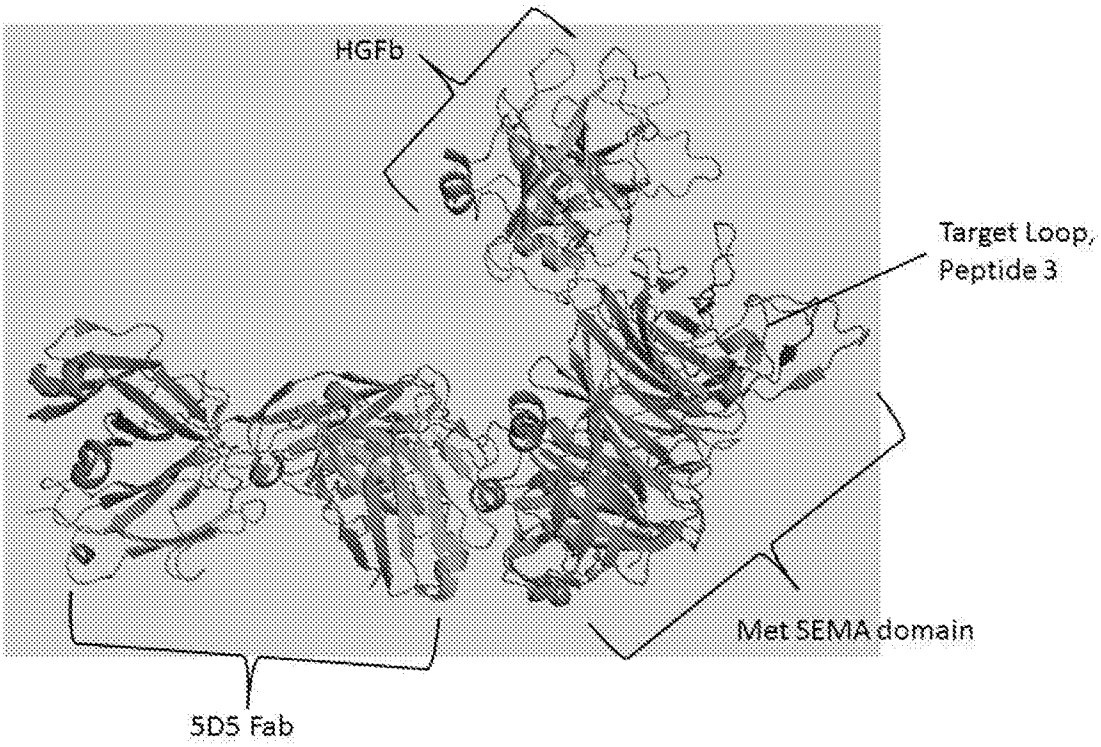
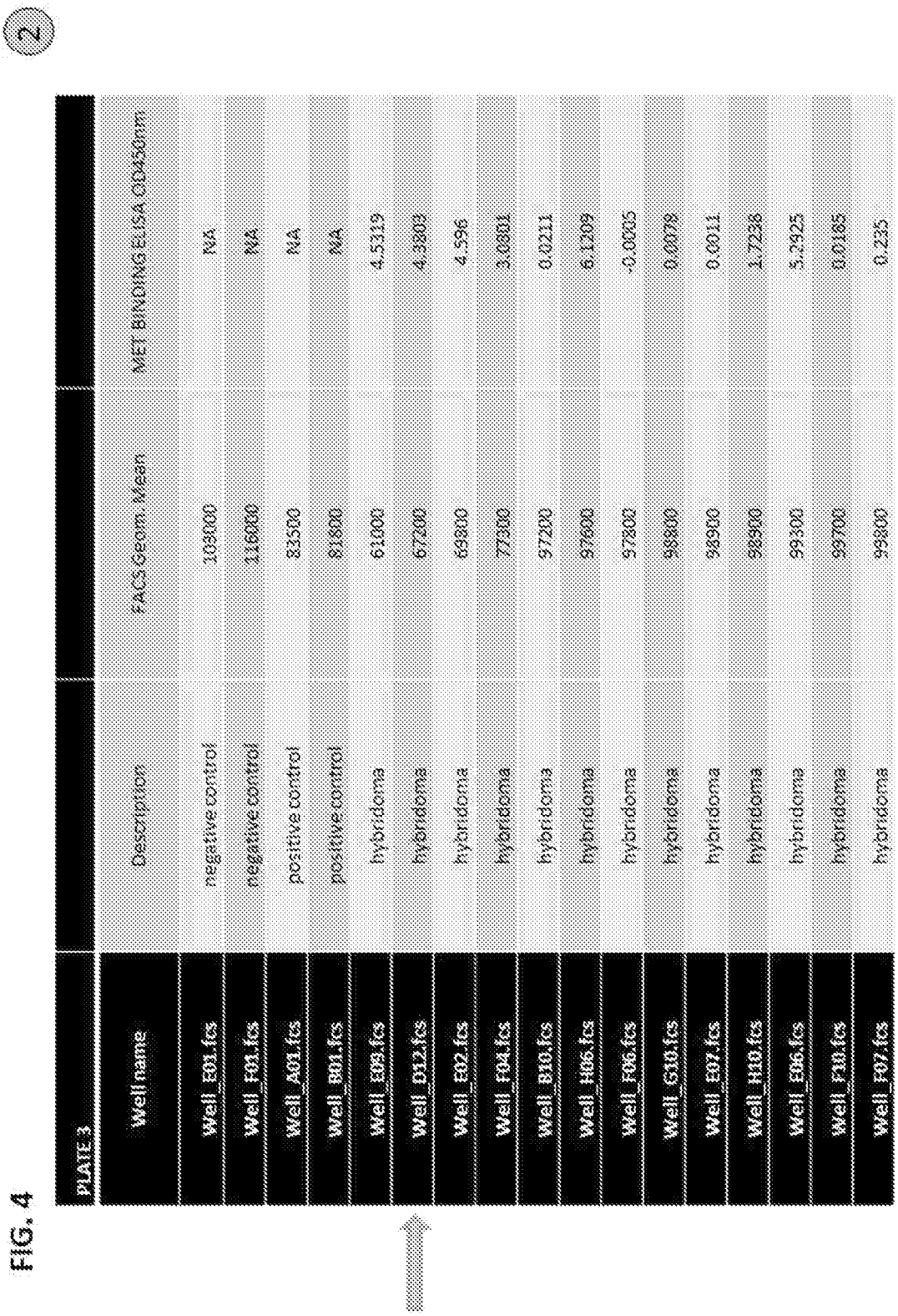
Boosts:
50ug/mouse in IFA, IP
1 week
2 weeks
h cMET-Fc
h cMET-Fc
h cMET-Fc
Fusion 1A, 1A thawed
Fusion 2A, 2B, 2B thawed
m cMET-Fc
h cMET-Fc
m cMET-Fc
h cMET-Fc
h cMET-Fc
Fusion 1B
Fusion 5
2 weeks
h cMET-Fc
Peptide4/5 KLH
25ug of each peptide
Peptide4/5 KLH
25ug of each peptide
Fusion 3A, 3B
Peptide 3-KLH
Peptide 3-KLH
Immunization:
100ug/mouse in CFA, IP
Peptide-3KLH
Peptide-3KLH
Peptide-3KLH
Peptide-3KLH
Peptide-3KLH
Fusion 4
Peptide4/5 KLH
Peptide4/5 KLH
Peptide4/5 KLH
Peptide4/5 KLH
Peptide4/5 KLH
50ug of each peptide
25ug of each peptide
25ug of each peptide
25ug of each peptide
25ug of each peptide
NEW Immunizations:
100ug/mouse in CFA, IP
h cMET-Fc
h cMET-Fc
h cMET-Fc
h cMET-Fc
RIMMS
Fusion 6A, 6B, 6C
h cMET-Fc
h cMET-Fc
h cMET-Fc
Fusion 7
Peptide-6KLH
Peptide-6KLH
Peptide-6KLH
Additional boosts with KLH, no KLH, 5X no KLH

[Fig. 3]

FIG. 3



[Fig. 4]


2
PLATE 3
Well name
Description
FACS Geom. Mean
MET BINDING ELISA OD450nm
Well_E01.fcs
negative control
103000
NA
Well_F01.fcs
negative control
116000
NA
Well_A01.fcs
positive control
83500
NA
Well_B01.fcs
positive control
81800
NA
Well_E08.fcs
hybridoma
61000
4.5319
Well_D12.fcs
hybridoma
67200
4.3809
Well_E02.fcs
hybridoma
69800
4.596
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hybridoma
77300
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Well_B10.fcs
hybridoma
97200
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hybridoma
97600
6.1209
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hybridoma
97800
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Well_G10.fcs
hybridoma
98800
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Well_E07.fcs
hybridoma
98900
0.0011
Well_H10.fcs
hybridoma
98900
1.7238
Well_E06.fcs
hybridoma
99300
5.2925
Well_F10.fcs
hybridoma
99700
0.0185
Well_F07.fcs
hybridoma
99800
0.235

FIG. 4

[Fig. 5]

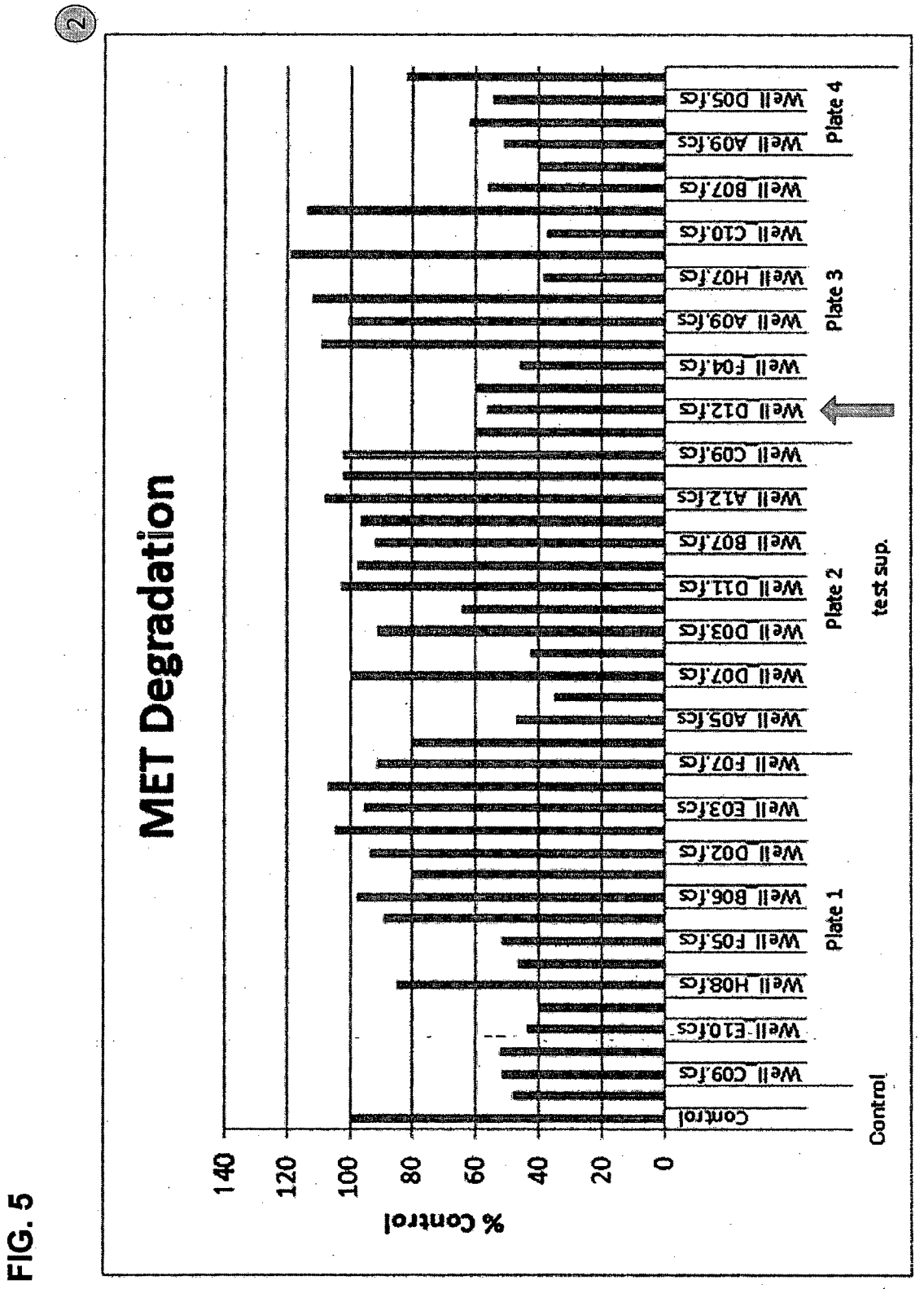
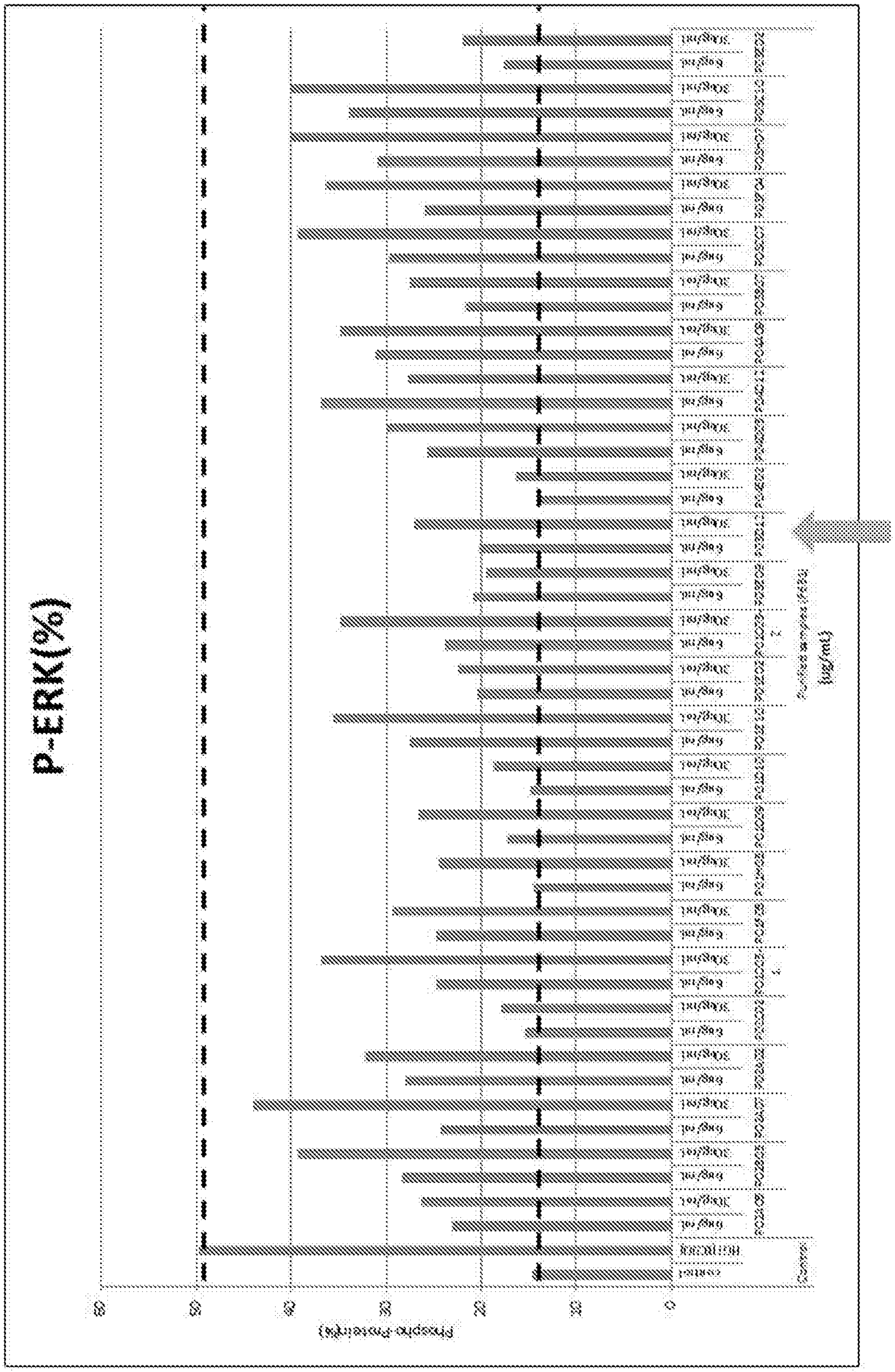

MET Degradation
% Control
140
120
100
80
60
40
20
0
Control
Well C09.fcs
Well E10.fcs
Well H08.fcs
Well F05.fcs
Well B06.fcs
Well D02.fcs
Well E03.fcs
Well F07.fcs
Well A05.fcs
Well D07.fcs
Well D03.fcs
Well D11.fcs
Well B07.fcs
Well A12.fcs
Well C09.fcs
Well D12.fcs
Well F04.fcs
Well A09.fcs
Well H07.fcs
Well C10.fcs
Well B07.fcs
Well A09.fcs
Well D05.fcs
Plate 1
Plate 2
Plate 3
Plate 4
test sup.

FIG. 5

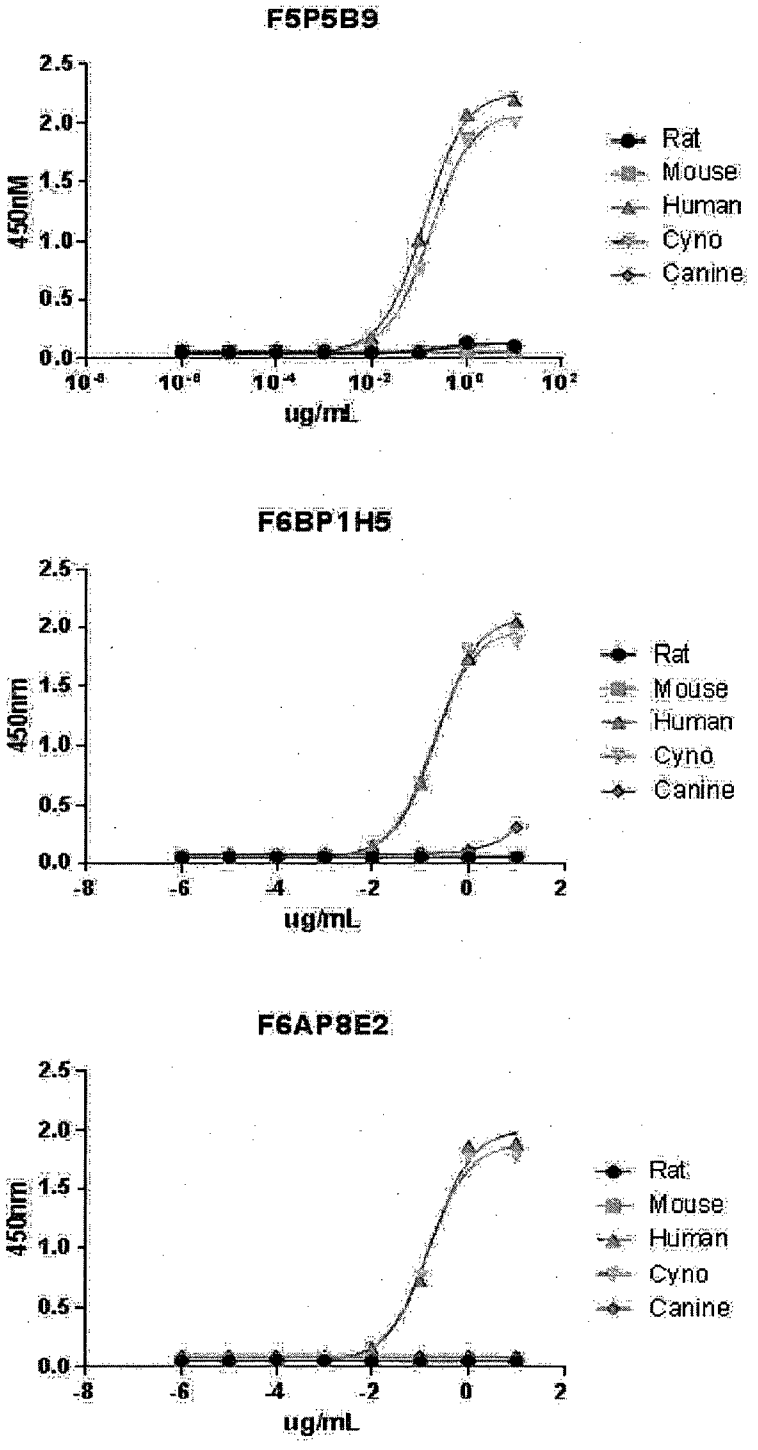
[Fig. 6]

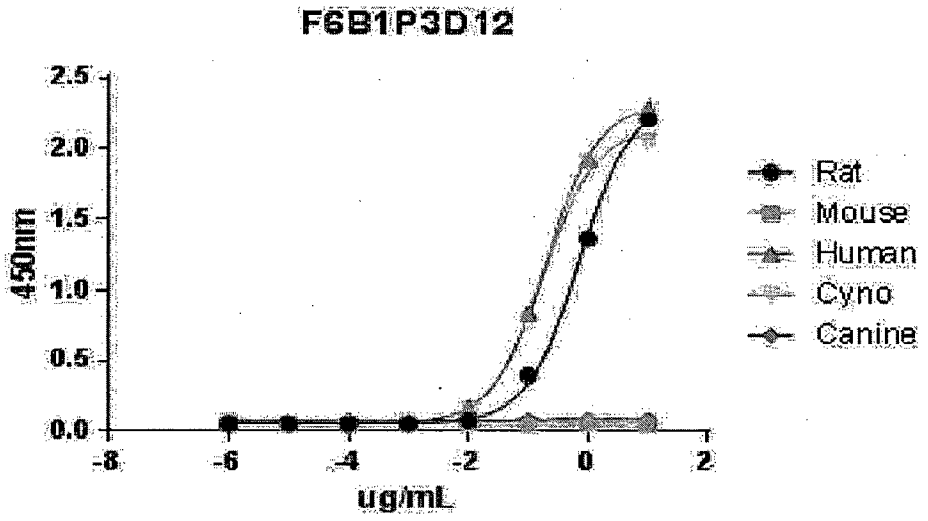
FIG. 6

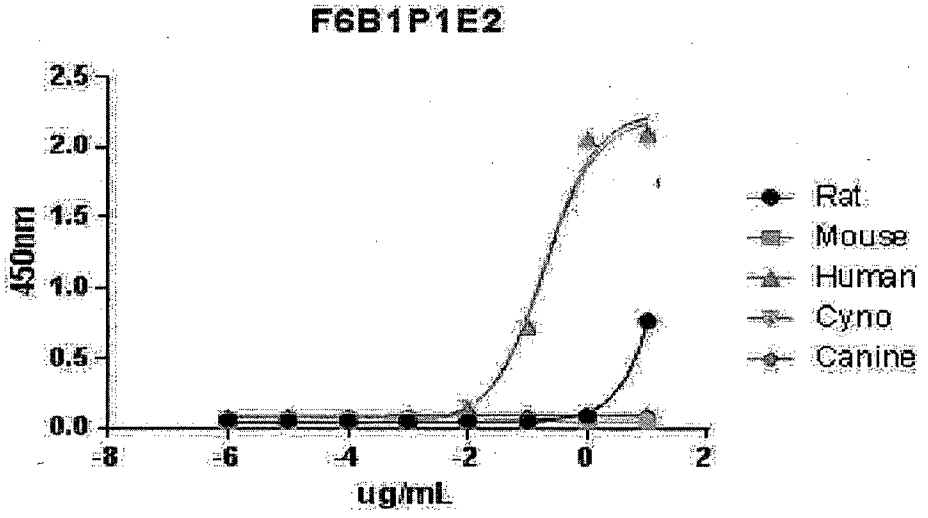


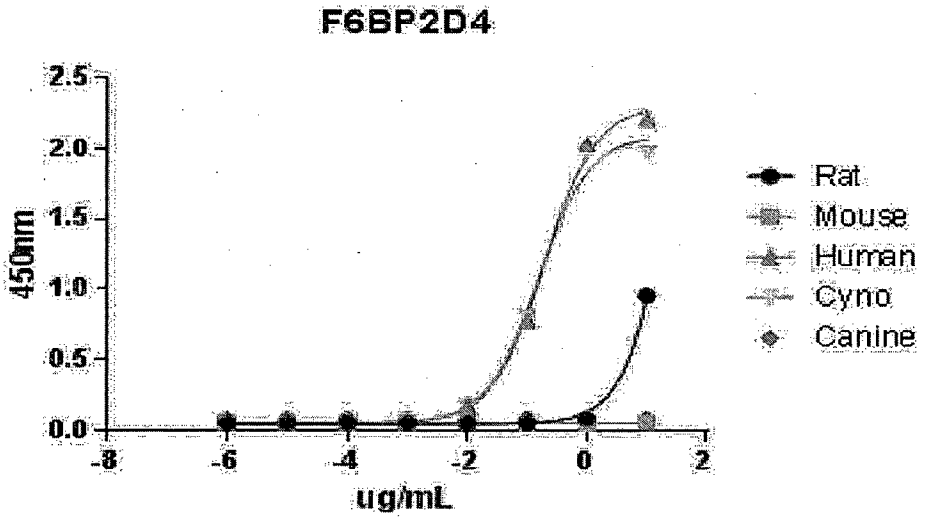
[Fig. 7]

FIG. 7 Anti-Met antibodies species cross-reactivity




F6B1P3D12
450nm
2.5
2.0
1.5
1.0
0.5
0.0
-8
-6
-4
-2
0
2
ug/mL
Rat
Mouse
Human
Cyno
Canine


F6B1P1E2
450nm
2.5
2.0
1.5
1.0
0.5
0.0
-8
-6
-4
-2
0
2
ug/mL
Rat
Mouse
Human
Cyno
Canine


F6BP2D4
450nm
2.5
2.0
1.5
1.0
0.5
0.0
-8
-6
-4
-2
0
2
ug/mL
Rat
Mouse
Human
Cyno
Canine

[Fig. 8]

FIG. 8A
Sequences of top 9 murine clones. Two clones were duplicated giving 7 unique sequences
Light Chain
SEQ ID NO:
F5_P5_B9_L (1) --DVLMTQTPLSLPVSLGDQASISCRSSQ-TIVHGTGNT-YLEWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPYTFGGGTKLEIKR 37
F6A_P8_E2_L (1) --DIVMTQSPKSMSMSVGERVTLSCKAS------ENVGT-YVSWYQQKPDQSPKLLIYGASNRYTGVPDRFTGSGSATDFTLTISSVQAEDLADYHCGQSYSYPLTFGAGTKLELKR 38
F6AP12F12_L (1) --DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSINQKN-YLAWYQQIPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISRVKAEDLALYYCQQYYTYPLTFGAGTKLELKR 39
F6B_P1_H5_L (1) RCDIQMTQSPASLSVSVGETVTITCRASENIYN------TLAWYLQKGKSPQLLVYAATNLADGVPSRFSGSGSGTQYSLKINSLQSEDFGSYYCQHFWGTPYTFGGGTKLEIKR 40
F6B1_P3_D12_L (1) --QIVLTQSPAIMSASPGEKVTLTCSASSSVTS------NYLYWYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAASYFCHQWSSYPPTFGSGTKLEIKR 41
F6B1_P3_E9_L (1) --QIVLTQSPAIMSASPGEKVTLTCSASSSWTS------NYLYWYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAASYFCHQWSSYPPTFGSGTKLEIKR 41
F6B_P2_D4_L (1) --QIVLTQSPAIMSASPGEKVTLTCSASSSVSS------NYLYWYQQKPGSSPKLWIYSTSNLASGVPVRFSGSGSGTSYSLTISSMEAEDAASYFCHQWSSYPPTFGSGTKLEIKR 42
F6B1_P1_E2_L (1) --QIVLTQSPAIMSASPGEKVTLTCSASSSVSS------NYLYWYHQKPGSSPKLWIYSTSNLASGVPVRFSGSGSGTSYSLTISSMEAEDAASYFCHQWSSYPPTFGSGTKLEIKR 43
F6B_P3_E2_L (1) --QIVLTQSPAIMSASPGEKVTLTCSASSSVSS------NYLYWYHQKPGSSPKLWIYSTSNLASGVPVRFSGSGSGTSYSLTISSMEAEDAASYFCHQWSSYPPTFGSGTKLEIKR 43
LC F6B1P1E2=F6BP3E2
LC F6B1P3D12=F6B1P3E9
FIG. 8B
Heavy Chain
SEQ ID NO:
F5_P5_B9_H (1) ---QVQLKESGPGLVAPSQSLSITCTVSGFSLTNYGVNWVRQPPGKGLEWLGLIWG---GGDTDYNSALKSRLSISKDNSKSQVFLKMETNSLQTDDTARYYCAR--------DYYGFDYWGQGTTLTVSS 94
F6A_P12_F12_H (1) ---EVKLVESGGGLVQPGGSLRLSCATSGFTFTDYYMSWVRQPPGKALEWLGFIRNKANGYTTKYSASVKGRFTISRDNSQS--ILYLQMNTLRAEDSATYYCSK--------DRGYFDYWGQGTTLTVSS 95
F6A_P8_E2_H (1) VNSEVQLQQSGAELVRPGALVKLSCKASGFNINDYFMHWVKQRPEQGLEWIGWIDP--ENGNTIYDPKFQGKASITADTSSN--TAYLQLSSLTSEDTAVYYCARGGNYLRESYYYAMDYWGQGTSVTVSS 96
F6B_P1_H5_H (1) VLSEVLLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHGKSLEWIGDINP--NNGGTIYNQKFKGKATLTVDKSSS--TAYMELRSLTSEDTAVYYRARGDYYGSSRYYYAMDYWGQGTSVTVSS 97
F6B1_P3_D12_H_79_13 (1) ---QVQLQQSGAELAKPGASVKMSCRASGYTFTSYWMHWVKQRPGQGLDWIGYIKP--STDNTEYNQKFKDKATLTADKSSS--TAYMQLSSLTSEDSAVYYCAR--SYGN---YPLMDYWGQGTSVTVSS 98
F6B1P3E9_H (1) ---QVQLQQSGAELAKPGASVKMSCRASGYTFTSYWMHWVKQRPGQGLDWIGYIKP--STDNTEYNQKFKDKATLTADKSSS--TAYMQLSSLTSEDSAVYYCAR--SYGN---YPLMDYWGQGTSVTVSS 99
F6B1_P1_E2_H_78_19 (1) ---QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWMHWVKQRPGQGLEWIGYINP--STDYTEYNQKFKDKATLTADKSST--TAYMQLSSLTSEDSAVYYCVR--SYGN---YPLMDYWGQGTSVTVSS 100
F6B_P3_E2_H (1) ---QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWMHWVKQRPGQGLEWIGYINP--STDYTEYNQKFKDKATLTADKSST--TAYMQLSSLTSEDSAVYYCVR--SYGN---YPLMDYWGQGTSVTVSS 101
F6B_P2_D4_H (1) ---QVQLQQSGAELAKPGASVKMSCKASGYTFTSYWMHWVKQRPGQGLEWIGYINP--STDYIEYNQKFKDKATLTAGKSSS--TAYMQLSSLTSEDSAVYYCAR--SYGN---FPLMDYWGQGTSVTVSS 102
HC F6B1P3D12H7913=F6B1P3E9
HC F6B1P1E2H7819=F6BP3E2

[Fig. 9]

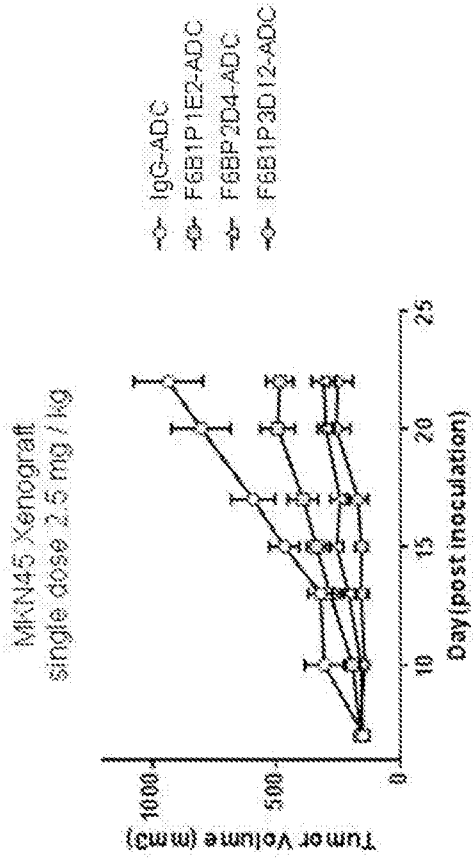


FIG. 9A

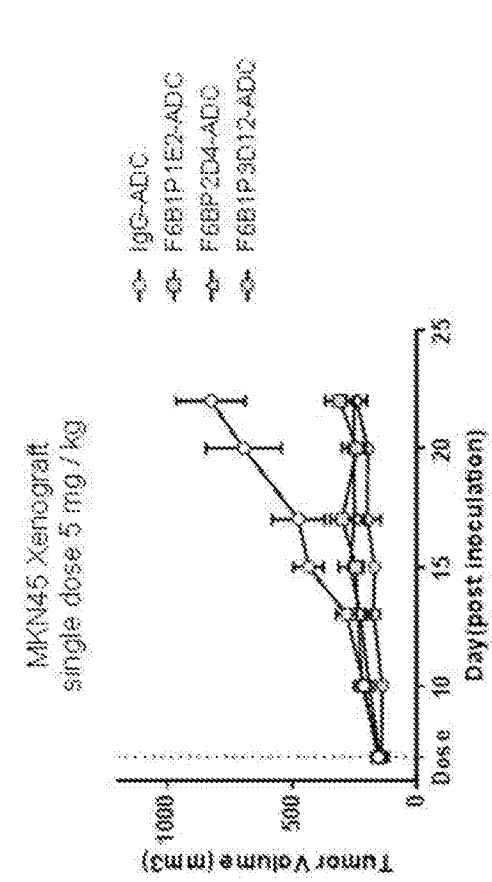


FIG. 9B

[Fig. 10]

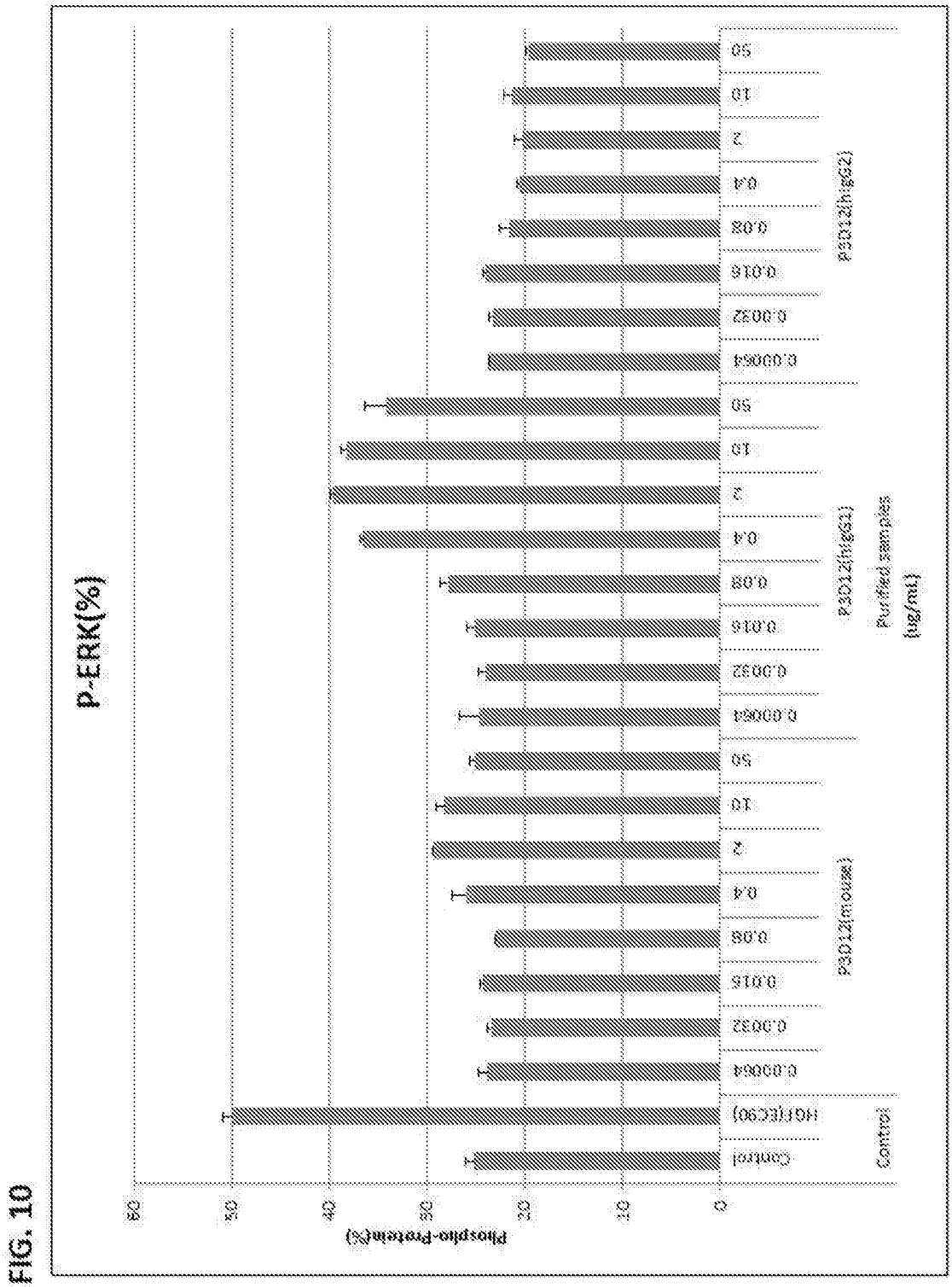

P-ERK(%)
Phospho-Protein(%)
80
60
40
20
0
Control
Control
HGF(EC90)
P3D12(mouse)
0.00064
0.0032
0.016
0.08
0.4
2
10
50
P3D12(higG1)
0.00064
0.0032
0.016
0.08
0.4
2
10
50
P3D12(higG2)
0.00064
0.0032
0.016
0.08
0.4
2
10
50
Purified samples
(ug/ml)

FIG. 10

[Fig. 11]

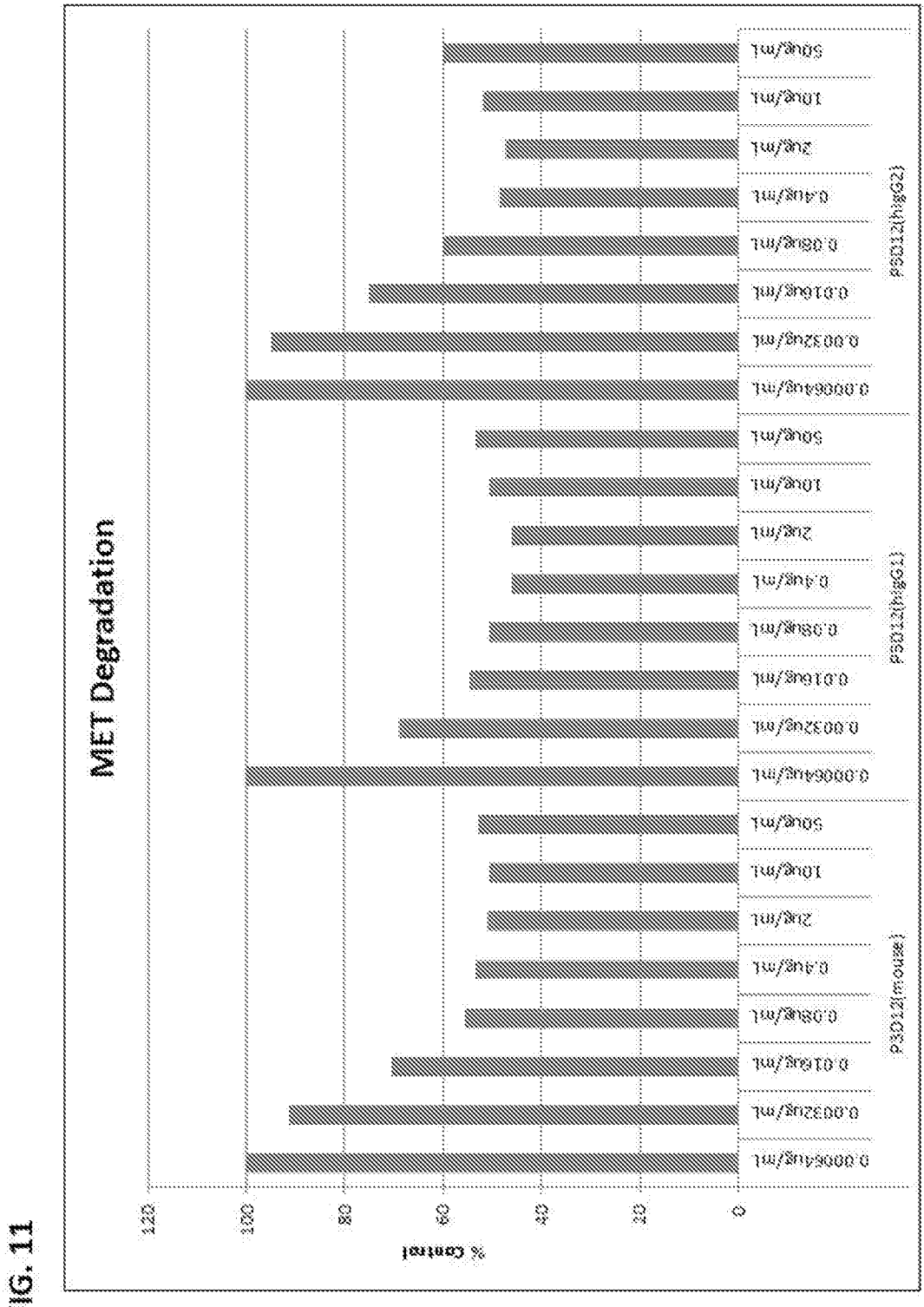

MET Degradation
% control
120
100
80
60
40
20
0
P3D12(mouse)
0.0064ug/mL
0.032ug/mL
0.16ug/mL
0.8ug/mL
4ug/mL
2ug/mL
10ug/mL
50ug/mL
P3D12(hIgG1)
0.0064ug/mL
0.032ug/mL
0.16ug/mL
0.8ug/mL
4ug/mL
2ug/mL
10ug/mL
50ug/mL
P3D12(hIgG2)
0.0064ug/mL
0.032ug/mL
0.16ug/mL
0.8ug/mL
4ug/mL
2ug/mL
10ug/mL
50ug/mL

FIG. 11

[Fig. 12]

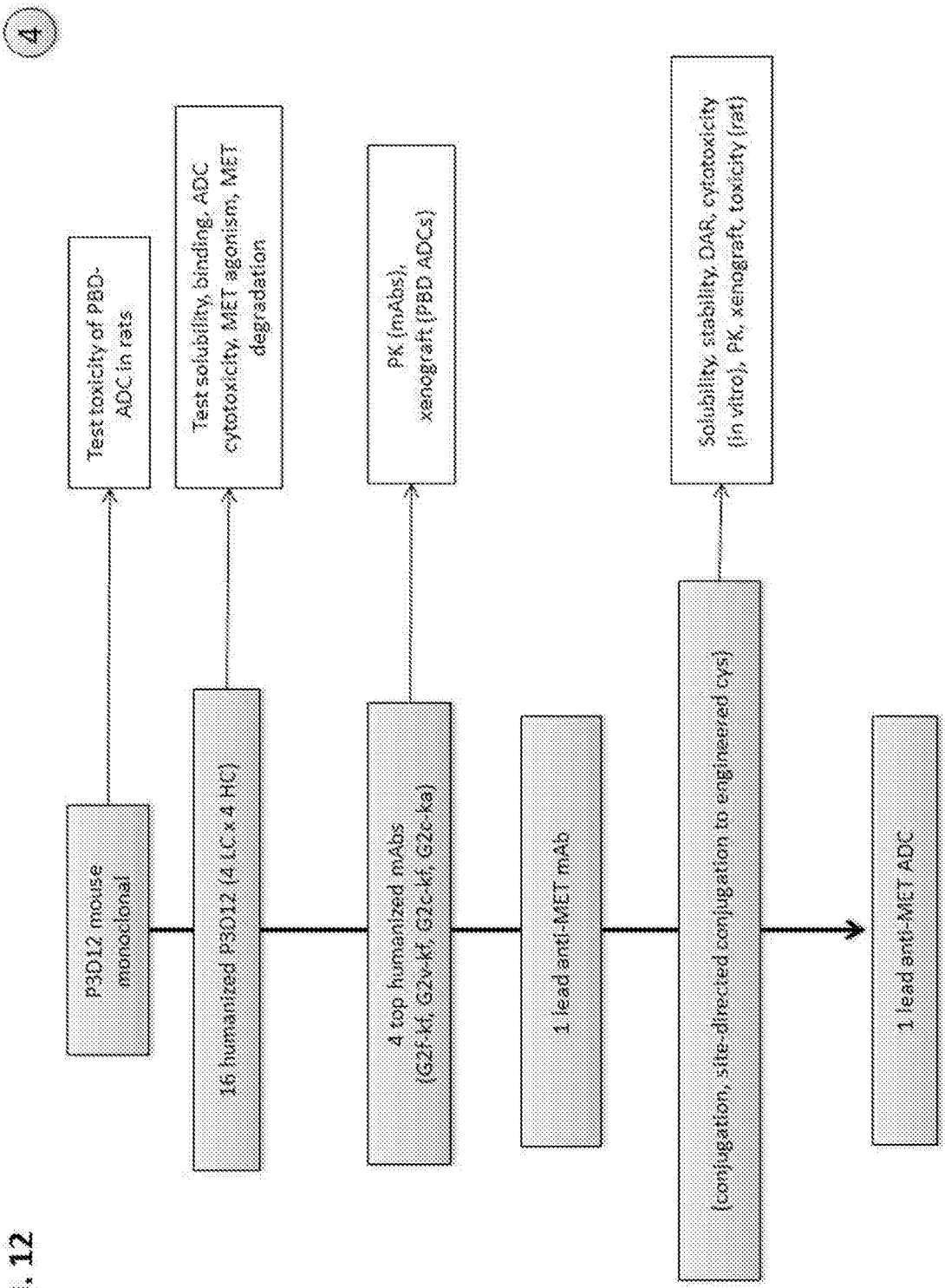
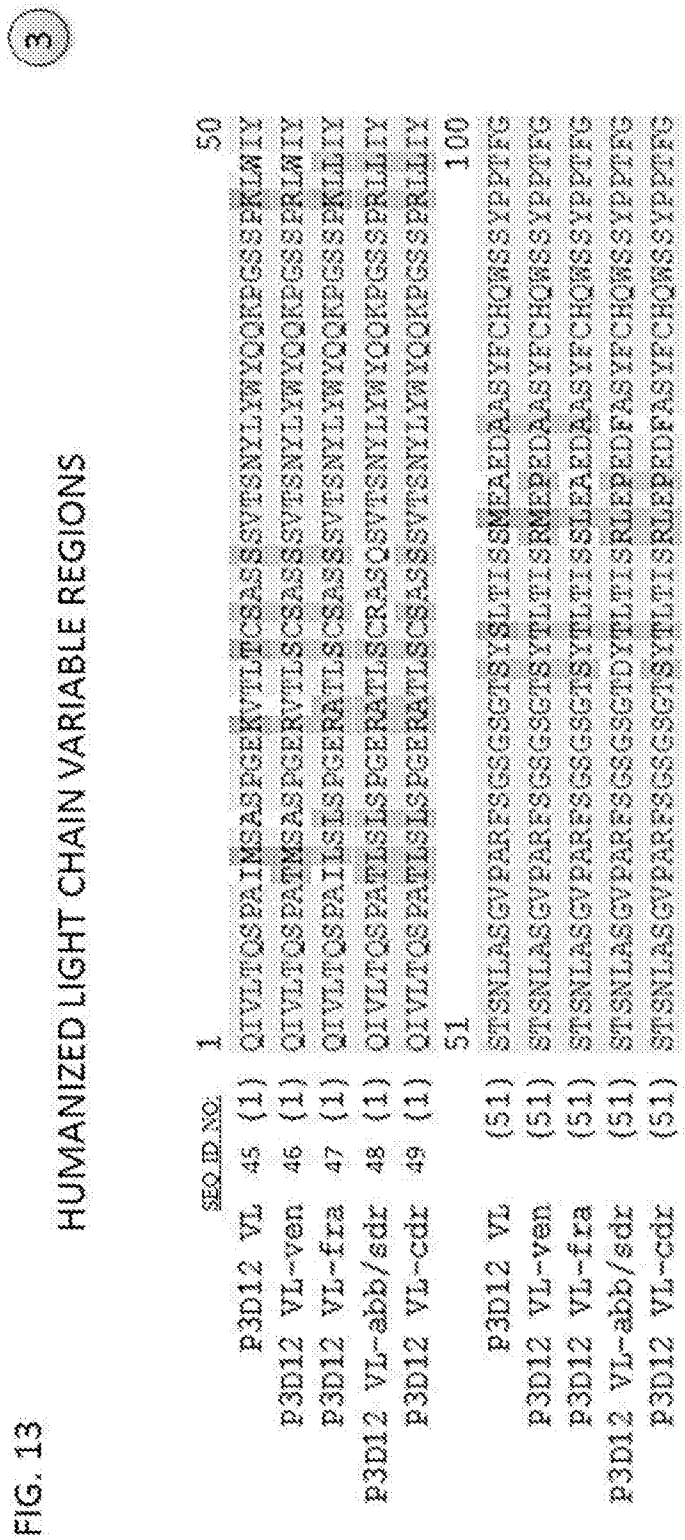

4
P3D12 mouse monoclonal
16 humanized P3D12 (4 LC x 4 HC)
4 top humanized mAbs (G2f-k4, G2v-k4, G2c-k4, G2c-ka)
1 lead anti-MET mAb
(conjugation, site-directed conjugation to engineered cys)
1 lead anti-MET ADC
Test toxicity of PBD-ADC in rats
Test solubility, binding, ADC cytotoxicity, MET agonism, MET degradation
PK (mAbs), xenograft (PBD ADCs)
Solubility, stability, DAR, cytotoxicity (in vitro), PK, xenograft, toxicity (rat)

FIG. 12

[Fig. 13]

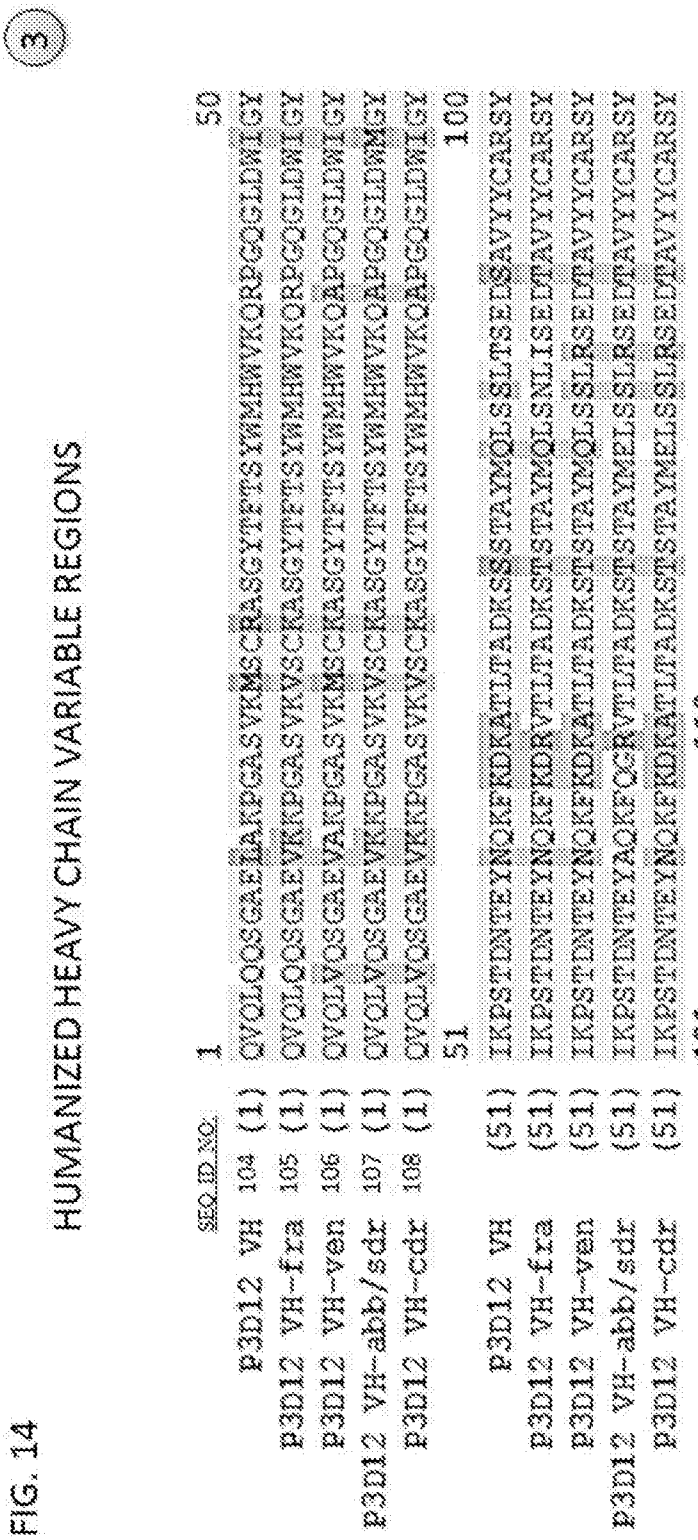
FIG. 13


3
HUMANIZED LIGHT CHAIN VARIABLE REGIONS
SEQ ID NO:
P3D12 VL 45 (1)
P3D12 VL-ven 46 (1)
P3D12 VL-fra 47 (1)
P3D12 VL-abb/sdr 48 (1)
P3D12 VL-cdr 49 (1)
P3D12 VL (51)
P3D12 VL-ven (51)
P3D12 VL-fra (51)
P3D12 VL-abb/sdr (51)
P3D12 VL-cdr (51)
P3D12 VL (101)
P3D12 VL-ven (101)
P3D12 VL-fra (101)
P3D12 VL-abb/sdr (101)
P3D12 VL-cdr (101)

[Fig. 14]

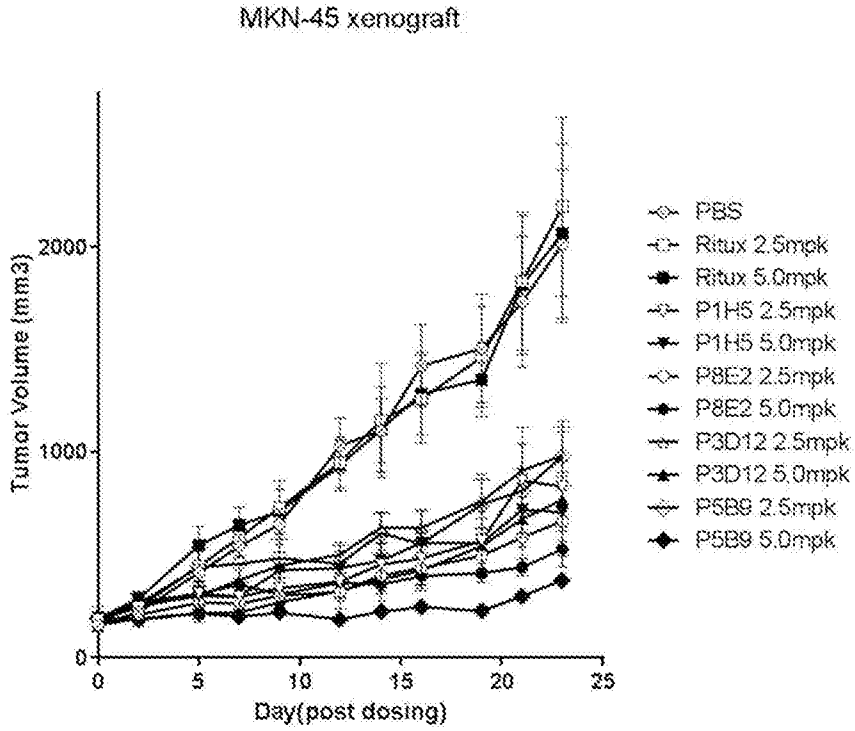
FIG. 14

HUMANIZED HEAVY CHAIN VARIABLE REGIONS



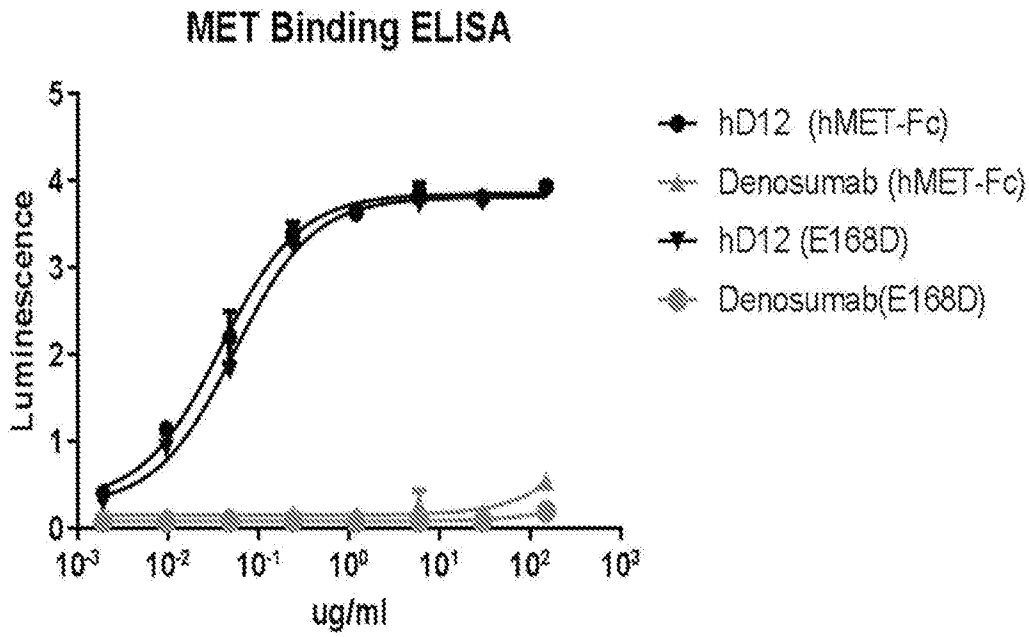
[Fig. 15]

FIG. 15



[Fig. 16]

FIG. 16



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2017/035259

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. C07K16/28(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. C07K16/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2017
Registered utility model specifications of Japan 1996-2017
Published registered utility model applications of Japan 1994-2017

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAplus/REGISTRY/MEDLINE/EMBASE/BIOSIS/WPIDS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/106159 A1 (ENUMERAL BIOMEDICAL HOLDING, INC.) 2016.06.30, Claims 27-28, 35, Paragraphs [0040], [0060], [00110]-[00115], Examples 2, 3, Fig. 2, Table 3 & US 2016/0251436 A1	1,4-6,10-11, 14-20,26-45, 50-51
A		2-3,7-9,12-13,21-25,46-49
X	WO 2007/090807 A1 (UNIVERSITA DEGLI STUDI DI TORINO) 2007.08.16, Claims 1, 4, Page 18 Lines 14-20, Examples 2-5 & US 2009/0285807 A1	1-51

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19.12.2017	26.12.2017

Name and mailing address of the ISA/JP	Authorized officer	
Japan Patent Office	ICHIJIMA, Yosuke	4B 5804
3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	Telephone No. +81-3-3581-1101 Ext. 3448	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2017/035259

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/042412 A1 (SYMPHOGEN A/S) 2016.03.24, Examples1, 3, 5, 7, 9,16, Paragraphs [0142]-[0143], [0223] & CA 2961323 A1	1-51
A	US 2009/0298079 A1 (BASILICO, Cristina) 2009.12.03, Claims & JP 2009-291191 A	1-51

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2017/035259

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

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☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

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2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments: