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**Lee et al.**

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(54) **USE OF CBL AS BIOMARKER FOR IDENTIFYING SUBJECT SUITABLE FOR TREATMENT WITH ANTI-C-MET ANTIBODY**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Sep. 14, 2012 (KR) ..... 10-2012-0102395

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**G01N 33/53** (2006.01)  
**G01N 33/574** (2006.01)  
**C07K 16/30** (2006.01)  
**A61K 39/395** (2006.01)  
**C07K 16/28** (2006.01)  
**A61K 39/00** (2006.01)

(52) **U.S. Cl.**

CPC .... **G01N 33/57492** (2013.01); **A61K 39/39558** (2013.01); **C07K 16/2863** (2013.01); **C07K 16/30** (2013.01); **C12Q 1/6886** (2013.01); **A61K 2039/505** (2013.01); **C07K 2317/24** (2013.01); **C07K 2317/565** (2013.01); **C07K 2317/622** (2013.01); **C07K 2317/73** (2013.01); **C07K 2317/76** (2013.01); **C12Q 2600/106** (2013.01); **C12Q 2600/156** (2013.01); **G01N 2800/52** (2013.01)

(58) **Field of Classification Search**

None  
See application file for complete search history.

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(57) **ABSTRACT**

A method of identifying a cell sample or a subject suitable for treatment with an anti-c-Met antibody or antigen binding fragment thereof that specifically binds to an epitope within a SEMA domain of a c-Met protein by determining a Cbl concentration, a Cbl mutation, and/or a mutation of a site of c-Met for interaction with Cbl in a cell sample from a subject, as well as related compositions and methods.

**12 Claims, 21 Drawing Sheets**  
**(6 of 21 Drawing Sheet(s) Filed in Color)**



FIG. 1C

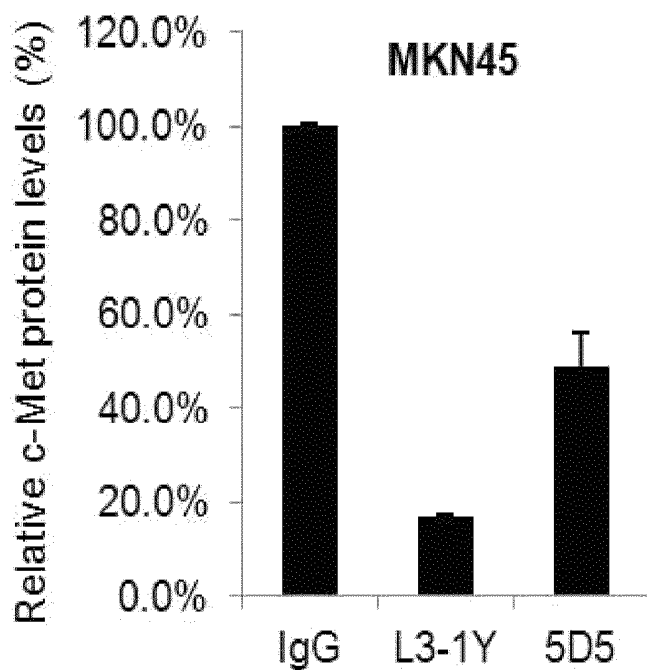


FIG. 1D

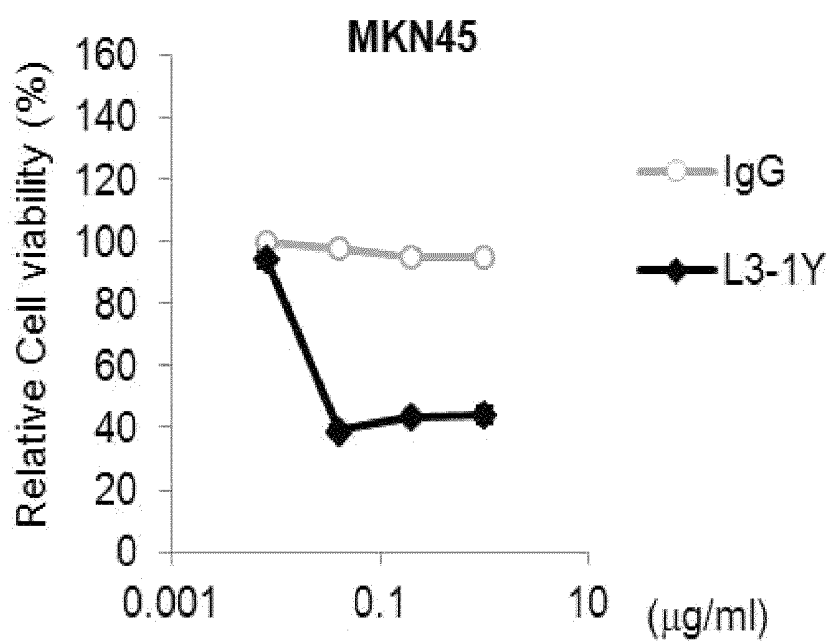


FIG. 2A

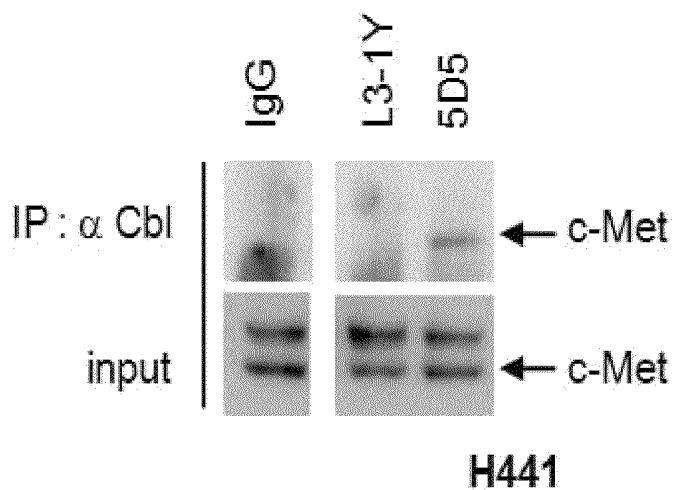


FIG. 2B

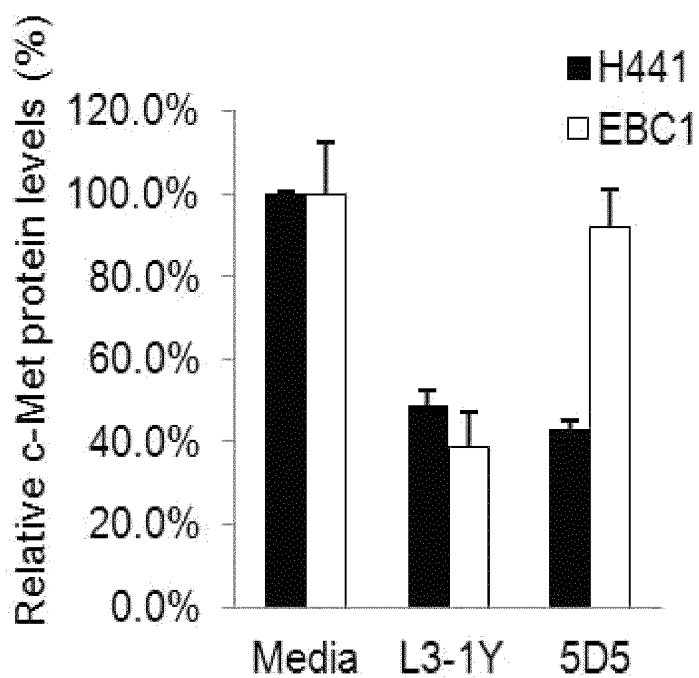


FIG. 2C

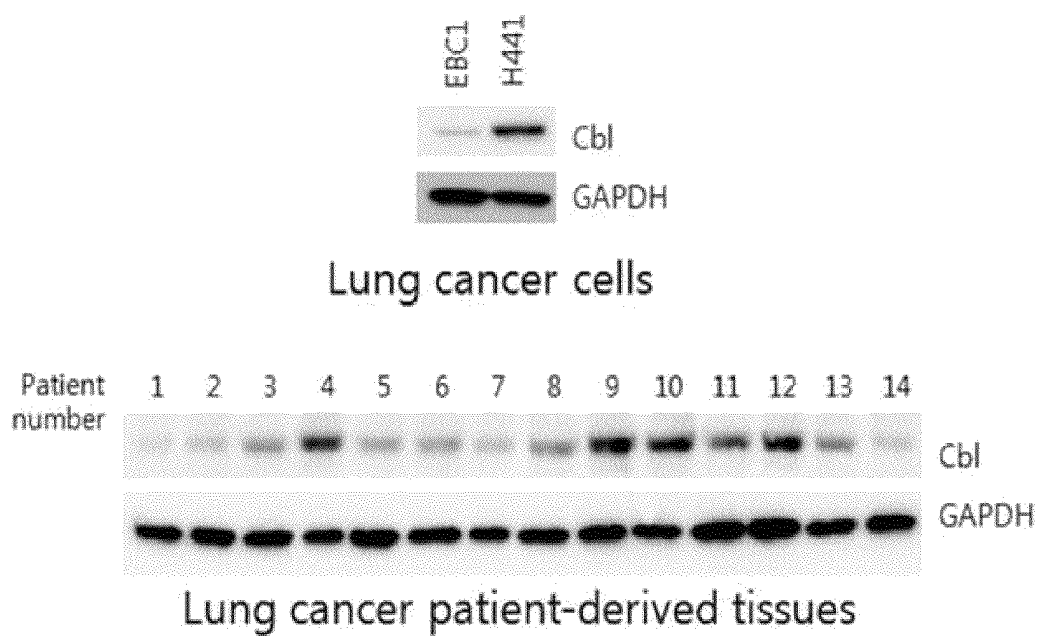


FIG. 2D

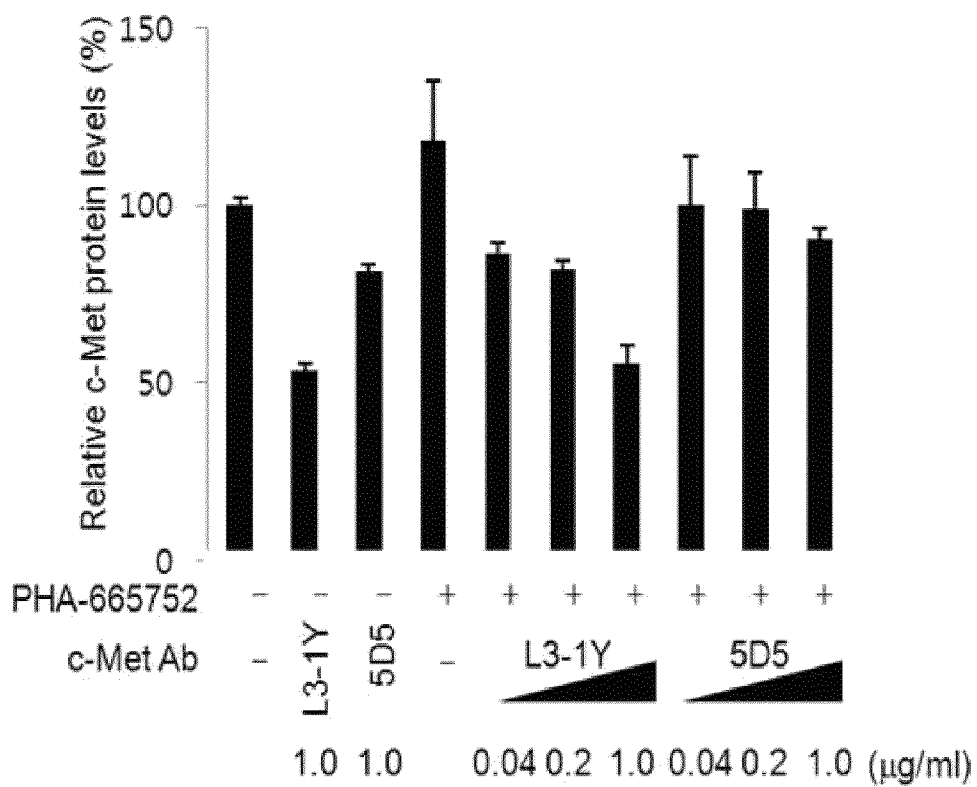


FIG. 2E

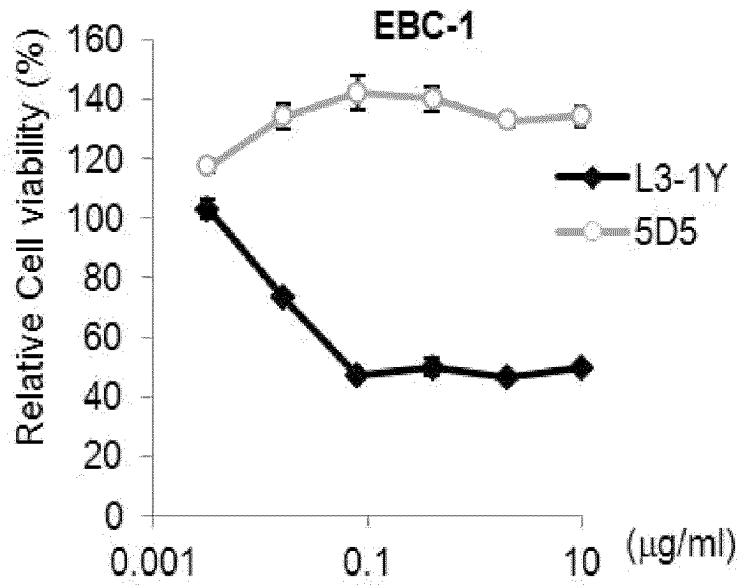


FIG. 3A

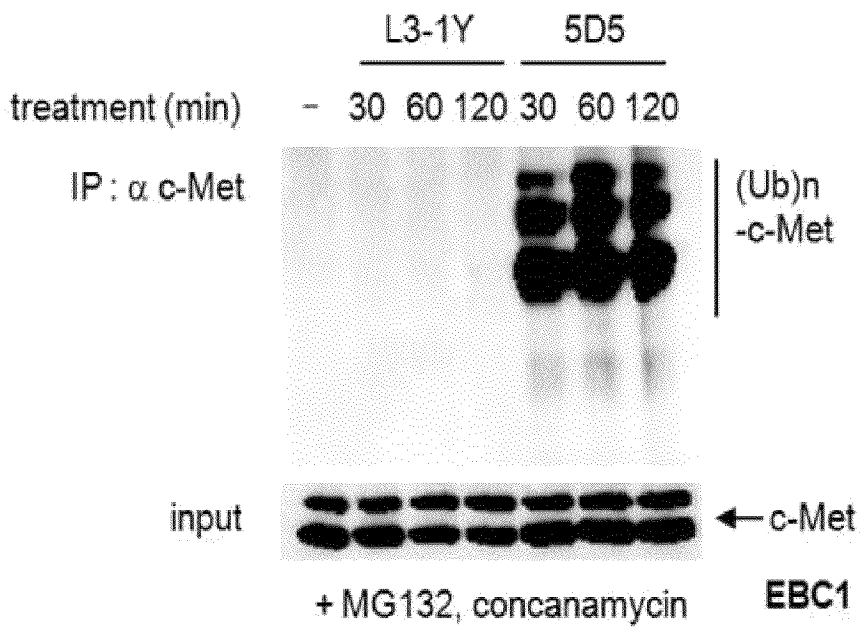


FIG. 3B

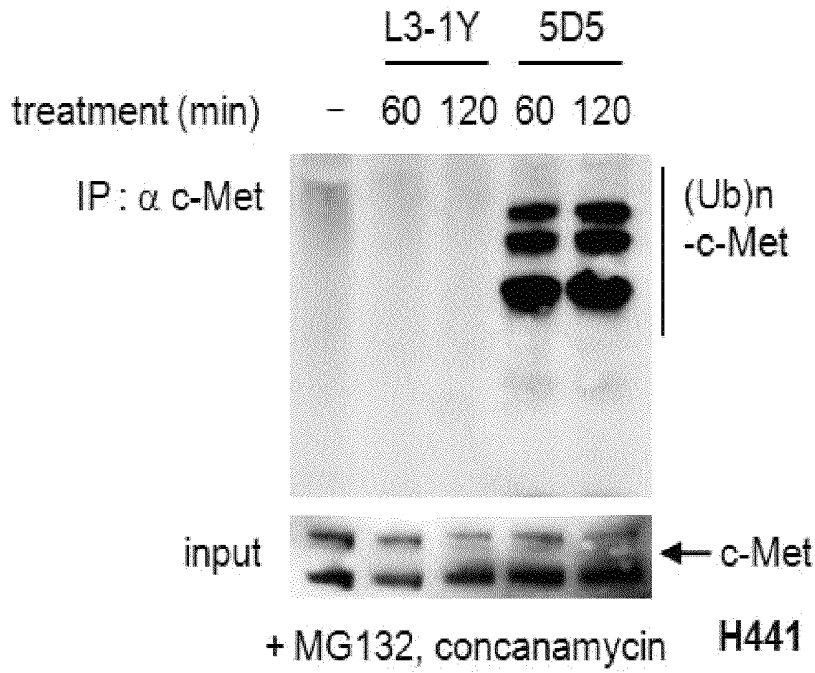


FIG. 3C

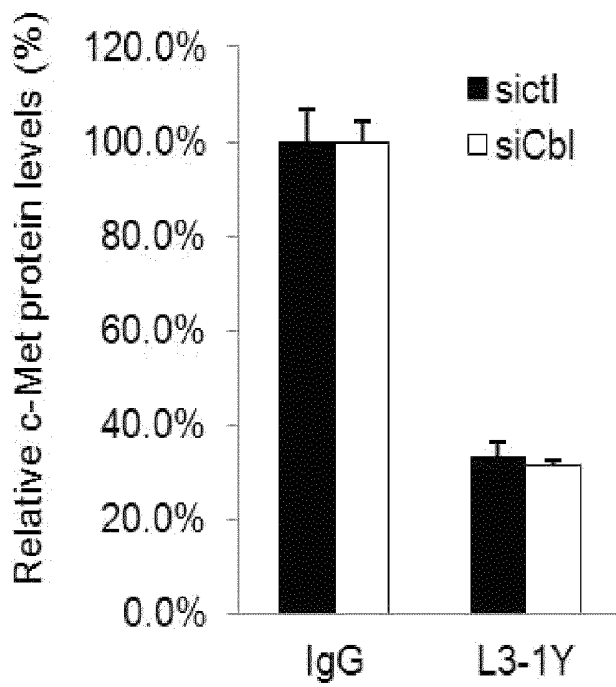


FIG. 3D

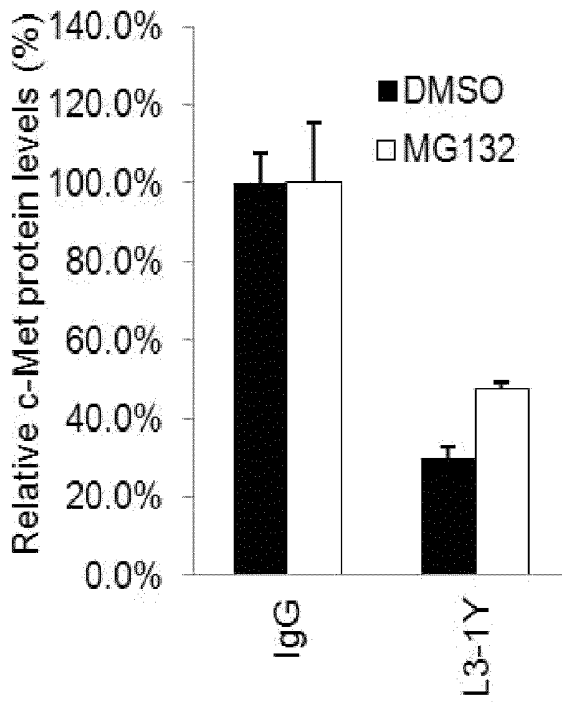


FIG. 3E

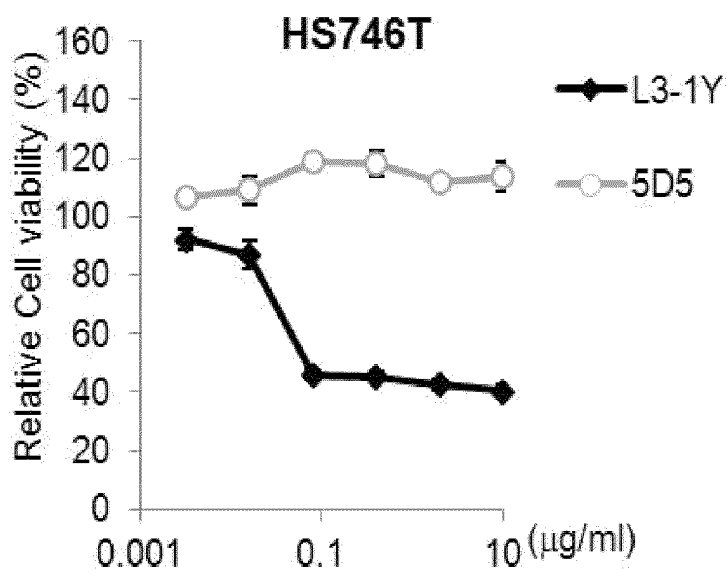


FIG. 3F

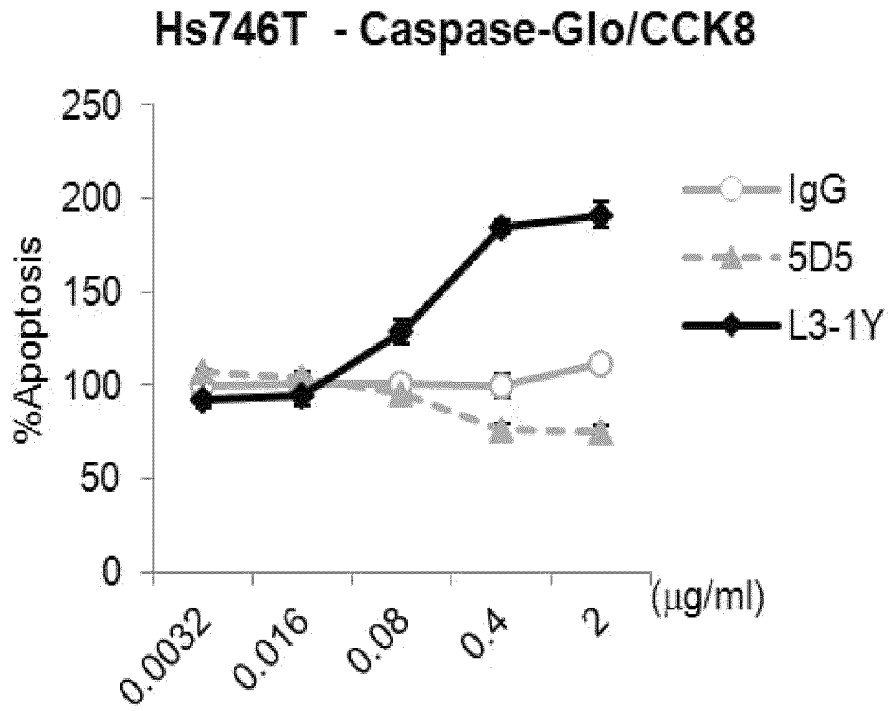


FIG. 3G

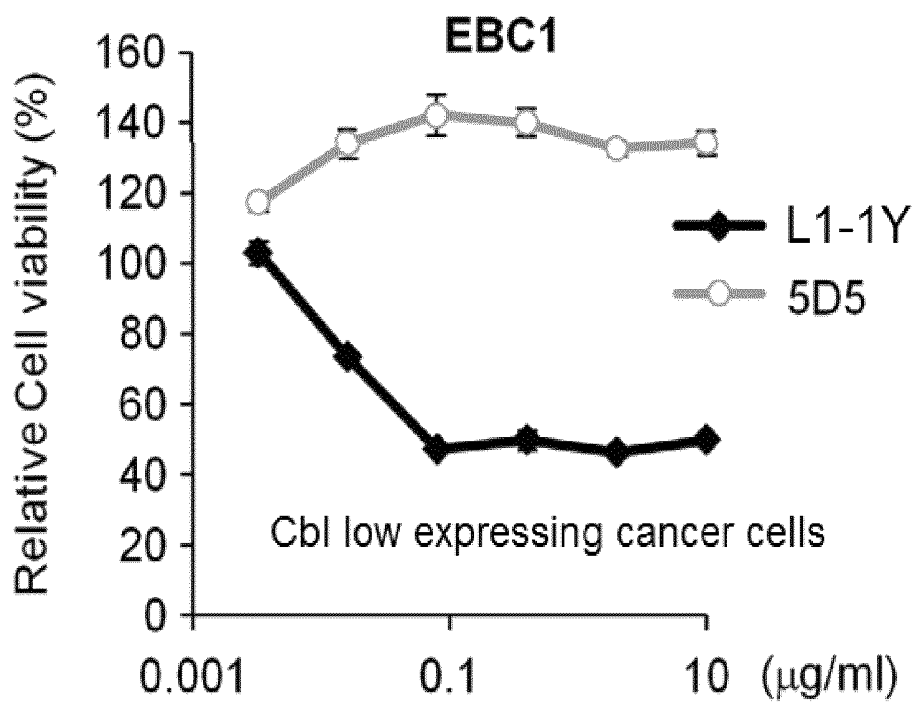


FIG. 4A

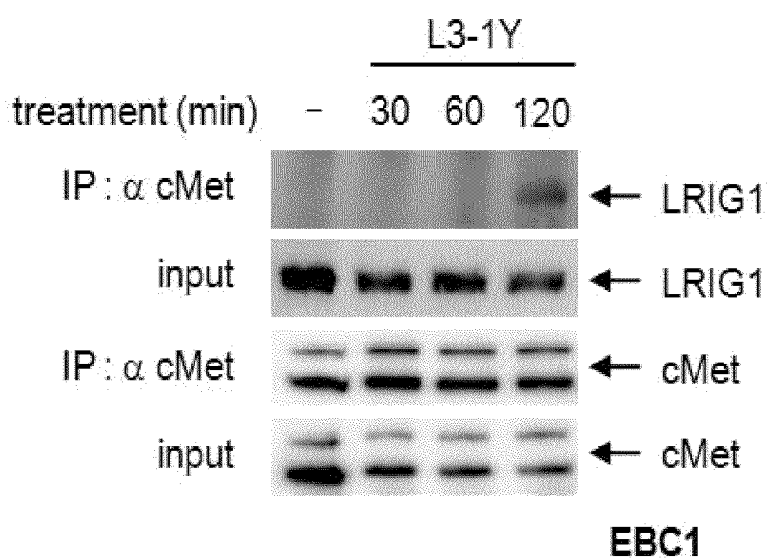
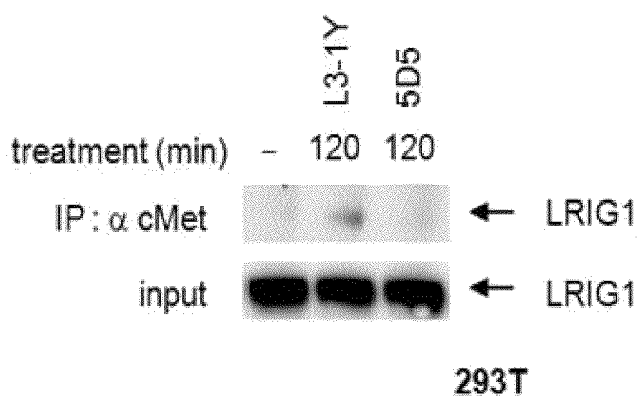


FIG. 4B



LRIG1-complex purification using 293 systems  
In vitro binding (domain mapping) between c-Met and LRIG1

FIG. 4C

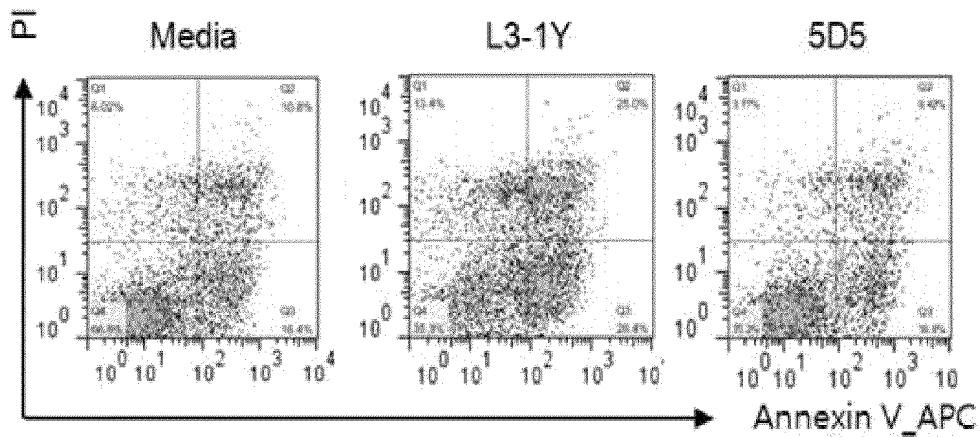
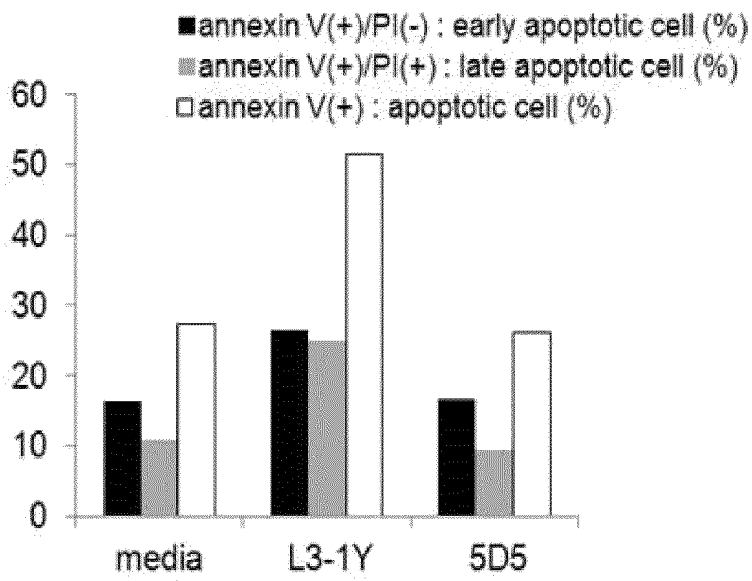


FIG. 4D

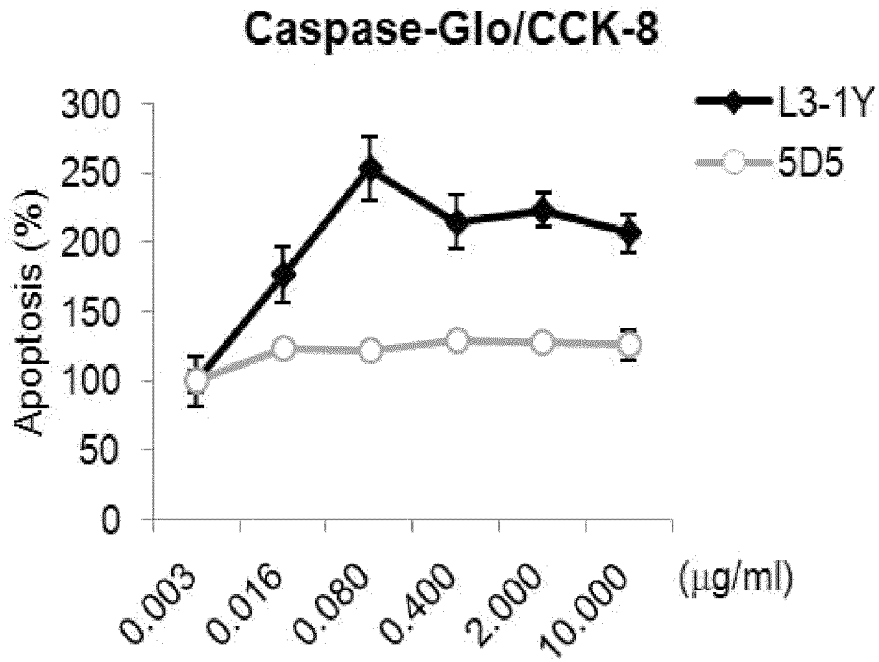


FIG. 4E

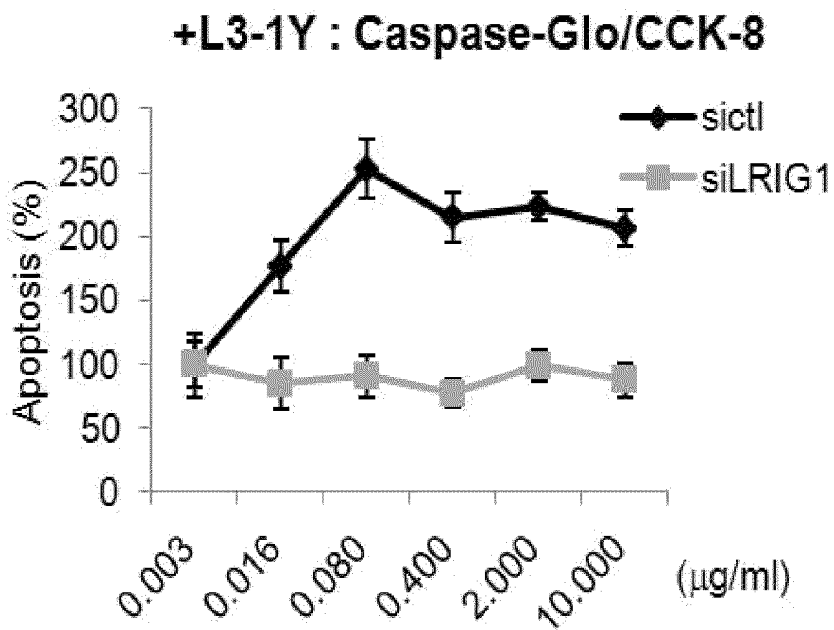


FIG. 4F

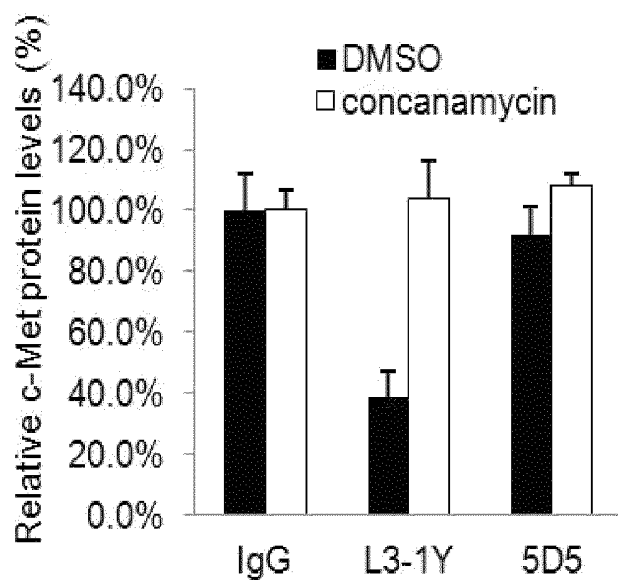
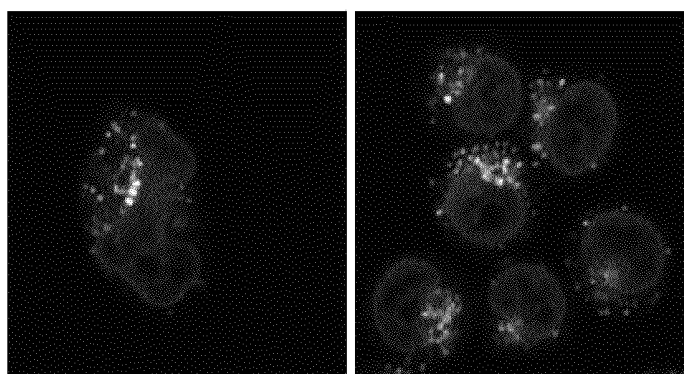


FIG. 4G

L3-1Y 4hr  
L3-1Y APC (red)  
Lysosome (green)  
Nucleus (blue)



EBC1

MKN45

FIG. 5A

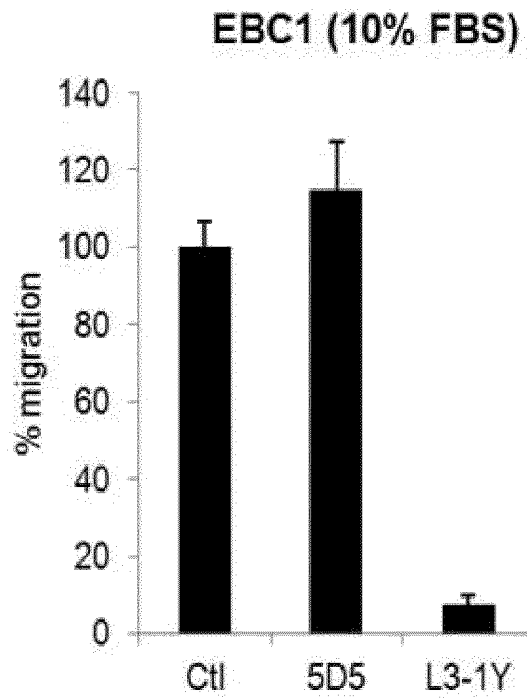


FIG. 5B

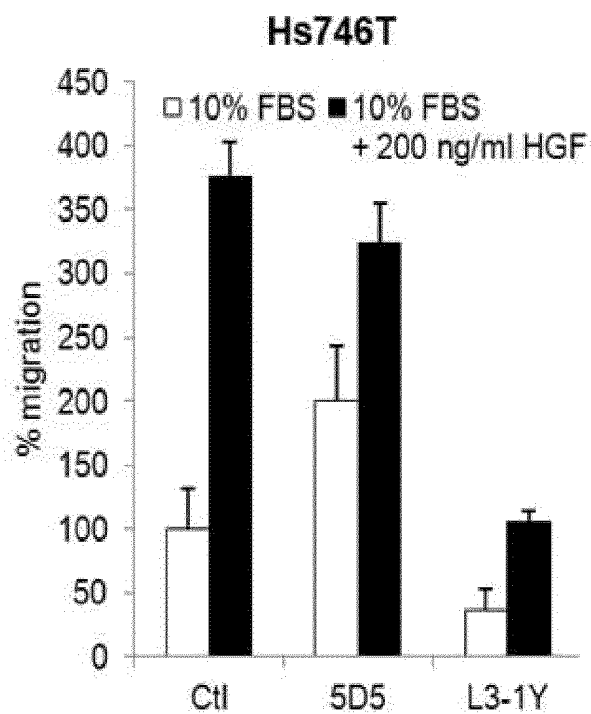


FIG. 5C

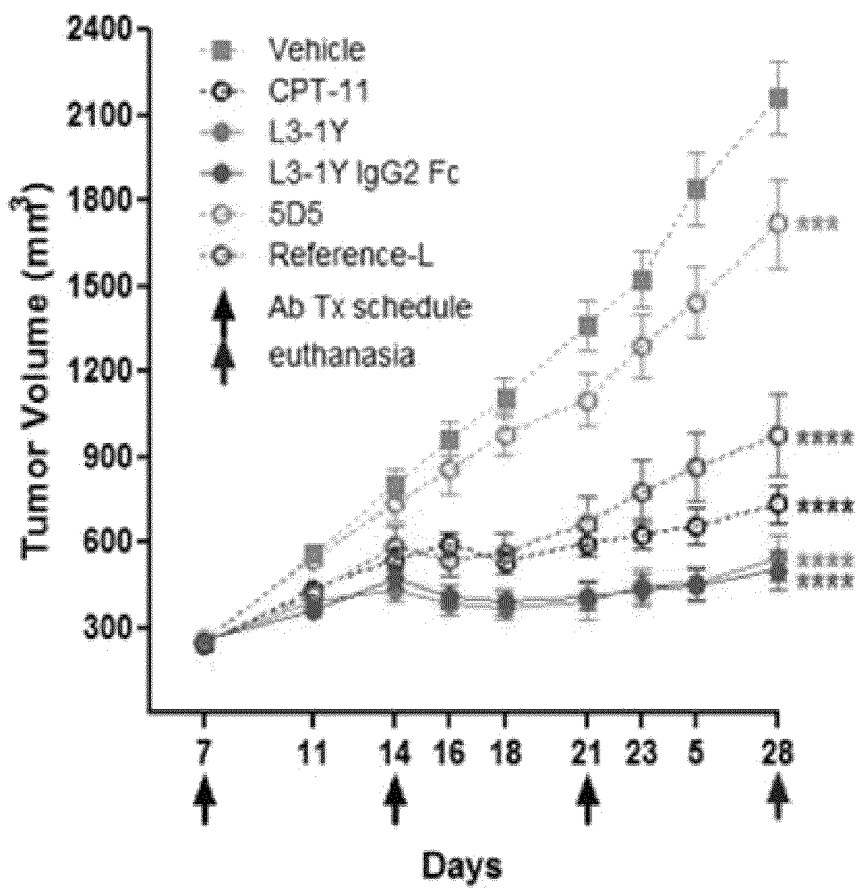


FIG. 5D

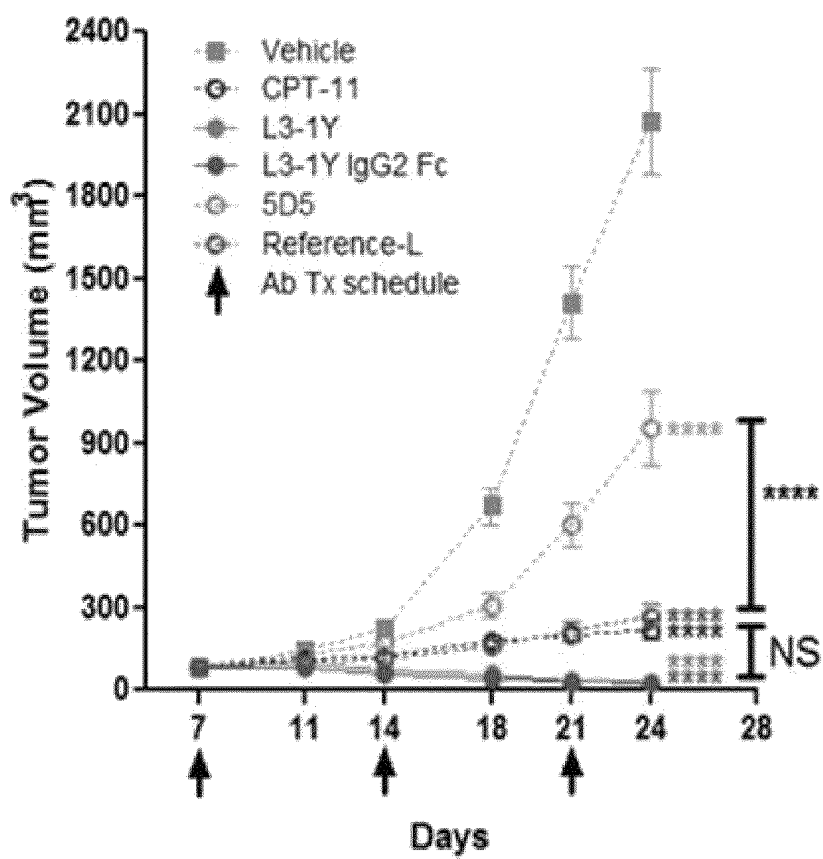
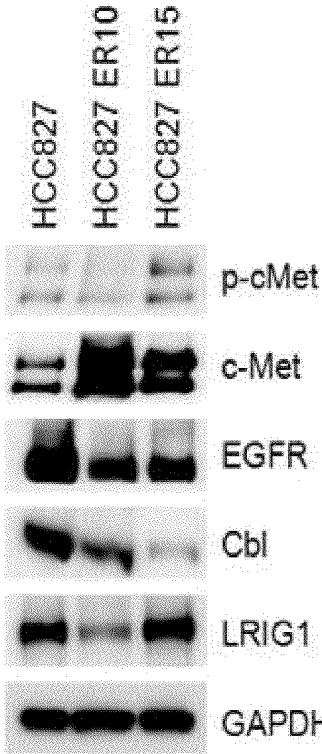


FIG. 6A



HCC827 ER : Elrotinib resistant

FIG. 6B

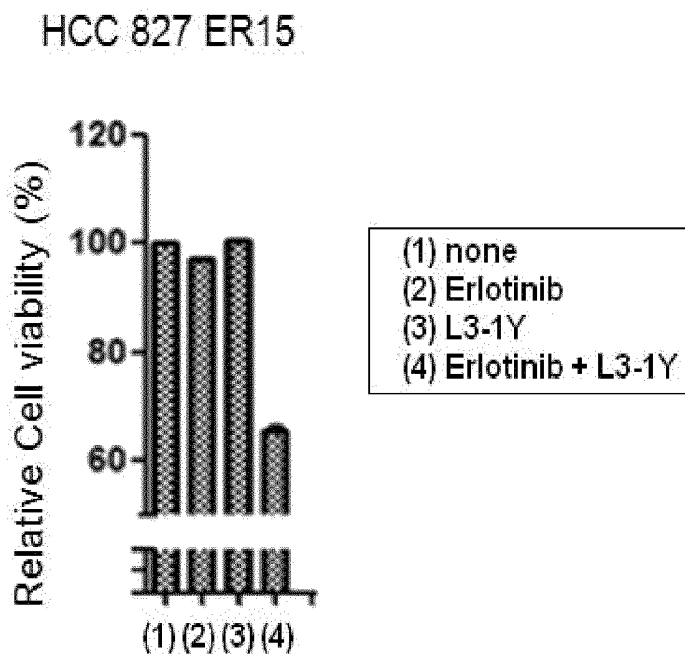


FIG. 6C

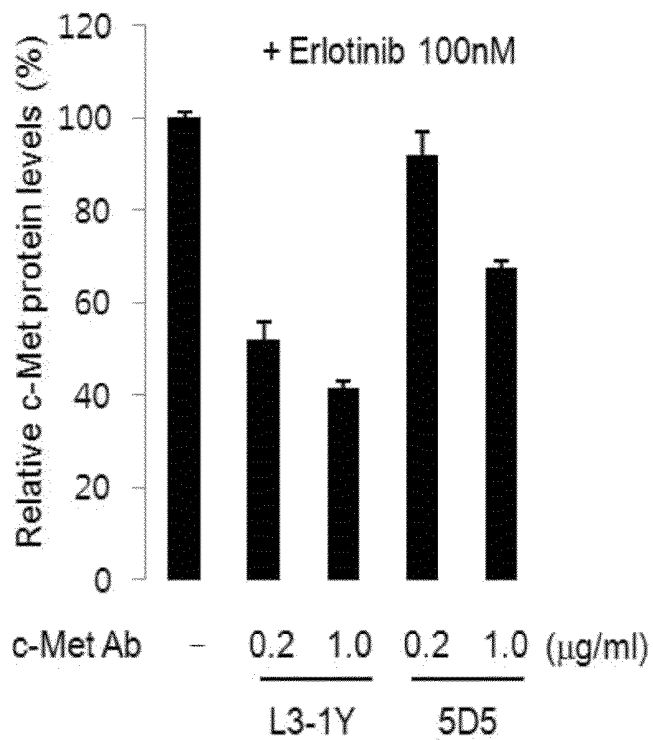


FIG. 6D

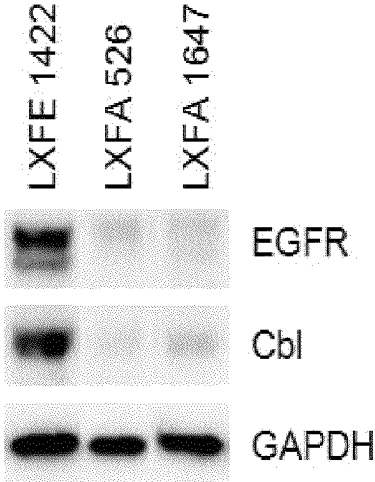


FIG. 6E

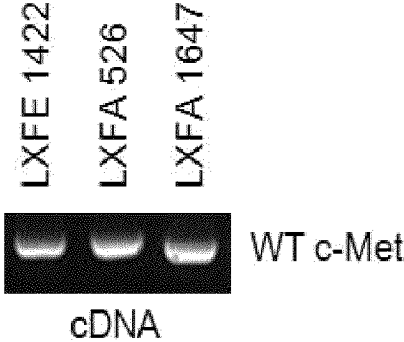


FIG. 6F

Efficacy : % of (-) ctr : Colony # at  
Max dose (100ug/ml)

Tumor	Efficacy (L3-1Y)
LXFE1422	no
LXFA 526	++ (56)
LXFA 1647	+ (67)

FIG. 7

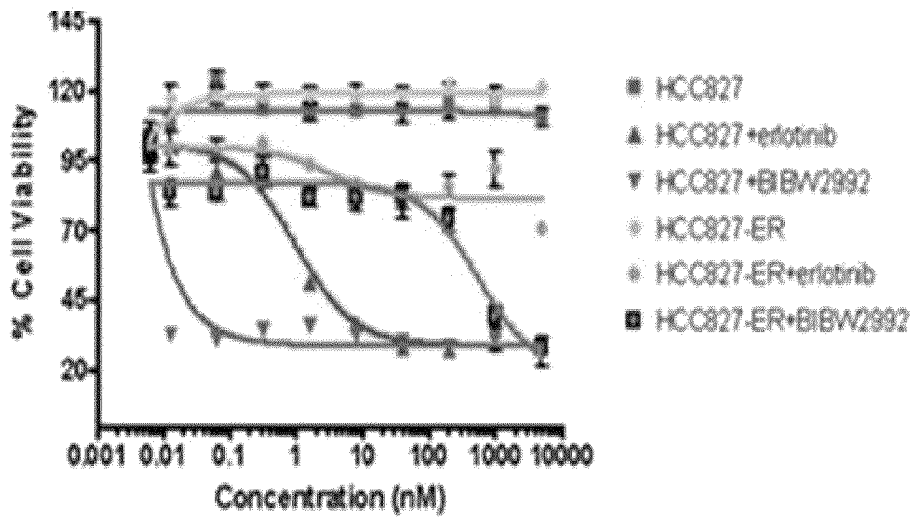
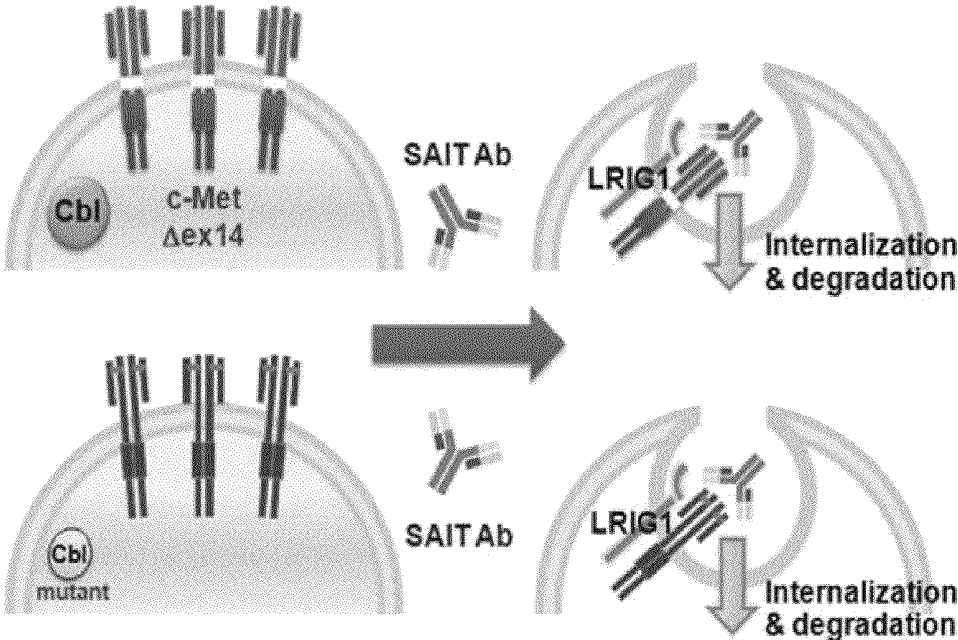


FIG. 8



**USE OF CBL AS BIOMARKER FOR  
IDENTIFYING SUBJECT SUITABLE FOR  
TREATMENT WITH ANTI-C-MET ANTIBODY**

CROSS-REFERENCE TO RELATED  
APPLICATIONS

This application claims the benefit of Korean Patent Application No. 10-2012-0080145, filed on Jul. 23, 2012 and Korean Patent Application No. 10-2012-0102395, filed on Sep. 14, 2012, in the Korean Intellectual Property Office, the disclosures of which are herein incorporated by reference in their entirety.

INCORPORATION-BY-REFERENCE OF  
MATERIAL SUBMITTED ELECTRONICALLY

Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 178,498 Byte ASCII (Text) file named "712415\_ST25-Revised2.TXT" created on Jul. 24, 2015.

BACKGROUND

1. Field

The present disclosure relates to a biomarker for identifying a subject suitable for treatment with anti-c-Met antibodies, a method of identifying the subject including determining a level of Cbl, a mutation of Cbl, and/or a mutation of a site of c-Met for interaction with Cbl in tumor cells of the subject, and a method for inhibiting c-Met activity and/or for preventing and/or treating c-Met-related diseases, including administering an effective amount of an anti-c-Met antibody to the identified subject.

2. Description of the Related Art

c-Met is a receptor for hepatocyte growth factor (HGF), a cytokine that binds the extracellular region of the c-Met receptor tyrosine kinase to induce cell division, movement, morphogenesis, and angiogenesis of various normal cells and tumor cells. c-Met is a representative receptor tyrosine kinase existing on the surface of cells, is itself a proto-oncogene, and is sometimes involved in various mechanisms related to cancer, such as cancer development, metastasis, migration, invasion, and angiogenesis, independent from a ligand, HGF. Thus, c-Met has been recently emerging as a new target for anti-cancer therapy.

In particular, c-Met is known to be involved in induction of resistance to commonly used anti-cancer drugs, and thus is regarded as important with respect to personalized treatments. Representative anti-cancer therapeutic drugs targeting epidermal growth factor receptor EGFR (ERBB1), i.e., Erlotinib or Tarceva, work by blocking the signaling related to cancer development. In addition, Herceptin, which is well known as a breast cancer therapeutic drug, targets ERBB2 (HER2) and works by blocking the transduction of signals necessary for cell proliferation. Among patients resistant to the drugs described above, the signal transduction pathway that induces cell proliferation is not blocked due to the over-expression of c-Met. Thus, c-Met has emerged as a target of interest for many pharmaceutical companies. Still, there is a need for additional anti-c-Met antibodies and related methods and compositions.

Some of the antibodies developed were found to have adverse effects. When they retain their intrinsic structures, anti-c-Met antibodies interfere with the binding of the ligand HGF to c-Met receptor, but may also act as an agonist to

trigger the signaling pathway of oncogenesis by antibody-mediated dimerization of the c-Met receptor. To avoid c-Met dimerization, anti-c-Met antibodies were structurally changed from a two-armed configuration to a one-armed configuration by genetic recombination. One-armed antagonistic antibodies to c-Met were effective when used in combination with another anticancer agent, but did not exhibit significant anticancer effects when used alone.

Cbl (E3 ligase) is known to play a leading role in the degradation of c-Met. Many c-Met inhibitors initiate Cbl-mediated c-Met degradation through ubiquitination. However, c-Met inhibitors do not show the desired therapeutic effect in patients in which Cbl cannot properly interact with c-Met due to a mutation or a quantitative reduction of Cbl or due to a mutation of c-Met.

In addition, when c-Met is activated by the ligand HGF, phosphorylation at Y1003 allows the recruitment of the Cbl enzyme to c-Met. In other words, the activation of the c-Met is a prerequisite for the recruitment of the Cbl enzyme to c-Met. Accordingly, an anticancer therapy based on Cbl-mediated c-Met degradation is executed necessarily under the condition of c-Met activation which results in an adverse effect (agonism).

There is therefore a need for a novel technique by which c-Met activity may be effectively inhibited according to kind of cancer and/or a patient's genetic makeup, with a great reduction in adverse effects.

SUMMARY

Provided is a biomarker for identifying a cancer cell and/or a patient to which an anti-c-Met antibody is applicable.

Further provided is a composition and a kit for identifying a subject suitable for application of an anti-c-Met antibody, including a biomarker.

Further provided is a method of identifying a subject suitable for application of an anti-c-Met antibody, by measuring a biomarker.

Further provided is a method of inhibiting c-Met activity, including administering a therapeutically effective amount of an anti-c-Met antibody to a subject who is identified as being suitable for treatment with an anti-c-Met antibody.

Further provided is a method of preventing and/or treating a c-Met-related disease, including administering a therapeutically effective amount of an anti-c-Met antibody to a subject who is identified as being suitable for treatment with an anti-c-Met antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

These and/or other aspects will become apparent and more readily appreciated from the following description of the embodiments, taken in conjunction with the accompanying drawings of which:

FIG. 1A-1D shows differences in the in vitro inhibitory activity of antibodies against c-Met, wherein

FIG. 1A is a graph showing c-Met levels in NCI-H441 cells incubated for 24 hours with anti-c-Met antibodies, as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA,

FIG. 1B shows Western blot photographs of the phosphorylation of kinases downstream of c-Met in NCI-H441 cells (left panel) and Caki-1 cells (right panel),

FIG. 1C is a graph showing c-Met levels in MKN45 cells incubated for 24 hours with anti-c-Met antibodies as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA, and

FIG. 1D is a graph showing the viability of MKN45 cells incubated for 72 hours with various concentrations of IgG (○) or the anti-c-Met antibody L3-1Y (◆) as percentages of the viability of the control (no antibody treated, 100%), as measured by a CCK-8 assay (mean±SD);

FIG. 2A-2E shows c-Met signaling and Cbl-mediated c-Met degradation, wherein

FIG. 2A shows photographs of co-immunoprecipitation with anti-c-Met antibodies,

FIG. 2B is a graph showing c-Met levels in EBC-1 and NCI-H441 cells incubated for 4 hours with anti-c-Met antibodies as percentages of the c-Met level in the control (medium), as measured by ELISA,

FIG. 2C shows photographs of Cbl protein levels in EBC-1 and NCI-H441 cells as analyzed by Western blotting,

FIG. 2D is a graph of c-Met levels in cells plotted against treatment factors including the c-Met inhibitor PHA-665752 (Selleck Chemicals) and the anti-c-Met antibody L3-1Y or 5D5, showing that L3-1Y may trigger c-Met degradation although c-Met activity is inhibited, unlike 5D5, and

FIG. 2E is a graph showing the viability of EBC-1 cells incubated for 72 hours with various concentrations of antibodies 5D5 (○) and L3-1Y (◆) as percentages of the viability of the control (no antibody treated, 100%), as measured by a CCK-8 assay;

FIG. 3A-3G illustrates the ability of the antibody L3-1Y to induce c-Met degradation in a Cbl-independent mechanism, wherein

FIGS. 3A and 3B are photographs showing immunoblots of protein extracts from EBC-1 cells (3A) and NCI-H441 cells (3B) incubated with L3-1Y or 5D5, detected with an anti-Ub antibody,

FIG. 3C is a graph showing c-Met levels in Cbl siRNA-transformed EBC-1 cells incubated with anti-c-Met antibodies as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA,

FIG. 3D is a graph showing c-Met levels in EBC-1 cells incubated with anti-c-Met antibodies, and DMSO or MG132 as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA,

FIG. 3E is a graph showing relative viability of HS746T cells incubated with various concentrations of antibody 5D5 (○) or L3-1Y (◆) as measured by a CCK-8 assay,

FIG. 3F is a graph showing the relative apoptosis of HS746T cells treated with various concentrations of IgG (○), L3-1Y (◆) and 5D5 (▲) as measured by Caspase 3/7 Glo assay, and

FIG. 3G is a graph showing the relative apoptosis of EBC-1 cells treated with various concentrations of L3-1Y and 5D5 as measured by Caspase 3/7 Glo assay;

FIG. 4A-4G illustrates the mediation of anti-c-Met antibody L3-1Y-induced c-Met degradation by LRIG1, wherein

FIG. 4A is a photograph after lysates from EBC-1 cells treated with L3-1Y were immunoprecipitated with anti-c-Met antibody-conjugated beads and subjected to immunoblotting with the anti-LRIG1 antibody, showing that the antibody L3-1Y induces the association of c-Met and LRIG1 both present at endogenous levels,

FIG. 4B is a graph showing co-immunoprecipitation with LRIG1 and c-Met in HEK-293T cells incubated for 120 min with L3-1Y or 5D5,

FIG. 4C shows 5D5- or L3-1Y-induced apoptosis in EBC-1 cells, as measured by FACS analysis,

FIG. 4D is a graph showing the relative apoptosis of EBC-1 cells treated for 72 hours with various concentrations of L3-1Y (◆) or 5D5 (○) as measured by Caspase 3/7 Glo assay,

FIG. 4E is a graph showing relative apoptosis of LRIG1-knockdown in EBC-1 cells treated with L3-1Y (◆),

FIG. 4F is a graph showing c-Met levels in EBC-1 cells incubated with anti-c-Met antibodies, and DMSO or concanamycin as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA, and

FIG. 4G shows immunofluorescence images of the colocalization of L3-1Y and lysosomes in EBC-1 cells (left panel) and MKN45 (right panel);

FIG. 5A-5D illustrates that LRIG1 mediates c-Met degradation and tumor growth inhibition in Cbl mutant tumors or Cbl-negative tumors in vivo, wherein

FIGS. 5A and 5B are graphs showing migration ability of EBC-1 cells (5C) and HS746T cells (5D), and

FIGS. 5C and 5D are graphs showing the growth of tumor volumes of EBC-1 (5C) and HS746T (5D) with time (n=15);

FIG. 6A-6F illustrates therapeutic effects of the antibody L3-1Y on tumors resistant to EGFR-targeted therapy, wherein

FIG. 6A is a photograph of immunoblots obtained with respective antibodies to p-c-Met, c-Met, EGFR, Cbl, LRIG1, and GAPDH in HCC827, HCC827 ER10, and HCC827 ER15 cells,

FIG. 6B is a graph showing the relative viability of HCC827 ER15 cells incubated for 72 hours with Erlotinib and/or L3-1Y, as measured by a CTG assay.

FIG. 6C is a graph showing c-Met levels in HCC827 ER15 cells incubated for 24 hours with anti-c-Met antibodies and 100 nM Erlotinib as percentages of the c-Met level in the control (IgG treated, 100%), as measured by ELISA,

FIG. 6D is a graph showing the levels of EGFR, Cbl, and the control GAPDH in LXFE 1422, LXFA 526, and LXFA 1647 patient samples as measured by Western blot analysis,

FIG. 6E is a graph showing RT-PCR products containing the exon 14 of the c-Met gene from LXFE 1422, LXFA 526, and LXFA 1647 samples, separated on agarose gel by electrophoresis, and

FIG. 6F shows clonogenicity of LXFE 1422, LXFA 526, and LXFA 1647, all incubated with the antibody L3-1Y, in comparison with the non-treated control;

FIG. 7 is a graph showing the conversion of erlotinib-sensitive cells into erlotinib-resistant cells; and

FIG. 8 is a schematic diagram showing the hypothesis of L3-1Y-triggered, Cbl-independent c-Met-degradation.

#### DETAILED DESCRIPTION

When Cbl does not interact with c-Met normally, due to a low level of the Cbl enzyme or a mutation in Cbl and/or c-Met, previously known anti-c-Met antibodies do not induce c-Met degradation and, thus, are not effective for the therapy of c-Met-related diseases. The present invention provides an anti-c-Met antibody (hereinafter referred to as "specific anti-c-Met antibody" unless otherwise stated) which initiates c-Met degradation even when the Cbl enzyme does not interact with the c-Met normally. The specific anti-c-Met antibody is highly effective for the therapy of c-Met-related diseases in a Cbl-independent manner.

Accordingly, an embodiment provides a biomarker for identifying a subject to which the specific anti-c-Met antibody is applicable (hereinafter referred to as "anti-c-Met antibody-applicable subject"). The biomarker may be selected from the group consisting of a Cbl protein, a Cbl gene, an mRNA transcribed from a Cbl gene, a site of c-Met

for interaction with Cbl, and a combination thereof. The anti-c-Met antibody-applicable subject may be a cell and/or a patient from which the cell is derived. In particular, the anti-c-Met antibody-applicable subject is cancer cells and/or patients with cancer cells.

The term "Cbl", "Cbl protein", or "Cbl enzyme," as used herein, refers to E3 ligase involved in cell signalling and protein ubiquitination. This protein has functions of intracellular internalization of c-Met protein positioned on tumor cell membrane and degradation thereof. The protein may be a polypeptide encoded by the nucleotide sequence of GenBank Accession Number (NM\_005188, NM\_007619, NM\_170662, or NM\_001033238) or a polypeptide having the amino acid sequence of GenBank Accession Number (NP\_005199, NP\_031645, NP\_733762, or NP\_001028410).

The term "c-Met" or "c-Met protein" refers to a receptor tyrosine kinase (RTK) which binds hepatocyte growth factor (HGF). c-Met may be a c-Met protein from any species, particularly a mammal or primate, for instance, human c-Met (e.g., NP\_000236), or monkey c-Met (e.g., *Macaca mulatta*, NP\_001162100), or rodents such as mouse c-Met (e.g., NP\_032617.2), rat c-Met (e.g., NP\_113705.1), and the like. The c-Met protein may include a polypeptide encoded by the nucleotide sequence identified as GenBank Accession Number NM\_000245, a polypeptide having the amino acid sequence identified as GenBank Accession Number NP\_000236 or extracellular domains thereof. The receptor tyrosine kinase c-Met participates in various mechanisms, such as cancer development, metastasis, migration of cancer cell, invasion of cancer cell, angiogenesis, and the like.

As used herein, the term "a site of c-Met for interaction with Cbl" refers to a c-Met site that recognizes and interacts with Cbl protein, thereby allowing Cbl to perform c-Met internalization and degradation. Representative sites of c-Met for interaction with Cbl may be tyrosine at amino acid position 1003 (Y1003) to which Cbl binds, or a region encoded by exon 14 of the c-Met gene in which Y1003 is positioned. The exon 14 region of the c-Met gene ranges from the 3075th to 3215th positions on the full-length nucleotide sequence of NM\_000245, or corresponds to a region ranging from the 964th to 1009th positions on the full-length amino acid sequence of NP\_000236.

Most of the existing anti-c-Met antibodies induce c-Met internalization and degradation through interaction between Cbl and c-Met. Hence, when Cbl is absent or present at a low level in cells or when Cbl or c-Met is mutated at the site responsible for interaction with Cbl (such as a binding site), the preexisting anti-c-Met antibodies cannot induce c-Met degradation, thus rendering them therapeutically ineffective.

In contrast, the specific anti-c-Met antibody is found to induce c-Met degradation independent of whether Cbl interacts with c-Met. Hence, an embodiment of the present invention provides a method of identifying a subject to which the specific anti-c-Met antibody is applicable by measuring the level of biomarker and/or determining a mutation, whereby excellent c-Met degradation may be achieved and thus c-Met-related diseases may be effectively treated even in subjects in which the preexisting antibody therapy is ineffective.

Another embodiment provides a method of identifying (selecting) a subject suitable for application of an anti-c-Met antibody, including determining a level of Cbl, a mutation of Cbl, and/or a mutation of a site of c-Met for interaction with Cbl in a cell sample.

The method of identifying a subject suitable for application of the specific anti-c-Met antibody includes determining a Cbl concentration, a Cbl mutation, and/or a mutation of a site

of c-Met for interaction with Cbl in a cell sample, wherein when Cbl is present at a low level or absent in the cell sample and/or when a mutation is present on either or both of Cbl and the site of c-Met that interacts with Cbl, the cell or the patient from which the cell is derived (separated) is determined to be a subject suitable for application of the specific anti-c-Met antibody.

As used herein, the "determining" step includes measuring the factor of interest qualitatively or quantitatively, and/or evaluating the measured results.

The cell sample may be an artificially constructed cell, a cell separated from a patient of interest, a culture of the cell, a lysate of the cell, or an extract from the cell; or a protein, DNA, and/or RNA derived from the cell, the cell culture, the cell lysate, or the cell extract. The cell may be a cancer cell (tumor cell). For example, the cancer cell may be selected from the group consisting of squamous cell carcinoma, small cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, peritoneal carcinoma, dermal cancer, dermal or intraocular melanoma, rectal cancer, perianal cancer, esophageal cancer, small intestine cancer, endocrine gland cancer, parathyroid cancer, adrenal gland cancer, soft tissue sarcoma, urethral cancer, chronic or acute leukemia, lymphocyte lymphoma, hepatoma, stomach cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatic tumor, breast cancer, colon cancer, large intestine cancer, endometrial cancer, uterine cancer, salivary gland cancer, renal cancer, prostate cancer, vulvar cancer, thyroid cancer, and head and neck cancer.

In one embodiment, the method is carried out using a very small amount of protein, DNA, or RNA extracted from the cell. For example, the amount of protein may range from about 0.1 to about 100  $\mu\text{g}$ , from about 0.5 to about 50  $\mu\text{g}$ , or from about 1 to about 10  $\mu\text{g}$ , for example, from about 3 to about 7  $\mu\text{g}$ , and/or the amount of DNA or RNA may range from about 0.1 to about 50  $\mu\text{g}$ , from about 0.3 to about 30  $\mu\text{g}$ , from about 0.5 to about 5  $\mu\text{g}$ , for example from about 0.8 to about 1.2  $\mu\text{g}$  suffices for the execution of the method.

Examples of the patient may be mammals including primates such as humans, monkeys, etc., and rodents such as mice, rats, etc., with preference for humans. For example, the patient may suffer from a cancer selected from the group consisting of squamous cell carcinoma, small cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, peritoneal carcinoma, dermal cancer, dermal or intraocular melanoma, rectal cancer, perianal cancer, esophageal cancer, small intestine cancer, endocrine gland cancer, parathyroid cancer, adrenal gland cancer, soft tissue sarcoma, urethral cancer, chronic or acute leukemia, lymphocyte lymphoma, hepatoma, stomach cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatic tumor, breast cancer, colon cancer, large intestine cancer, endometrial cancer, uterine cancer, salivary gland cancer, renal cancer, prostate cancer, vulvar cancer, thyroid cancer, head and neck cancer, and the like.

Another embodiment provides a composition for the identification (diagnosis) of a subject suitable for application of the specific anti-c-Met antibody, including at least one selected from the group consisting of a Cbl detection agent for determining a Cbl concentration, an agent for detecting a Cbl mutation, and an agent for detecting a c-Met mutation.

Another embodiment provides a kit for the identification (diagnosis) of a subject suitable for application of the specific anti-c-Met antibody, including at least one selected from the group consisting of a Cbl detection agent for determining a

Cbl concentration, an agent for detecting a Cbl mutation, and an agent for detecting a c-Met mutation.

The determination of Cbl concentration may be conducted by any suitable method of determining expression, such as by mRNA detection/quantification or measuring a gene copy number, or by measuring a Cbl concentration using a protein quantification means known in the relevant art, and/or evaluating the measured results. By way of example, a Cbl concentration may be determined through an enzyme reaction, a fluorescence reaction, a luminescence action, and/or a radiation reaction using a Cbl-specific antibody or aptamer. The Cbl concentration may be analyzed using a method including, but not limited to, immunochromatography, immunohistochemistry, enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), enzyme immunoassay (EIA), fluorescence immunoassay (FIA), luminescence immunoassay (LIA), and Western blotting. The Cbl detection agent for determining a Cbl concentration may be selected from the group consisting of an anti-Cbl antibody, an aptamer specifically binding to Cbl, and a combination thereof.

When Cbl is absent or present at a low level in cancer cells, preexisting anti-c-Met antibodies cannot induce c-Met degradation, showing a poor therapy for c-Met-related diseases. In contrast, the specific anti-c-Met antibody having a Cbl-independent activity may encourage c-Met degradation and thus is highly effective for the therapy of c-Met-related diseases even at a low or no level of Cbl. Cbl is present at a "low" level in a cancer cell or tissue sample if the level of Cbl is less than typically found in a cancer cell or tissue sample of the same type. For instance, the Cbl level of a cancer cell or tissue sample may be "low" if it is less than typically found in a cancer cell of the same type that is sensitive (not resistant) to an anti-c-Met antibody (e.g., 5D5 antibody, and the like) other than the specific anti-c-Met antibody or EGFR targeted therapy. For example, the Cbl level of a cancer cell or tissue sample may be "low" if it is less than (e.g., the minimum level) found in a cancer cell of the same type on which an anti-c-Met antibody (e.g., 5D5 antibody) other than the specific anti-c-Met antibody has therapeutic effect. Because it can be difficult to quantitatively analyze protein concentrations in a cell sample, qualitative or semi-quantitative analysis may be used as an alternative. Qualitative methods, including immunohistochemical staining, are well known in the art. For example, the level of a protein of interest may be determined by immunohistochemical staining using an antibody (e.g., antibody #2747 (Cell signaling) for Cbl, ab36707 (Abcam) for LRIG1, and the like) that binds to a protein in a sample. The staining may be scored on a scale ranging, e.g., from '-1' or '0' to '+3', wherein a score (stain intensity) of '-1' or '0' represents no protein expression (no signal), score of '+1' represents no or a slight protein expression (corresponding to a background signal), and scores of '+2' to '+3' represent progressively higher levels of protein expression (a case with a signal higher than '+3' is incorporated in the score of '+3'). In the present invention, "the absence of Cbl or the presence of Cbl at a low level" may be defined as the stain intensity of '-1' or '+1', respectively, when analyzed by immunohistochemical staining using an anti-Cbl antibody or as equivalent results when analyzed by other protein analysis methods. Moreover, "the presence of LRIG1" may be defined as a stain intensity of '+2' or '+3' when analyzed by immunohistochemical staining using an anti-LRIG1 antibody or as equivalent results when analyzed by other protein analysis methods.

Thus, when the level of Cbl in a cell sample is determined to be '+1' or '-1' in terms of stain intensity as measured by immunohistochemical staining using an anti-Cbl antibody,

the patient from which the cell sample is originated (separated) may be determined as a subject suitable for application of the specific anti-c-Met antibody.

In one embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody includes:

- (1') determining a Cbl concentration in a cell sample; and
- (2') optionally, determining the subject from which the cell sample is originated as a subject suitable for application of the specific anti-c-Met antibody when Cbl is absent or present at a low level in the cell sample.

The absence of Cbl or the presence of Cbl at a low level in the cell sample may be determined as a stain intensity of '-1' or '+1', when analyzed by immunohistochemical staining using an anti-Cbl antibody.

The Cbl mutation refers to any mutation of the nucleotide sequence of the Cbl gene and/or of the amino acid sequence or structure of Cbl protein which causes the loss of a function responsible for interaction with c-Met (e.g., binding) and/or c-Met internalization and/or c-Met degradation. In one embodiment, the Cbl mutation may be a deletion or substitution of 51 or more consecutive nucleotide residues, for example, 51 to 200 consecutive nucleotide residues, within a range from nt. 1169 to nt. 1411 of the nucleotide sequence of GenBank Accession Number NM\_005188, or a deletion or substitution of 17 or more consecutive amino acid residues, for example, 17 to 100 consecutive amino acid residues within a range from a.a. 343 to a.a. 424 of the amino acid sequence of GenBank Accession Number NP\_005179. This mutation modifies the RING finger motif of Cbl, resulting in the loss of the E3 ligase function. That is, Cbl loses the ability to degrade other proteins due to the mutation of the nucleotides or amino acids.

The Cbl mutation leading to the incapacitation of Cbl may be determined using a method including, but not limited to, the direct analysis of nucleotide sequences or amino acid sequences, RT-PCR, and DNA sequencing.

The agent for detecting a Cbl mutation may be selected from the group consisting of a probe or primer capable of detecting the mutation, an anti-Cbl antibody specifically binding to a mutated Cbl, and an aptamer specifically binding to a mutated Cbl. The probe capable of detecting the Cbl mutation may be an about 10- to about 50-mer or about 20- to about 50-mer nucleotide sequence including a mutation region of the mutated Cbl gene and/or a complementary sequence thereto, or a sequence having a similarity of about 80% or higher, about 90% or higher, or about 95% or higher therewith. The primer capable of detecting the Cbl mutation may be an about 10- to about 50-mer or about 20- to about 30-mer oligonucleotide having a nucleotide sequence capable of hybridization with 5' and/or 3' terminus of a mutation region (about 50 to about 200 bp including the mutation site of Cbl) of the mutated Cbl gene, wherein the nucleotide sequence capable of hybridization may be a complementary sequence thereto, or a sequence having a similarity of about 80% or higher, about 90% or higher, or about 95% or higher therewith.

In the cells wherein the interaction between Cbl and c-Met and/or c-Met internalization and/or c-Met degradation is lost, preexisting anti-c-Met antibodies cannot induce c-Met degradation and thus are unable to treat c-Met-related diseases. However, the specific anti-c-Met antibody of the present invention may encourage c-Met degradation and thus is effective for the therapy of c-Met-related diseases even upon the loss of Cbl functions.

Therefore, if the Cbl protein or a Cbl gene encoding it is found to have such a mutation in a cell sample taken from a

patient, the patient may be determined to be a subject suitable for application of the specific anti-c-Met antibody.

In one embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody may include:

(1") determining the presence of a mutation of a Cbl protein or a Cbl gene encoding the Cbl protein in a cell sample taken from a patient; and

(2") optionally, deciding the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when the mutation is present.

As used herein, the term "c-Met mutation" refers to a mutation on a c-Met site responsible for recognizing or binding Cbl, particularly to a mutation which incapacitates the interaction of Cbl with c-Met (e.g., binding) even though Cbl is present at a sufficient level or does not undergo such a mutation that leads to functional loss.

As used herein, the term "site of c-Met for interaction with Cbl" is intended to refer to a c-Met site which is recognized by Cbl so as to allow for c-Met internalization and degradation. Representative among the sites of c-Met for interaction with Cbl are tyrosine at amino acid position 1003 (Y1003) and a region encoded by exon 14 of the c-Met gene. The exon 14 region of c-Met gene ranges from nt. 3075 to nt. 3215 of the full-length nucleotide sequence of NM\_000245, or corresponds to a region stretching from a.a. 964 to a.a. 1009 of the full-length amino acid sequence of NP\_000236. The c-Met mutation may be a deletion or a substitution of tyrosine at position 1003 (Y1003) with another amino acid residue (e.g., alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, valine, asparagine, cysteine, glutamine, glycine, serine, threonine, aspartic acid, glutamine acid, arginine, histidine, and lysine, and preferably phenylalanine), or a deletion or a substitution of 141 or more consecutive nucleotide residues, for example, 141 to 300 consecutive nucleotide residues of exon 14 of the c-Met gene with other nucleotide residues, and/or a deletion or a substitution of 46 or more consecutive amino acid residues, for example, 46 to 100 consecutive amino acid residues of a polypeptide encoded by exon 14 with other amino acid residues. In an embodiment, the c-Met mutation may be a deletion of tyrosine at position 1003 of c-Met (Y1003), a substitution of the tyrosine residue with phenylalanine (Y1003F), a deletion of exon 14 of the c-Met gene, or a deletion of the polypeptide encoded by exon 14.

The c-Met mutation may be determined using a method including, but not limited to, the direct analysis of nucleotide sequences or amino acid sequences, RT-PCR, and DNA sequencing. The agent for detecting a c-Met mutation may be selected from the group consisting of a probe or primer capable of detecting the mutation as described above, an anti-Cbl antibody specifically binding to a mutated Cbl, and an aptamer specifically binding to a mutated Cbl.

Whereas preexisting anti-c-Met antibodies cannot induce Cbl-mediated c-Met degradation in the cells where a c-Met site which is recognized by Cbl or binds Cbl is mutated and thus are unable to treat c-Met-related diseases, the specific anti-c-Met antibody may successfully treat c-Met-related activity due to its Cbl-independent activity.

When the cell sample is found to have such a mutation on c-Met protein or c-Met gene encoding the protein, the cell or the patient from which the cell sample is taken (separated) may be determined to be a subject suitable for application of the specific anti-c-Met antibody.

In one embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody includes:

(1") determining the presence of a mutation on a site of c-Met for interaction with Cbl or on a region of c-Met gene corresponding to the site of c-Met for interaction with Cbl in a cell sample taken from a patient; and

(2") optionally, determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when the mutation is present.

Unlike preexisting anti-c-Met antibodies, the specific anti-c-Met antibody of the present invention exhibits a Cbl-independent c-Met degradation activity because the antibody induces LRIG1 (leucine-rich repeats and immunoglobulin-like domains protein 1) to bind to c-Met, the resulting LRIG1-c-Met being internalized and degraded. Accordingly, the specific anti-c-Met antibody may act as an effective negative regulator of c-Met in the presence of LRIG1 in cells, particularly, when LRIG1 is overexpressed in cells.

"LRIG1 (Leucine-rich repeats and immunoglobulin-like domains protein 1)" refers to a transmembrane protein which interacts with receptor tyrosine kinases of the EGFR-family, MET, and RET. LRIG1 may be derived from mammals including primates such as humans and monkeys, and rodents such as rats and mice. For example LRIG1 may be human LRIG1 (Accession No. NM\_015541 or NP\_056356).

The determination of the presence/absence and/or an intracellular level of LRIG1 may be determined by any suitable method of determining expression, such as by mRNA detection/quantification, or by measuring an LRIG1 level in a cell sample by use of a protein quantification means and/or evaluating the measurement. By way of example, the presence/absence and/or an intracellular level of LRIG1 may be determined by measuring fluorescence, luminescence, and/or radiation intensity after reaction with an LRIG1-specific antibody or aptamer in conjunction with an enzyme. In detail, the presence/absence and/or an intracellular level of LRIG1 may be analyzed using a method including, but not limited to, immunochromatography, immunohistochemistry, enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), enzyme immunoassay (EIA), fluorescence immunoassay (FIA), luminescence immunoassay (LIA), and Western blotting.

In an embodiment, the presence of LRIG1, particularly at a high level in cells, may be defined as the stain intensity of +2 or +3 when analyzed by immunohistochemical staining using an anti-LRIG1 antibody or as equivalent results when analyzed by other protein analysis methods.

Hence, the method of identifying a subject suitable for application of the specific anti-c-Met antibody may further include determining the level of LRIG1 in a cell sample. In detail, the method of identifying a subject suitable for application of the specific anti-c-Met antibody may further include (1-1), (1-1'), (1-1"), or (1-1''') determining a level of LRIG1 in a cell sample ahead of the step (2), (2'), (2''), or (2'''), respectively. In addition, the method may further include determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when LRIG1 is present. For example, the presence of LRIG1 in the cell sample is defined as a stain intensity of '+2' or '+3' when analyzed by immunohistochemical staining using an anti-LRIG1 antibody.

In detail, the method of identifying a subject suitable for application of the specific anti-c-Met antibody includes:

(1) determining a Cbl concentration, a Cbl mutation, and/or a mutation of a site of c-Met for interaction with Cbl in a cell sample taken from a patient;

(1-1) determining a level of LRIG1 in the cell sample; and

(2) optionally, determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met

antibody when Cbl is present at a low level or absent in the cell sample (wherein the Cbl concentration is expressed as a stain intensity of ‘-’ or ‘+1’ as analyzed by immunohistochemical staining using an anti-Cbl antibody) and/or when a mutation is present on either or both Cbl and the site of c-Met for interaction with Cbl if the LRIG1 is present (for example, the case that the level of LRIG1 in the cell sample is expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody).

In another embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody includes:

(1’) determining a Cbl concentration in a cell sample taken from a patient;

(1-1’) determining a level of LRIG1 in the cell sample; and

(2’) optionally, determining the patient to be a subject suitable for application of the specific anti-c-Met antibody when Cbl is absent or present at a low level in the cell sample while LRIG1 is present.

The absence of Cbl or the presence of Cbl at a low level in the cell sample may be defined as a stain intensity of ‘-’ or ‘+1’, when analyzed by immunohistochemical staining using an anti-Cbl antibody, and the presence of LRIG1 in the cell sample may be expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody.

In another embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody may include:

(1'') determining the presence of a mutation on a Cbl protein or a Cbl gene coding for the Cbl protein in a cell sample taken from a patient;

(1-1'') determining a level of LRIG1 in the cell sample; and

(2'') optionally, determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when the mutation is present while LRIG1 is present,

wherein the presence of LRIG1 in the cell sample may be expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody.

In another embodiment, the method of identifying a subject suitable for application of the specific anti-c-Met antibody includes:

(1''') determining the presence of a mutation on a site of c-Met for interaction with Cbl or on a region of c-Met gene corresponding to the site of c-Met for interaction with Cbl in a cell sample taken from a patient;

(1-1''') determining a level of LRIG1 in the cell sample; and

(2''') optionally, determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when the mutation is present while LRIG1 is present,

wherein the presence of LRIG1 in the cell sample may be expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody.

Contemplated according to another embodiment of the present invention is a composition for the identification of a subject suitable for application of the specific anti-c-Met antibody including at least one selected from the group consisting of a Cbl detection agent for determining a Cbl concentration, an agent for detecting a Cbl mutation and an agent for detecting a c-Met mutation, and an LRIG1 detection agent for determining an LRIG1 level.

In another embodiment, the kit for the identification of a subject suitable for application of the specific anti-c-Met

antibody may further include an LRIG1 detection agent for determining an LRIG1 level. In detail, the kit includes:

at least one selected from the group consisting of a Cbl detection agent for determining a Cbl concentration, an agent for detecting a Cbl mutation, and an agent for detecting a c-Met mutation;

an LRIG1 detection agent for determining an LRIG1 level; and  
a detection means.

The LRIG1 detection agent for determining an LRIG1 level may be selected from the group consisting of anti-LRIG1 antibody, an aptamer specifically binding to LRIG1, and a combination thereof.

The detection means used in the kit may be any means conventionally used in determining a Cbl concentration, a Cbl mutation, a c-Met mutation, and/or an LRIG1 level. A person having ordinary skill in the art to which the present invention pertains may readily take a suitable detection means.

In accordance with still another aspect thereof, the present invention addresses a method for inhibiting c-Met activity, including administering a pharmaceutically effective amount of the specific anti-c-Met antibody to the identified subject.

In accordance with yet a further aspect thereof, the present invention addresses a method for the prophylaxis and/or therapy of c-Met-related diseases, including administering a pharmaceutically effective amount of the specific anti-c-Met antibody to a subject in need thereof.

The methods for inhibiting c-Met activity or for preventing and/or treating of c-Met-related diseases may further include identifying a subject suitable for application of the specific anti-c-Met antibody.

This identifying step is the same as in the identifying method described above. Thus, it may be carried out in the same manner as in the identifying method.

In one embodiment, the method for inhibiting c-Met activity or for the prophylaxis or therapy of c-Met-related diseases includes:

identifying a subject suitable for application of the specific anti-c-Met antibody; and

administering a pharmaceutically effective amount of the specific anti-c-Met antibody to the subject.

In another embodiment, the method for inhibiting c-Met activity or for the prophylaxis or therapy of c-Met-related diseases includes:

(1) determining a Cbl concentration, a Cbl mutation, and/or a mutation of a site of c-Met for interaction with Cbl in a cell sample taken from a patient;

(2) determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when Cbl is present at a low level or absent in the cell sample and/or when a mutation is present on either or both Cbl and the site of c-Met for interaction with Cbl; and

(3) administering an effective amount of the specific anti-c-Met antibody to the cell or the patient,

wherein the absence of Cbl or the presence of Cbl at a low level in the cell sample is defined as a stain intensity of ‘-’ or ‘+1’, when analyzed by immunohistochemical staining using an anti-Cbl antibody.

In another embodiment, the method for inhibiting c-Met activity or for the prophylaxis or therapy of c-Met-related diseases includes:

(1’) determining a Cbl concentration in a cell sample taken from a patient;

(2’) determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when Cbl is absent or present at a low level in the cell sample; and

(3) administering an effective amount of the specific anti-c-Met antibody to the cell or the patient,

wherein the absence of Cbl or the presence of Cbl at a low level in the cell sample is defined as a stain intensity of ‘-’ or ‘+1’, when analyzed by immunohistochemical staining using an anti-Cbl antibody.

In another embodiment, the method for inhibiting c-Met activity or for the prophylaxis and/or therapy of c-Met-related diseases includes:

(1<sup>st</sup>) determining the presence of a mutation on a Cbl protein or a Cbl gene coding for the Cbl protein in a cell sample taken from a patient;

(2<sup>nd</sup>) determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody when the mutation is present; and

(3) administering an effective amount of the specific anti-c-Met antibody to the cell or the patient.

In another embodiment, the method for inhibiting c-Met activity or for the prophylaxis and/or therapy of c-Met-related diseases includes:

(1<sup>st</sup>) determining the presence of a mutation on a site of c-Met for interaction with Cbl or on a region of a c-Met gene corresponding to the site of c-Met for interaction with Cbl in a cell sample taken from a patient; and

(2<sup>nd</sup>) determining the cell or the patient to be a subject suitable for application of the specific anti-c-Met antibody; and

(3) administering an effective amount of the specific anti-c-Met antibody to the cell or the patient.

As described above, the method for the prophylaxis and/or therapy of c-Met-related diseases may further include (1-1), (1-1’), (1-1<sup>st</sup>), or (1-1<sup>st</sup>) determining a level of LRIG1 in a cell sample ahead of the step (2), (2’), (2<sup>nd</sup>), or (2<sup>nd</sup>), respectively.

The specific anti-c-Met antibody of the present invention is applied to a subject. Thus, the application of the specific anti-c-Met antibody of the present invention to the subject forms an aspect of the present invention. In detail, the present invention provides the use of the specific anti-c-Met antibody in application or administration to a cell or a patient in which the absence of Cbl or the presence of Cbl at a low level (the Cbl concentration is expressed as a stain intensity of ‘-’ or ‘+1’ as analyzed by immunohistochemical staining using an anti-Cbl antibody) and/or in which a functional mutation is present on a Cbl protein or a Cbl gene and/or in which a mutation is present on a site of c-Met for interaction with Cbl or on a region of a c-Met gene corresponding to the site of c-Met for interaction with Cbl, thereby inhibiting c-Met activity or treating a c-Met-related disease. The c-Met-related disease is as described above.

In one embodiment, the present invention provides the use of the specific anti-c-Met antibody in application or administration to a cell or a patient in which the absence of Cbl or the presence of Cbl at a low level (the Cbl concentration is expressed as a stain intensity of ‘-’ or ‘+1’ as analyzed by immunohistochemical staining using an anti-Cbl antibody) and/or in which a functional mutation is present on a Cbl protein or a Cbl gene and/or in which a mutation is present on a site of c-Met for interaction with Cbl or on a region of c-Met gene corresponding to the site of c-Met for interaction with Cbl, with the proviso that LRIG1 is present in the cell sample (for example, wherein the level of LRIG1 in the cell sample is expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody), thereby inhibiting c-Met activity or treating a c-Met-related disease.

In another embodiment, the present invention provides the use of the specific anti-c-Met antibody in preparing a drug

applicable to a cell in which the absence of Cbl or the presence of Cbl at a low level (the Cbl concentration is expressed as a stain intensity of ‘-’ or ‘+1’ as analyzed by immunohistochemical staining using an anti-Cbl antibody) and/or in which a functional mutation is present on a Cbl protein or a Cbl gene and/or in which a mutation is present on a site of c-Met for interaction with Cbl or on a region of c-Met gene corresponding to the site of c-Met for interaction with Cbl, thereby inhibiting c-Met activity or treating a c-Met-related disease. The drug may be a c-Met inhibitor or a therapeutic for a c-Met-related disease.

In another embodiment, the present invention provides the use of the specific anti-c-Met antibody in preparing a c-Met inhibitor and/or a therapeutic for a c-Met-related disease, applicable or administrable to a cell or a patient in which the absence of Cbl or the presence of Cbl at a low level (the Cbl concentration is expressed as a stain intensity of ‘-’ or ‘+1’ as analyzed by immunohistochemical staining using an anti-Cbl antibody) and/or in which a functional mutation is present on a Cbl protein or a Cbl gene and/or in which a mutation is present on a site of c-Met for interaction with Cbl or on a region of a c-Met gene corresponding to the site of c-Met for interaction with Cbl, with the proviso that LRIG1 is present in the cell sample (wherein, for example, the level of LRIG1 in the cell sample is expressed as a stain intensity of ‘+2’ or ‘+3’ as analyzed by immunohistochemical staining using an anti-LRIG1 antibody), thereby inhibiting c-Met activity or treating a c-Met-related disease.

The term “c-Met-related disease” refers to any disease caused by the expression or overexpression of c-Met. Cancer is representative of a c-Met-related disease. Examples of cancer include squamous cell carcinoma, small cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, peritoneal carcinoma, dermal cancer, dermal or intraocular melanoma, rectal cancer, perianal cancer, esophageal cancer, small intestine cancer, endocrine gland cancer, parathyroid cancer, adrenal gland cancer, soft tissue sarcoma, urethral cancer, chronic or acute leukemia, lymphocyte lymphoma, hepatoma, stomach cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatic tumor, breast cancer, colon cancer, large intestine cancer, endometrial cancer, uterine cancer, salivary gland cancer, renal cancer, prostate cancer, vulvar cancer, thyroid cancer, and head and neck cancer, but are not limited thereto. Gestational diabetes also falls within the scope of c-Met-related diseases.

The term “pharmaceutically effective amount” or “therapeutically effective amount” means a dosage of a particular active agent, in this case the specific anti-c-Met antibody, to exhibit a desired effect, for instance inhibiting (degrading) c-Met, and preventing or treating c-Met-related diseases in a subject in need thereof, and may vary depending on various factors including a desired result, kinds of diseases or symptoms, the severity of illness, the route of administration, dosage forms, etc.

As described above, “c-Met” or “c-Met protein” is receptor tyrosine kinase (RTK) which binds hepatocyte growth factor (HGF). c-Met may be a c-Met protein from any species, particularly a mammal, for instance, primates such as human c-Met (e.g., NP\_000236), or monkey c-Met (e.g., *Macaca mulatta*, NP\_001162100), or rodents such as mouse c-Met (e.g., NP\_032617.2), rat c-Met (e.g., NP\_113705.1), and the like. The c-Met protein may include a polypeptide encoded by the nucleotide sequence identified as GenBank Accession Number NM\_000245, a polypeptide having the amino acid sequence identified as GenBank Accession Number NP\_000236 or extracellular domains thereof. The receptor

tyrosine kinase c-Met participates in various mechanisms, such as cancer development, metastasis, migration of cancer cell, invasion of cancer cell, angiogenesis, and the like.

The antigen binding fragment of the anti-c-Met antibody may refer to a fragment including an antigen binding region of the anti-c-Met antibody, and be selected from the group consisting of a complementarity determining region (CDR), fragment including CDR and Fc region, scFv, (scFv)<sub>2</sub>, Fab, Fab', and F(ab')<sub>2</sub> of the anti-c-Met antibody.

The anti-c-Met antibody may also include a variant of the antibody. The variant of the antibody may be any isotypes of antibodies derived from human and other animals and/or one including any Fc region of antibodies (e.g., IgA, IgD, IgE, IgG (IgG1, IgG2, IgG3, or IgG4), IgM, and the like) derived from human and other animals, having mutated hinge wherein at least one amino acid is changed, deleted or added. Unless stated otherwise, the anti-c-Met antibody may include variants of the antibody as well as the antibody with no variation.

Unless stated otherwise, the term "specific anti-c-Met antibody," as used herein, is intended to mean an antibody or an antigen-binding fragment. The specific anti-c-Met antibody may recognize a specific region of c-Met, e.g., a specific region of the SEMA domain, as an epitope. It may be any antibody or an antigen-binding fragment that acts on c-Met to induce c-Met intracellular internalization and degradation.

c-Met, a receptor for hepatocyte growth factor, may be divided into three portions: extracellular, transmembrane, and intracellular. The extracellular portion is composed of an  $\alpha$ -subunit and a  $\beta$ -subunit which are linked to each other through a disulfide bond, and contains a SEMA domain responsible for binding HGF, a PSI domain (plexin-sema- phorins-integrin homology domain) and an IPT domain (immunoglobulin-like fold shared by plexins and transcriptional factors domain). The SEMA domain of c-Met protein may have the amino acid sequence of SEQ ID NO: 79, and is an extracellular domain that functions to bind HGF. A specific region of the SEMA domain, that is, a region having the amino acid sequence of SEQ ID NO: 71, which corresponds to a range from a.a. 106 to a.a. 124, is a loop region between the second and the third propellers within the epitopes of the SEMA domain. It acts as an epitope for the specific anti-c-Met antibody of the present invention.

The term "epitope," as used herein, refers to an antigenic determinant, a part of an antigen recognized by an antibody. In one embodiment, the epitope may be a region including 5 or more consecutive amino acid residues within the SEMA domain (SEQ ID NO: 79) of c-Met protein, for instance, 5 to 19 consecutive amino acid residues corresponding to a range from a.a. 106 to a.a. 124 within the SEMA domain (SEQ ID NO: 79) of a c-Met protein. For example, the epitope may be a polypeptide having 5 to 19 consecutive amino acids selected from among partial combinations of the amino acid sequence of SEQ ID NO: 71, with the amino sequence of SEQ ID NO: 73 (EEPSQ) serving as an essential element for the epitope. For example, the epitope may be a polypeptide including the amino acid sequence of SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73. As used herein, the term "consecutive amino acid residues" refers to amino acid residues positioned consecutively in an amino acid sequence or three-dimensional structure.

The epitope having the amino acid sequence of SEQ ID NO: 72 corresponds to the outermost part of the loop between the second and third propellers within the SEMA domain of a c-Met protein, the epitope having the amino acid sequence of SEQ ID NO: 73 is a site to which the antibody or an antigen-

binding fragment according to one embodiment of the present invention most specifically binds.

Thus, the specific anti-c-Met antibody may specifically bind to an epitope which has 5 to 19 consecutive amino acids, selected from among partial combinations of the amino acid sequence of SEQ ID NO: 71, including SEQ ID NO: 73 as an essential element. For example, the anti c-Met antibody may specifically bind to an epitope including the amino acid sequence of SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.

In one embodiment, the specific anti-c-Met antibody may be an antibody or an antigen-binding fragment which includes:

a heavy chain variable region including the amino acid sequence of at least one heavy chain complementarity determining region (CDR) selected from the group consisting of CDR-H1 including the amino acid sequence of SEQ ID NO: 4; CDR-H2 including the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 2, or including an amino acid sequence of 8 to 19 consecutive amino acids including amino acid residues from 3rd to 10th positions within the amino acid sequence of SEQ ID NO: 2; and CDR-H3 including the amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 85, or including an amino acid sequence of 6 to 13 consecutive amino acids including amino acid residues from 1st to 6th positions within the amino acid sequence of SEQ ID NO: 85; and

a light chain variable region including the amino acid sequence of at least one light chain complementarity determining region (CDR) selected from the group consisting of CDR-L1 including the amino acid sequence of SEQ ID NO: 7; CDR-L2 including the amino acid sequence of SEQ ID NO: 8, and CDR-L3 including the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 86, or including an amino acid sequence of 9 to 17 consecutive amino acids including amino acid residues from 1st to 9th positions within the amino acid sequence of SEQ ID NO: 89.

Herein, the amino acid sequences of SEQ ID NOS: 4 to 9 are respectively represented by following Formulas I to VI, below:

Formula I (SEQ ID NO: 4)  
Xaa<sub>1</sub>-Xaa<sub>2</sub>-Tyr-Tyr-Met-Ser,

wherein Xaa<sub>1</sub> is absent or Pro or Ser, and Xaa<sub>2</sub> is Glu or Asp,

Formula II (SEQ ID NO: 5)  
Arg-Asn-Xaa<sub>3</sub>-Xaa<sub>4</sub>-Asn-Gly-Xaa<sub>5</sub>-Thr,

wherein Xaa<sub>3</sub> is Asn or Lys, Xaa<sub>4</sub> is Ala or Val, and Xaa<sub>5</sub> is Asn or Thr,

Formula III (SEQ ID NO: 6)  
Asp-Asn-Trp-Leu-Xaa<sub>6</sub>-Tyr,

wherein Xaa<sub>6</sub> is Ser or Thr,

Formula IV (SEQ ID NO: 7)  
Lys-Ser-Ser-Xaa<sub>7</sub>-Ser-Leu-Leu-Ala-Xaa<sub>8</sub>-Gly-Asn-

Xaa<sub>9</sub>-Xaa<sub>10</sub>-Asn-Tyr-Leu-Ala

wherein Xaa<sub>7</sub> is His, Arg, Gln, or Lys, Xaa<sub>8</sub> is Ser or Trp, Xaa<sub>9</sub> is His or Gln, and Xaa<sub>10</sub> is Lys or Asn,

Formula V (SEQ ID NO: 8)  
 Trp-Xaa<sub>11</sub>-Ser-Xaa<sub>12</sub>-Arg-Val-Xaa<sub>13</sub>

wherein Xaa<sub>11</sub> is Ala or Gly, Xaa<sub>12</sub> is Thr or Lys, and Xaa<sub>13</sub> is Ser or Pro, and

Formula VI (SEQ ID NO: 9)  
 Xaa<sub>14</sub>-Gln-Ser-Tyr-Ser-Xaa<sub>15</sub>-Pro-Xaa<sub>16</sub>-Thr

wherein Xaa<sub>14</sub> is Gly, Ala, or Gln, Xaa<sub>15</sub> is Arg, His, Ser, Ala, Gly, or Lys, and Xaa<sub>16</sub> is Leu, Tyr, Phe, or Met.

In one embodiment, the CDR-H1 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 22, 23, and 24. The CDR-H2 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 25, and 26. The CDR-H3 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 27, 28, and 85.

The CDR-L1 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 10, 29, 30, 31, 32, 33, and 108. The CDR-L2 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 11, 34, 35, and 36. The CDR-L3 may have an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 13, 14, 15, 16, 37, 86, and 89.

In another embodiment, the antibody or an antigen-binding fragment of the present invention includes a heavy variable region including a polypeptide (CDR-H1) having an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 22, 23, and 24, a polypeptide (CDR-H2) having an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 25, and 26, and a polypeptide (CDR-H3) having an amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 27, 28, and 85; and a light variable region including a polypeptide (CDR-L1) having an amino acid sequence selected from the group consisting of SEQ ID NOS: 10, 29, 30, 31, 32, 33 and 108, a polypeptide (CDR-L2) having an amino acid sequence selected from the group consisting of SEQ ID NOS: 11, 34, 35, and 36, and a polypeptide (CDR-L3) having an amino acid sequence selected from the group consisting of SEQ ID NOS 12, 13, 14, 15, 16, 37, 86, and 89.

Animal-derived antibodies produced by immunizing non-immune animals with a desired antigen generally invoke immunogenicity when injected to humans for the purpose of medical treatment, and thus chimeric antibodies have been developed to inhibit such immunogenicity. Chimeric antibodies are prepared by replacing constant regions of animal-derived antibodies that cause an anti-isotype response with constant regions of human antibodies by genetic engineering. Chimeric antibodies are considerably improved in an anti-isotype response compared to animal-derived antibodies, but animal-derived amino acids still have variable regions, so that chimeric antibodies have side effects with respect to a potential anti-idiotypic response. Humanized antibodies are developed to reduce such side effects. Humanized antibodies are produced by grafting complementarity determining regions (CDR) which serve an important role in antigen binding in variable regions of chimeric antibodies into a human antibody framework.

The most important thing in CDR grafting to produce humanized antibodies is choosing the optimized human antibodies for accepting CDR of animal-derived antibodies. Antibody databases, analysis of a crystal structure, and technology for molecule modeling are used. However, even when the CDRs of animal-derived antibodies are grafted to the most

optimized human antibody framework, amino acids positioned in a framework of the animal-derived CDRs affecting antigen binding are present. Therefore, in many cases, antigen binding affinity is not maintained, and thus application of additional antibody engineering technology for recovering the antigen binding affinity is necessary.

The anti-c-Met antibodies may be mouse-derived antibodies, mouse-human chimeric antibodies, humanized antibodies, or human antibodies. The antibodies or antigen-binding fragments thereof may be isolated from a living body.

The antibody may be a monoclonal antibody. The monoclonal antibody may be produced from a hybridoma of Accession No. KCLRF-BP-00220 deposited on Oct. 6, 2009, at the Korean Cell Line Research Foundation located at the Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-gong, Chongno-Gu, Seoul, 110-744, Korea.

An intact antibody includes two full-length light chains and two full-length heavy chains, in which each light chain is linked to a heavy chain by disulfide bonds. The antibody has a heavy chain constant region and a light chain constant region. The heavy chain constant region is of a gamma ( $\gamma$ ), mu ( $\mu$ ), alpha ( $\alpha$ ), delta ( $\delta$ ), or epsilon ( $\epsilon$ ) type, which may be further categorized as gamma 1 ( $\gamma$ 1), gamma 2 ( $\gamma$ 2), gamma 3 ( $\gamma$ 3), gamma 4 ( $\gamma$ 4), alpha 1 ( $\alpha$ 1), or alpha 2 ( $\alpha$ 2). The light chain constant region is of either a kappa ( $\kappa$ ) or lambda ( $\lambda$ ) type.

As used herein, the term "heavy chain" refers to full-length heavy chain, and fragments thereof, including a variable region VH that includes amino acid sequences sufficient to provide specificity to antigens, and three constant regions, CH1, CH2, and CH3, and a hinge. The term "light chain" refers to a full-length light chain and fragments thereof, including a variable region VL that includes amino acid sequences sufficient to provide specificity to antigens, and a constant region CL.

The term "complementarity determining region (CDR)" refers to an amino acid sequence found in a hyper variable region of a heavy chain or a light chain of immunoglobulin. The heavy and light chains may respectively include three CDRs (CDRH1, CDRH2, and CDRH3; and CDRL1, CDRL2, and CDRL3). The CDR may provide contact residues that play an important role in the binding of antibodies to antigens or epitopes. The terms "specifically binding" or "specifically recognized" is well known to one of ordinary skill in the art, and indicates that an antibody and an antigen specifically interact with each other to lead to an immunological activity.

In one embodiment, the antibody may be an antigen-binding fragment selected from the group consisting of scFv, (scFv)<sub>2</sub>, Fab, Fab', and F(ab')<sub>2</sub>.

The term "antigen-binding fragment" used herein refers to fragments of an intact immunoglobulin including portions of a polypeptide including antigen-binding regions having the ability to specifically bind to the antigen. For example, the antigen-binding fragment may be scFv, (scFv)<sub>2</sub>, Fab, Fab', or F(ab')<sub>2</sub>, but is not limited thereto. Among the antigen-binding fragments, Fab that includes light chain and heavy chain variable regions, a light chain constant region, and a first heavy chain constant region CH1, has one antigen-binding site.

The Fab' fragment is different from the Fab fragment, in that Fab' includes a hinge region with at least one cysteine residue at the C-terminal of CH1.

The F(ab')<sub>2</sub> antibody is formed through disulfide bridging of the cysteine residues in the hinge region of the Fab' fragment. Fv is the smallest antibody fragment with only a heavy

chain variable region and a light chain variable region. Recombination techniques of generating the Fv fragment are widely known in the art.

Two-chain Fv includes a heavy chain variable region and a light chain region which are linked by a non-covalent bond. Single-chain Fv generally includes a heavy chain variable region and a light chain variable region which are linked by a covalent bond via a peptide linker or linked at the C-terminals to have a dimer structure like the two-chain Fv. The antigen-binding fragments may be attainable using protease (for example, the Fab fragment may be obtained by restricted cleavage of a whole antibody with papain, and the F(ab')<sub>2</sub> fragment may be obtained by cleavage with pepsin), or may be prepared by using a genetic recombination technique.

The term "hinge region," as used herein, refers to a region between CH1 and CH2 domains within the heavy chain of an antibody which functions to provide flexibility for the antigen-binding site.

When an animal antibody undergoes a chimerization process, the IgG1 hinge of animal origin is replaced with a human IgG1 hinge while the disulfide bridges between two heavy chains are reduced from three to two in number. In addition, an animal-derived IgG1 hinge is shorter than a human IgG1 hinge. Accordingly, the rigidity of the hinge is changed. Thus, a modification of the hinge region may bring about an improvement in the antigen binding efficiency of the humanized antibody. The modification of the hinge region through amino acid deletion, addition, or substitution is well-known to those skilled in the art.

In one embodiment, the specific anti-c-Met antibody or an antigen-binding fragment thereof may be modified by the deletion, addition, or substitution of at least one amino acid residue on the amino acid sequence of the hinge region so that it exhibits enhanced antigen-binding efficiency. For example, the antibody may include a hinge region having the amino acid sequence of SEQ ID NO: 100, 101, 102, 103, 104, or 105. Preferably, the hinge region has the amino acid sequence of SEQ ID NO: 100 or 101.

In one embodiment of the specific anti-c-Met antibody or an antigen-binding fragment, the variable domain of the heavy chain includes the amino acid sequence of SEQ ID NO: 17, 74, 87, 90, 91, 92, 93, or 94 and the variable domain of the light chain includes the amino acid sequence of SEQ ID NO: 18, 19, 20, 21, 75, 88, 95, 96, 97, 98, 99 or 109.

In one embodiment, the specific anti-c-Met antibody is a monoclonal antibody, produced by the hybridoma cell line deposited with Accession No. KCLRF-BP-00220, binding specifically to the extracellular region of c-Met protein (refer to Korean Patent Publication No. 2011-0017698, the disclosure of which is incorporated in its entirety herein by reference).

The specific anti-c-Met antibody may include all the antibodies defined in Korean Patent Publication No. 2011-0017698, which is incorporated herein by reference.

By way of further example, the anti-c-Met antibody or antibody fragment may include a heavy chain including the amino acid sequence of SEQ ID NO: 62 (wherein the amino acid sequence from 1st to 17th positions is a signal peptide) or the amino acid sequence from 18th to 462nd positions of SEQ ID NO: 62 and a light chain including the amino acid sequence of SEQ ID NO: 68 (wherein the amino acid sequence from 1st to 20th positions is a signal peptide) or the amino acid sequence from 21st to 240th positions of SEQ ID NO: 68; or a heavy chain including the amino acid sequence of SEQ ID NO: 64 (wherein the amino acid sequence from 1st to 17th positions is a signal peptide) or the amino acid sequence from 18th to 461st positions of SEQ ID NO: 64 and

a light chain including the amino acid sequence of SEQ ID NO: 68 or the amino acid sequence from 21st to 240th of SEQ ID NO: 68; or a heavy chain including the amino acid sequence of SEQ ID NO: 66 (wherein the amino acid sequence from 1st to 17th positions is a signal peptide) or the amino acid sequence from 18th to 460th positions of SEQ ID NO: 66 and a light chain including the amino acid sequence of SEQ ID NO: 68 or the amino acid sequence from 21st to 240th of SEQ ID NO: 68.

Additional examples of anti-c-Met antibodies include those in which the anti-c-Met antibody includes a heavy chain including the amino acid sequence of SEQ ID NO: 62 or the amino acid sequence from 18th to 462nd positions of SEQ ID NO: 62 and a light chain including the amino acid sequence of SEQ ID NO: 70 (wherein the amino acid sequence from 1st to 20th positions is a signal peptide) or the amino acid sequence from 21st to 240th positions of SEQ ID NO: 70; a heavy chain including the amino acid sequence of SEQ ID NO: 64 or the amino acid sequence from 18th to 461st positions of SEQ ID NO: 64 and a light chain including the amino acid sequence of SEQ ID NO: 70 or the amino acid sequence from 21st to 240th positions of SEQ ID NO: 70; or a heavy chain including the amino acid sequence of SEQ ID NO: 66 or the amino acid sequence from 18th to 460th of SEQ ID NO: 66 and a light chain including the amino acid sequence of SEQ ID NO: 70 or the amino acid sequence from 21st to 240th positions of SEQ ID NO: 70.

In still other examples, the anti-c-Met antibody may include a heavy chain including the amino acid sequence of SEQ ID NO: 62 or the amino acid sequence from 18th to 462nd positions of SEQ ID NO: 62 and a light chain including the amino acid sequence of SEQ ID NO: 110; a heavy chain including the amino acid sequence of SEQ ID NO: 64 or the amino acid sequence from 18th to 461st positions of SEQ ID NO: 64 and a light chain including the amino acid sequence of SEQ ID NO: 110; or a heavy chain including the amino acid sequence of SEQ ID NO: 66 or the amino acid sequence from 18th to 460th positions of SEQ ID NO: 66 and a light chain including the amino acid sequence of SEQ ID NO: 110.

In an embodiment, the anti-c-Met antibody may include a heavy chain including the amino acid sequence from 18th to 460th positions of SEQ ID NO: 66 and a light chain including the amino acid sequence from 21st to 240th positions of SEQ ID NO: 68; or a heavy chain including the amino acid sequence from 18th to 460th positions of SEQ ID NO: 66 and a light chain including the amino acid sequence of SEQ ID NO: 110.

The specific anti-c-Met or the antigen-binding fragment thereof according to the present invention may be used in a pharmaceutical composition. Accordingly, a pharmaceutical composition including a pharmaceutically effective amount of the specific anti-c-Met or the antigen-binding fragment thereof, optionally together with a pharmaceutically acceptable vehicle, a diluent, and/or an excipient, form yet another aspect of the present invention.

So long as it is usually used in drug formulations, any pharmaceutically acceptable vehicle may be contained in the pharmaceutical composition including the anti-c-Met antibody according to the present invention. Examples of the pharmaceutically acceptable vehicle available for the pharmaceutical composition of the present invention include lactose, dextrose, sucrose, sorbitol, mannitol, starch, acacia gum, calcium phosphate, alginate, gelatin, calcium silicate, microcrystalline cellulose, polyvinyl pyrrolidone, cellulose, water, syrup, methyl cellulose, methyl hydroxybenzoate, propylhydroxybenzoate, talc, magnesium stearate, and mineral oil, but are not limited thereto. The pharmaceutical composi-

tion may further include an additive selected from the group consisting of a diluent, an excipient, a lubricant, a wetting agent, a sweetener, a flavorant, an emulsifier, a suspending agent, a preservative, and a combination thereof.

The specific anti-c-Met or the pharmaceutical composition including a pharmaceutically effective amount thereof may be administered orally or parenterally. For parenteral administration, the administration may be carried out via intravenous, subcutaneous, intramuscular, intraperitoneal, intradermal, local, intranasal, intrapulmonary, and intrarectal routes, but is not limited thereto. For oral administration, however, the pharmaceutical composition is preferably coated or formulated to protect the active ingredient from being degraded in the stomach because the peptides are digested by pepsin. In addition, the administration may be performed with the aid of an instrument adapted for delivering the pharmaceutical composition to target cells.

The effective amount may vary depending on various factors including the type of formulation, the patient's age, weight, and sex, the severity of the disorder being treated, diet, the time of administration, the route of administration, the rate of excretion, and sensitivity. For example, the composition of the present invention may be administered at a single dose ranging from about 0.001 mg to about 100 mg for adults, for example, from about 0.001 mg to about 0.1 mg, from about 0.1 mg to about 1 mg, from about 1 mg to about 10 mg, or from about 10 mg to about 100 mg.

According to a method that is well known to those skilled in the art, the anti-c-Met antibody or the pharmaceutical composition of the present invention may be formulated, together with pharmaceutically acceptable carriers and/or excipients, into unit dose forms, or may be included within a multiple dose package. In this context, the pharmaceutical composition may be formulated into solutions in oil or aqueous media, suspensions, syrup, emulsions, elixirs, powders, granules, tablets, or capsules, and may further include a dispersant or a stabilizer.

The anti-c-Met antibody or the pharmaceutical composition of the present invention may be administered alone or in combination with other therapeutics. In this case, they are administered sequentially or simultaneously together with conventional therapeutics.

The composition including an antibody or an antigen-binding fragment can be formulated into immunoliposomes. Liposomes including an antibody may be prepared using methods that are well-known in the art. The immunoliposomes may be produced from a lipid composition including phosphatidylcholine, cholesterol, and PEGylated phosphatidylethanolamine by reverse-phase evaporation. To quote an example, Fab' may be conjugated to liposomes by disulfide reformation. The liposome may further contain an anticancer agent such as doxorubicin.

In one embodiment, the antibody may act as an antagonist of c-Met protein.

As used herein, the term "antagonist" is intended to encompass all molecules that at least partially block, suppress, or neutralize at least one of the biological activities of a target (e.g., c-Met). By way of example, an "antagonist" antibody means an antibody that represents suppression or inhibition against the biological activity of the antigen to which the antibody binds (e.g., c-Met). An antagonist may function to reduce ligand-induced receptor phosphorylation or to incapacitate or kill cells which have been activated by ligands. Also, an antagonist may completely interfere with receptor-ligand interaction or substantially reduce the interaction by changing the three-dimensional structure of the receptor or by down regulation.

The present invention may expand the choice of application of the specific anti-c-Met antibody. That is, the present invention may expand the choice of application of an anti-c-Met antibody by identifying the cells (cancer cells) on which preexisting anti-c-Met antibodies cannot induce c-Met degradation due to a quantitative reduction in Cbl or a mutation on Cbl or c-Met, or patients with the cells, thereby effectively treating c-Met-related diseases through a Cbl-independent c-Met degradation mechanism. Accordingly, the present invention enables a tailored treatment pertinent to patients of c-Met-related diseases.

Further, anticancer agents based on Cbl-mediated mechanisms may exhibit the adverse effect of c-Met activation, whereas the Cbl-independent mechanism, as suggested in the present invention, allows for targeting c-Met, whether activated or not, thus reducing the adverse effects attributable to the agonism.

In addition, the present invention may identify a subject suitable for application of the specific anti-c-Met antibody by use of a very small amount of proteins or RNA, thus enjoying advantages in terms of the cost, time, and efficacy of anticancer therapy.

The present invention pertains to a specific anti-c-Met antibody which may be applied to subjects showing c-Met degradation independent of or partially dependent on Cbl. Conventional therapeutics, which induce c-Met degradation in a Cbl-dependent manner, cannot work at all when c-Met is abnormally up-regulated due to a problem with Cbl. However, the specific anti-c-Met antibody of the present invention may be used to treat c-Met-related diseases even upon the up-regulation of c-Met due to Cbl mutation. Accordingly, it is necessary to molecularly diagnose a patient population which does not allow Cbl to bind to c-Met or to function normally in order to apply the specific anti-c-Met antibody thereto.

Due to its ability to induce Cbl-independent c-Met degradation, the specific anti-c-Met antibody may be applied to a variety of cancers irrespective of the presence or absence or mutation of Cbl. Accordingly, provided herein is a method of treating cancer characterized by low or absent Cbl expression or by a mutation in Cbl or c-Met that inhibits interaction between Cbl and c-Met, or a cancer resistant to treatment with EGFR-targeted therapy in a subject, the method comprising administering an antibody or antigen-binding fragment thereof that specifically binds to an epitope within a SEMA domain of a c-Met protein to the subject. The cancer may be further characterized by the presence of LRIG1. The method may, therefore, also include steps of (i) determining that expression of Cbl in a cell or sample or the cancer from the subject is low, or detecting a mutation in Cbl or c-Met that inhibits interaction between Cbl and c-Met, and/or (ii) detecting or otherwise confirming the presence of LRIG1 in a cell or sample of the cancer from the subject. All other aspects of this method are as described with respect to other methods provided herein.

Because preexisting anti-c-Met antibodies induce c-Met degradation only in a Cbl enzyme (E3 ligase)-dependent manner, they cannot exert anticancer activity in the case of abnormal Cbl. An experiment showed that the lung cancer cell line EBC-1 expressed a very low level of Cbl, compared to H4441, which is a different lung cancer cell line (refer to FIG. 2C). EBC-1 cells were, thus, observed to abnormally increase in c-Met protein level because of the lack of Cbl-mediated c-Met degradation. As demonstrated by an experiment (refer to FIG. 2E), the specific anti-c-Met antibody, which is able to target c-Met in a Cbl-independent manner, inhibited the growth of the lung cancer cell line EBC-1 in a dose-dependent manner, whereas the preexisting antibody

5D5 promoted the cell growth. In addition, the stomach cancer cell line HS746T in which c-Met is truncated at a site for interaction with Cbl was observed to die upon treatment with the specific anti-c-Met antibody, but proliferated in the presence of 5D5 (refer to FIG. 3E).

When cancer cells are further proliferated as Cbl does not work in c-Met degradation, cancer progression continues if the cell death program does not work. In order to demonstrate that the anticancer effect of the specific anti-c-Met antibody is due to its ability to down-regulate c-Met irrespective of the presence or absence of Cbl, an apoptosis experiment was carried out. The specific anti-c-Met antibody of the present invention was found to induce the lung cancer cell line EBC-1 to undergo apoptosis in a dose-dependent manner, whereas the preexisting anti-c-Met antibody 5D5 cannot at all (refer to FIG. 3G).

The anticancer effect of the specific anti-c-Met antibody irrespective of Cbl was also demonstrated in the condition where Cbl was down-regulated with siRNA or was functionally inhibited by an inhibitor.

Transfection with siRNA causes the cancer cell line to decrease in intracellular protein as well as RNA level of Cbl. Thus, if the anticancer effect of an anti-c-Met antibody is monitored in cancer cells transfected with or without siRNA of Cbl, the dependency of the antibody on Cbl may be obtained. The anticancer effect of the specific anti-c-Met antibody was almost not changed in light of c-Met degradation whereas 5D5, dependent on Cbl, did not reduce the level of c-Met in Cbl-knockdown animals (refer to FIG. 3C).

MG132 is an inhibitor which reduces the degradation of ubiquitin-conjugated proteins through the proteasome pathway. E3 ligases including Cbl function to degrade proteins only through the proteasome pathway. Even after treatment with MG132, the specific anti-c-Met antibody was found to decrease the level of c-Met in cancer cells (refer to FIG. 3D), which demonstrates the independency of the specific anti-c-Met antibody on Cbl.

In addition, the adverse effects caused by preexisting antibodies were not detected with the specific anti-c-Met antibody of the present invention. 5D5, a preexisting anti-c-Met antibody, induces the activation of c-Met (phosphorylation at C-terminus Y1234 or Y1235). Thus, the phosphorylation of Akt and Erk oncogenes downstream of c-Met activation takes place, causing the adverse effect of the drug (agonism). Phosphorylated Akt and phosphorylated Erk are known as markers for determining agonism. In the lung cancer cell line NCI-H441 and the kidney cancer cell line Caki-1, adverse effects were significantly detected after the application of 5D5 to the cells, but little or not at all after the application of the specific anti-c-Met antibody, as measured for the agonism marker (refer to FIG. 1B). This data indicates that an anti-c-Met antibody which targets c-Met in a Cbl-independent manner exhibits improved anticancer effects with a reduction in side effects.

Further, a mouse tumor xenograft experiment and a cell migration assay demonstrated the independency of the specific anti-c-Met antibody of the present invention on Cbl in stomach and lung cancer cell lines (refer to Example 5, below). The anticancer effect of the specific anti-c-Met antibody was observed in vivo using a tumor xenograft experiment in which nude mice were subcutaneously transplanted with cancer cells and treated with drugs. In tumor xenograft experiments with mice transplanted with the lung cancer cell line EBC-1, which is low in intracellular Cbl level, or the stomach cancer cell line HS746T, which has a mutation on the site of c-Met for interaction with Cbl, 5D5 did not suppress cancer progression without a difference from the control.

However, the specific anti-c-Met antibody was found to have an effective anticancer mechanism in vivo thanks to its independency on Cbl, as measured by the tumor xenograft experiment (refer to FIGS. 5C and 5D).

With the advance of cancer progression, cancer cells acquire the ability to migrate along blood vessels, which results in cancer metastasis. A cell migration assay is an experiment by which the ability of cells to migrate may be observed in vitro. The specific anti-c-Met antibody was found to suppress the migration of cancer cells, but the preexisting antibody 5D5 did not, as measured by a cell migration assay using the lung cancer cell line EBC-1 and the stomach cancer cell line HS746T in both of which Cbl independency may be proven (refer to FIGS. 5A and 5B).

One or more embodiments of the present invention will now be described in further detail with reference to the following Examples. However, these examples are for the illustrative purposes only and are not intended to limit the scope of the invention.

## Reference Example 1

### Construction of Anti-c-Met Antibody

#### 1.1. Production of "AbF46", a Mouse Antibody to c-Met 1.1.1. Immunization of Mouse

To obtain immunized mice necessary for the development of a hybridoma cell line, each of five BALB/c mice (Japan SLC, Inc.), 4 to 6 weeks old, was intraperitoneally injected with a mixture of 100 µg of human c-Met/Fc fusion protein (R&D Systems) and one volume of complete Freund's adjuvant. Two weeks after the injection, second intraperitoneal injection was conducted on the same mice with a mixture of 50 µg of human c-Met/Fc protein and one volume of incomplete Freund's adjuvant. One week after the second immunization, the immune response was finally boosted. Three days later, blood was taken from the tail and the sera were 1/1000 diluted in PBS and used to examine a titer of antibody to c-Met by ELISA. Mice found to have a sufficient antibody titer were selected for use in the cell fusion process.

#### 1.1.2. Cell Fusion and Production of Hybridoma

Three days before cell fusion, BALB/c mice (Japan SLC, Inc.) were immunized with an intraperitoneal injection of a mixture of 50 µg of human c-Met/Fc fusion protein and one volume of PBS. The immunized mice were anesthetized before excising the spleen from the left half of the body. The spleen was meshed to separate splenocytes which were then suspended in a culture medium (DMEM, GIBCO, Invitrogen). The cell suspension was centrifuged to recover the cell layer. The splenocytes thus obtained ( $1 \times 10^8$  cells) were mixed with myeloma cells (Sp2/0) ( $1 \times 10^8$  cells), followed by spinning to give a cell pellet. The cell pellet was slowly suspended, treated with 45% polyethylene glycol (PEG) (1 mL) in DMEM for 1 min at 37° C., and supplemented with 1 mL of DMEM. To the cells was added 10 mL of DMEM over 10 min, after which incubation was conducted in water at 37° C. for 5 min. Then the cell volume was adjusted to 50 mL before centrifugation. The cell pellet thus formed was resuspended at a density of  $1 \sim 2 \times 10^5$  cells/mL in a selection medium (HAT medium) and 0.1 mL of the cell suspension was allocated to each well of 96-well plates which were then incubated at 37° C. in a CO<sub>2</sub> incubator to establish a hybridoma cell population.

#### 1.1.3. Selection of Hybridoma Cells Producing Monoclonal Antibodies to c-Met Protein

From the hybridoma cell population established in Reference Example 1.1.2, hybridoma cells which showed a specific

response to c-Met protein were screened by ELISA using human c-Met/Fc fusion protein and human Fc protein as antigens.

Human c-Met/Fc fusion protein was seeded in an amount of 50  $\mu$ L (2  $\mu$ g/mL)/well to microtiter plates and allowed to adhere to the surface of each well. The antibody that remained unbound was removed by washing. For use in selecting the antibodies that do not bind c-Met but recognize Fc, human Fc protein was attached to the plate surface in the same manner.

The hybridoma cell culture obtained in Reference Example 1.1.2 was added in an amount of 50  $\mu$ L to each well of the plates and incubated for 1 hour. The cells remaining unreacted were washed out with a sufficient amount of Tris-buffered saline and Tween 20 (TBST). Goat anti-mouse IgG-horseradish peroxidase (HRP) was added to the plates and incubated for 1 hour at room temperature. The plates were washed with a sufficient amount of TBST, followed by reacting the peroxidase with a substrate (OPD). Absorbance at 450 nm was measured on an ELISA reader.

Like this, hybridoma cell lines which secrete antibodies that specifically and strongly bind to human c-Met but not human Fc were selected repeatedly. From the hybridoma cell lines obtained by repeated selection, a single clone producing a monoclonal antibody was finally separated by limiting dilution. The single clone of the hybridoma cell line producing the monoclonal antibody was deposited with the Korean Cell Line Research Foundation, an international depository authority located at 28 Yongon-gong, Chongno-Gu, Seoul, Korea, on Oct. 6, 2009, with Accession No. KCLRF-BP-00220 according to the Budapest Treaty (refer to Korean Patent Laid-Open Publication No. 2011-0047698).

#### 1.1.4. Production and Purification of Monoclonal Antibody

The hybridoma cell line obtained in Reference Example 1.1.3 was cultured in a serum-free medium, and the monoclonal antibody were produced and purified from the cell culture.

First, the hybridoma cells cultured in 50 mL of a medium (DMEM) supplemented with 10% (v/v) FBS were centrifuged and the cell pellet was washed twice or more with 20 mL of PBS to remove the FBS therefrom. Then, the cells were resuspended in 50 mL of DMEM and incubated for 3 days at 37° C. in a CO<sub>2</sub> incubator.

After the cells were removed by centrifugation, the supernatant was stored at 4° C. before use or immediately used for the separation and purification of the antibody. An AKTA system (GE Healthcare) equipped with an affinity column (Protein G agarose column; Pharmacia, USA) was used to purify the antibody from 50 to 300 mL of the supernatant, followed by concentration with a filter (Amicon). The antibody in PBS was stored before use in the following examples.

#### 1.2. Construction of chAbF46, a Chimeric Antibody to c-Met

A mouse antibody is apt to elicit immunogenicity in humans. To solve this problem, chAbF46, a chimeric antibody, was constructed from the mice antibody AbF46 produced in Example 1 by replacing the constant region, but not the variable region responsible for antibody specificity, with an amino sequence of human IgG1 antibody.

In this regard, a gene was designed to include the nucleotide sequence of "EcoRI-signal sequence-VH-NheI-CH-TGA-XhoI" (SEQ ID NO: 38) for a heavy chain and the nucleotide sequence of "EcoRI-signal sequence-VL-BsiWI-CL-TGA-XhoI" (SEQ ID NO: 39) for a light chain and synthesized. Then, a DNA fragment having the heavy chain nucleotide sequence (SEQ ID NO: 38) and a DNA fragment having the light chain nucleotide sequence (SEQ ID NO: 39)

were digested with EcoRI (NEB, R0101S) and XhoI (NEB, R0146S) before cloning into a pOptiVECTM-TOPO TA Cloning Kit enclosed in an OptiCHO™ Antibody Express Kit (Cat no. 12762-019, Invitrogen), and a pcDNATM3.3-TOPO TA Cloning Kit (Cat no. 8300-01), respectively.

Each of the vectors thus constructed was amplified with the aid of a Qiagen Maxiprep kit (Cat no. 12662). The vectors which respectively carried the heavy chain and the light chain were co-transfected at a ratio of 4:1 (80  $\mu$ g:20  $\mu$ g) into 293T cells (2.5 $\times$ 10<sup>7</sup>). The transfection into 293T cells (2.5 $\times$ 10<sup>7</sup>) was performed in the presence of 360  $\mu$ L of 2M CaCl<sub>2</sub>.

Afterwards, the cells were incubated in DMEM supplemented with 10% (v/v) FBS for 5 hours at 37° C. under a 5% CO<sub>2</sub> condition and then in FBS-free DMEM for 48 hours at 37° C. under a 5% CO<sub>2</sub> condition.

After centrifugation, the supernatant was applied to AKTA prime (GE Healthcare) to purify the antibody. In this regard, 100 mL of the supernatant was loaded at a flow rate of 5 mL/min to AKTA Prime equipped with a Protein A column (GE healthcare, 17-0405-03), followed by elution with an IgG elution buffer (Thermo Scientific, 21004). The buffer was exchanged with PBS to purify a chimeric antibody AbF46 (hereinafter referred to as "chAbF46").

#### 1.3. Construction of Humanized Antibody huAbF46 from Chimeric Antibody chAbF46

##### 1.3.1. Heavy Chain Humanization

To design two domains H1-heavy and H3-heavy, human germline genes which share the highest homology with the VH gene of the mouse antibody AbF46 purified in Reference Example 1.2 were analyzed. An Ig BLAST result revealed that VH3-71 has a homology of 83% at the amino acid level. CDR-H1, CDR-H2, and CDR-H3 of the mouse antibody AbF46 were defined according to Kabat numbering. A design was made to introduce the CDR of the mouse antibody AbF46 into the framework of VH3-71. Hereupon, back mutations to the amino acid sequence of the mouse AbF46 were conducted at positions 30 (S $\rightarrow$ T), 48 (V $\rightarrow$ L), 73 (D $\rightarrow$ N), and 78 (T $\rightarrow$ L). Then, H1 was further mutated at positions 83 (R $\rightarrow$ K) and 84 (A $\rightarrow$ T) to finally establish H1-heavy (SEQ ID NO: 40) and H3-heavy (SEQ ID NO: 41).

For use in designing H4-heavy, human antibody frameworks were analyzed by a search for BLAST. The result revealed that the VH3 subtype, known to be most stable, is very similar in framework and sequence to the mouse antibody AbF46. CDR-H1, CDR-H2, and CDR-H3 of the mouse antibody AbF46 were defined according to Kabat numbering and introduced into the VH3 subtype to construct H4-heavy (SEQ ID NO: 42).

##### 1.3.2. Light Chain Humanization

To design two domains H1-light (SEQ ID NO: 43) and H2-light (SEQ ID NO: 44), human germline genes which share the highest homology with the VL gene of the mouse antibody AbF46 were analyzed. An Ig BLAST search result revealed that VK4-1 has a homology of 75% at the amino acid level. CDR-L1, CDR-L2, and CDR-L3 of the mouse antibody AbF46 were defined according to Kabat numbering. A design was made to introduce the CDR of the mouse antibody AbF46 into the framework of VK4-1. Hereupon, back mutations to the amino acid sequence of the mouse AbF46 were conducted at positions 36 (Y $\rightarrow$ H), 46 (L $\rightarrow$ M), and 49 (Y $\rightarrow$ I). Only one back mutation was conducted at position 49 (Y $\rightarrow$ I) on H2-light.

To design H3-light (SEQ ID NO: 45), human germline genes which share the highest homology with the VL gene of the mouse antibody AbF46 were analyzed by a search for BLAST. As a result, VK2-40 was selected as well. VL and VK2-40 of the mouse antibody AbF46 were found to have a

homology of 61% at an amino acid level. CDR-L1, CDR-L2, and CDR-L3 of the mouse antibody were defined according to Kabat numbering and introduced into the framework of VK4-1. Back mutations were conducted at positions 36 (Y→H), 46 (L→M), and 49 (Y→I) on H3-light.

For use in designing H4-light (SEQ ID NO: 46), human antibody frameworks were analyzed. A blast search revealed that the Vk1 subtype, known to be the most stable, is very similar in framework and sequence to the mouse antibody AbF46. CDR-L1, CDR-L2, and CDR-L3 of the mouse antibody AbF46 were defined according to Kabat numbering and introduced into the Vk1 subtype. Hereupon, back mutations were conducted at positions 36 (Y→H), 46 (L→M), and 49 (Y→I) on H4-light.

Thereafter, DNA fragments having the heavy chain nucleotide sequences (H1-heavy; SEQ ID NO: 47, H3-heavy; SEQ ID NO: 48, H4-heavy; SEQ ID NO: 49) and DNA fragments having the light chain nucleotide sequences (H1-light; SEQ ID NO: 50, H2-light; SEQ ID NO: 51, H3-light; SEQ ID NO: 52, H4-light; SEQ ID NO: 53) were digested with EcoRI (NEB, R0101S) and XhoI (NEB, R0146S) before cloning into a pOptiVECTM-TOPO TA Cloning Kit enclosed in an OptiCHOIM Antibody Express Kit (Cat no. 12762-019, Invitrogen) and a pcDNATM3.3-TOPO TA Cloning Kit (Cat no. 8300-01), respectively, so as to construct recombinant vectors for expressing a humanized antibody.

Each of the recombinant vectors was amplified using Qiagen Maxiprep kit (Cat no. 12662). The vectors which respectively carried the heavy chain and the light chain were co-transfected at a ratio of 4:1 (80 μg:20 μg) into 293T cells (2.5×10<sup>7</sup>). The transfection into 293T cells (2.5×10<sup>7</sup>) was performed in the presence of 360 μL of 2M CaCl<sub>2</sub>. Afterwards, the cells were incubated in DMEM supplemented with 10% (v/v) FBS for 5 hours at 37° C. under a 5% CO<sub>2</sub> condition, and then in FBS-free DMEM for 48 hours at 37° C. under a 5% CO<sub>2</sub> condition.

After centrifugation, the supernatant were applied to AKTA prime (GE Healthcare) to purify the antibody. In this regard, 100 mL of the supernatant was loaded at a flow rate of 5 mL/min to AKTA Prime equipped with a Protein A column (GE healthcare, 17-0405-03), followed by elution with an IgG elution buffer (Thermo Scientific, 21004). The buffer was exchanged with PBS to purify a humanized antibody AbF46 (hereinafter referred to as "huAbF46"). The humanized antibody huAbF46 used in the following examples included a combination of H4-heavy (SEQ ID NO: 42) and H4-light (SEQ ID NO: 46).

#### 1.4. Construction of scFV Library of huAbF46 Antibody

For use in constructing an scFv of the huAbF46 antibody from the heavy and light chain variable regions of the huAbF46 antibody, a gene was designed to have the structure of "VH-linker-VL" for each of the heavy and the light chain variable region, with the linker having the amino acid sequence "GLGGLGGGGSGGGGSGGSSGVGS" (SEQ ID NO: 54). A polynucleotide sequence (SEQ ID NO: 55) coding for the designed scFv of huAbF46 was synthesized in Bioneer and an expression vector for the polynucleotide had the nucleotide sequence of SEQ ID NO: 56.

After expression, the product was found to exhibit specificity to c-Met.

#### 1.5. Construction of Library Genes for Affinity Maturation

##### 1.5.1. Selection of Target CDR and Synthesis of Primer

The affinity maturation of huAbF46 was achieved. First, six complementary determining regions (CDRs) were defined according to Kabat numbering. The CDRs are given in Table 1, below.

TABLE 1

CDR	Amino Acid Sequence
CDR-H1	DYYMS (SEQ ID NO: 1)
CDR-H2	FIRNKANGYTTEYSASVKG (SEQ ID NO: 2)
CDR-H3	DNWFAY (SEQ ID NO: 3)
CDR-L1	KSSQSLLASGNQNNYLA (SEQ ID NO: 10)
CDR-L2	WASTRVS (SEQ ID NO: 11)
CDR-L3	QQSYSAPLT (SEQ ID NO: 12)

For use in the introduction of random sequences into the CDRs of the antibody, primers were designed as follows. Conventionally, N codons were utilized to introduce bases at the same ratio (25% A, 25% G, 25% C, 25% T) into desired sites of mutation. In this experiment, the introduction of random bases into the CDRs of huAbF46 was conducted in such a manner that, of the three nucleotides per codon in the wild-type polynucleotide encoding each CDR, the first and second nucleotides conserved over 85% of the entire sequence while the other three nucleotides were introduced at the same percentage (each 5%) and that the same possibility was imparted to the third nucleotide (33% G, 33% C, 33% T).

##### 1.5.2. Construction of Library of huAbF46 Antibodies and Affinity for c-Met

The construction of antibody gene libraries through the introduction of random sequences was carried out using the primers synthesized in the same manner as in Reference Example 1.5.1. Two PCR products were obtained, as shown in FIG. 2, using a polynucleotide covering the scFV of huAbF46 as a template, and were subjected to overlap extension PCR to give scFv library genes for huAbF46 antibodies in which only desired CDRs were mutated. Libraries targeting each of the six CDRs prepared from the scFV library genes were constructed.

The affinity for c-Met of each library was compared to that of the wildtype. Most libraries were lower in affinity for c-Met, compared to the wild-type. The affinity for c-Met was retained in some mutants.

##### 1.6. Selection of Antibody with Improved Affinity from Libraries

After maturation of the affinity of the constructed libraries for c-Met, the nucleotide sequence of scFv from each clone was analyzed. The nucleotide sequences thus obtained are summarized in Table 2 and were converted into IgG forms. Four antibodies which were respectively produced from clones L3-1, L3-2, L3-3, and L3-5 were used in the subsequent experiments.

TABLE 2

Clone	Library constructed	CDR Sequence
H11-4	CDR-H1	PEYYMS (SEQ ID NO: 22)
YC151	CDR-H1	PDYYMS (SEQ ID NO: 23)
YC193	CDR-H1	SDYYMS (SEQ ID NO: 24)
YC244	CDR-H2	RNNANGNT (SEQ ID NO: 25)
YC321	CDR-H2	RNKVNGYT (SEQ ID NO: 26)
YC354	CDR-H3	DNWLSY (SEQ ID NO: 27)

TABLE 2-continued

Clone	Library constructed CDR	Sequence
YC374	CDR-H3	DNWLTY (SEQ ID NO: 28)
L1-1	CDR-L1	KSSHLLASGNQNNYLA (SEQ ID NO: 29)
L1-3	CDR-L1	KSSRLLSSGNHKNYLA (SEQ ID NO: 30)
L1-4	CDR-L1	KSSKLLASGNQNNYLA (SEQ ID NO: 31)
L1-12	CDR-L1	KSSRLLASGNQNNYLA (SEQ ID NO: 32)
L1-22	CDR-L1	KSSHLLASGNQNNYLA (SEQ ID NO: 33)
L2-9	CDR-L2	WASKRVS (SEQ ID NO: 34)
L2-12	CDR-L2	WGSTRVS (SEQ ID NO: 35)
L2-16	CDR-L2	WGSTRVP (SEQ ID NO: 36)
L3-1	CDR-L3	QQSYSRPYT (SEQ ID NO: 13)
L3-2	CDR-L3	GQYSRPLT (SEQ ID NO: 14)
L3-3	CDR-L3	AQSYSHPPFS (SEQ ID NO: 15)
L3-5	CDR-L3	QQSYSRPFT (SEQ ID NO: 16)
L3-32	CDR-L3	QQSYSKPFT (SEQ ID NO: 37)

### 1.7. Conversion of Selected Antibodies into IgG

Respective polynucleotides coding for heavy chains of the four selected antibodies were designed to have the structure of "EcoRI-signal sequence-VH-NheI-CH-XhoI" (SEQ ID NO: 38). The heavy chains of huAbF46 antibodies were used as they were because their amino acids were not changed during affinity maturation. In the case of the hinge region, however, the U6-HC7 hinge (SEQ ID NO: 57) was employed instead of the hinge of human IgG1. Genes were also designed to have the structure of "EcoRI-signal sequence-VL-BsiWI-CL-XhoI" for the light chain. Polypeptides encoding light chain variable regions of the four antibodies which were selected after the affinity maturation were synthesized in Bioneer. Then, a DNA fragment having the heavy chain nucleotide sequence (SEQ ID NO: 38) and DNA fragments having the light chain nucleotide sequences (DNA fragment including L3-1-derived CDR-L3: SEQ ID NO: 58, DNA fragment including L3-2-derived CDR-L3: SEQ ID NO: 59, DNA fragment including L3-3-derived CDR-L3: SEQ ID NO: 60, and DNA fragment including L3-5-derived CDR-L3: SEQ ID NO: 61) were digested with EcoRI (NEB, R0101S) and XhoI (NEB, R0146S) before cloning into a pOptiVETM-TOPO TA Cloning Kit enclosed in an Opti-CHOTM Antibody Express Kit (Cat no. 12762-019, Invitrogen) and a pcDNATM3.3-TOPO TA Cloning Kit (Cat no. 8300-01), respectively, so as to construct recombinant vectors for expressing affinity-matured antibodies.

Each of the recombinant vectors was amplified using a Qiagen Maxiprep kit (Cat no. 12662). The vectors which respectively carried the heavy chain and the light chain were co-transfected at a ratio of 4:1 (80 µg:20 µg) into 293T cells (2.5×10<sup>7</sup>). The transfection into 293T cells (2.5×10<sup>7</sup>) was performed in the presence of 360 µL of 2M CaCl<sub>2</sub>. Afterwards, the cells were incubated in DMEM supplemented with 10% (v/v) FBS for 5 hours at 37° C. under a 5% CO<sub>2</sub> condition and then in FBS-free DMEM for 48 hours at 37° C. under a 5% CO<sub>2</sub> condition.

After centrifugation, the supernatant was applied to AKTA prime (GE Healthcare) to purify the antibody. In this regard,

100 mL of the supernatant was loaded at a flow rate of 5 mL/min to AKTA Prime equipped with a Protein A column (GE healthcare, 17-0405-03), followed by elution with an IgG elution buffer (Thermo Scientific, 21004). The buffer was exchanged with PBS to purify four affinity-matured antibodies (hereinafter referred to as "huAbF46-H4-A1 (L3-1 origin), huAbF46-H4-A2 (L3-2 origin), huAbF46-H4-A3 (L3-3 origin), and huAbF46-H4-A5 (L3-5 origin)," respectively).

### 1.8. Construction of Constant Region- and/or Hinge Region-Substituted huAbF46-H4-A1

Among the four antibodies selected in Reference Example 1.7, huAbF46-H4-A1 was found to be the highest in affinity for c-Met and the lowest in Akt phosphorylation and c-Met degradation degree. In the antibody, the hinge region, or the constant region and the hinge region, were substituted.

The antibody huAbF46-H4-A1 (U6-HC7) was composed of a heavy chain including the heavy chain variable region of huAbF46-H4-A1, U6-HC7 hinge and the constant region of human IgG1 constant region, and a light chain including the light chain variable region of huAbF46-H4-A1 and human kappa constant region. The antibody huAbF46-H4-A1 (IgG2 hinge) was composed of a heavy chain including a heavy chain variable region, a human IgG2 hinge region, and a human IgG1 constant region, and a light chain including the light chain variable region of huAbF46-H4-A1 and a human kappa constant region. The antibody huAbF46-H4-A1 (IgG2 Fc) was composed of the heavy chain variable region of huAbF46-H4-A1, a human IgG2 hinge region, and a human IgG2 constant region, and a light chain including the light variable region of huAbF46-H4-A1 and a human kappa constant region. Hereupon, the histidine residue at position 36 on the human kappa constant region of the light chain was changed into tyrosine in all of the three antibodies to increase antibody production.

For use in constructing the three antibodies, a polynucleotide (SEQ ID NO: 63) coding for a polypeptide (SEQ ID NO: 62) composed of the heavy chain variable region of huAbF46-H4-A1, a U6-HC7 hinge region, and a human IgG1 constant region, a polynucleotide (SEQ ID NO: 65) coding for a polypeptide (SEQ ID NO: 64) composed of the heavy chain variable region of huAbF46-H4-A1, a human IgG2 hinge region, and a human IgG1 region, a polynucleotide (SEQ ID NO: 67) coding for a polypeptide (SEQ ID NO: 66) composed of the heavy chain variable region of huAbF46-H4-A1, a human IgG2 region, and a human IgG2 constant region, and a polynucleotide (SEQ ID NO: 69) coding for a polypeptide (SEQ ID NO: 68) composed of the light chain variable region of huAbF46-H4-A1, with a tyrosine residue instead of histidine at position 36, and a human kappa constant region were synthesized in Bioneer. Then, the DNA fragments having heavy chain nucleotide sequences were inserted into a pOptiVETM-TOPO TA Cloning Kit enclosed in an OptiCHOTM Antibody Express Kit (Cat no. 12762-019, Invitrogen) while DNA fragments having light chain nucleotide sequences were inserted into a pcDNATM3.3-TOPO TA Cloning Kit (Cat no. 8300-01) so as to construct vectors for expressing the antibodies.

Each of the vectors thus constructed was amplified with the aid of a Qiagen Maxiprep kit (Cat no. 12662). The vectors which respectively carried the heavy chain and the light chain were co-transfected at a ratio of 4:1 (80 µg:20 µg) into 293T cells (2.5×10<sup>7</sup>). The transfection into 293T cells (2.5×10<sup>7</sup>) was performed in the presence of 360 µL of 2M CaCl<sub>2</sub>. Afterwards, the cells were incubated in DMEM supplemented with 10% (v/v) FBS for 5 hours at 37° C. under a 5% CO<sub>2</sub> condition and then in FBS-free DMEM for 48 hours at 37° C. under a 5% CO<sub>2</sub> condition.

After centrifugation, the supernatant was applied to AKTA prime (GE Healthcare) to purify the antibody. In this regard, 100 mL of the supernatant was loaded at a flow rate of 5 mL/min to AKTA Prime equipped with a Protein A column (GE healthcare, 17-0405-03), followed by elution with IgG elution buffer (Thermo Scientific, 21004). The buffer was exchanged with PBS to finally purify three antibodies (huAbF46-H4-A1(U6-HC7), huAbF46-H4-A1(IgG2 hinge), and huAbF46-H4-A1(IgG2 Fc)). Of them, huAbF46-H4-A1(U6-HC7) was selected as a representative anti-c-Met antibody and used in the following examples. For convenience, it was named anti-c-Met antibody L3-1 Y.

#### Reference Example 2

##### Preparation of Cell Line and Cell Culture

The human stomach cancer cell line MKN45 (JCRB0254) and the lung cancer cell line EBC-1 (JCRB0820) were purchased from the Health Science Research Resource Bank (Shinjuku, Japan), and the kidney cancer cell line Caki-1 (HTB-46), the stomach cancer cell line HS746T (HTB-135), and the human lung adenocarcinoma cell line NCI-H441 (HTB-174) were purchased from the American Type Culture Collection (ATCC, Manassas, Va.).

MKN45, EBC-1, and NCI-H441 cells were maintained in RPMI1640 (GIBCO) while HS746T and Caki-1 cells were cultured in DMEM supplemented with 10% (v/v) fetal bovine serum (FBS, GIBCO) and 1% (v/v) penicillin/streptomycin (GIBCO). Cell culturing was executed at 37° C. in a humidified atmosphere with 5% CO<sub>2</sub>. Cells were subcultured before reaching confluence and counted using a CEDEX Analyzer (Roche Diagnostics).

#### Example 1

##### Effect of Anti-c-Met Antibodies on c-Met

###### 1.1. c-Met Degradation in NCI-H441 Cells

IgG (negative control, eBioscience), the anti-c-Met antibody L3-1Y constructed in Reference Example 1, and the anti-c-Met antibody 5D5 known as an agonist (separated and purified form ATCC Cat. # HB-11895 hybridoma cells purchased from the American Type Culture Collection (ATCC, Manassas, Va.) (positive control) were tested for c-Met degradation. This test was to examine the efficacy of an antibody by comparing relative changes in total c-Met level, on the basis of the fact that when the antibody binds thereto, c-Met on the cell membrane is internalized and degraded.

NCI-H441 cells were seeded at a density of 2×10<sup>5</sup> cells/ml, together with 5 µg/ml of each antibody, into 96-well plates and incubated for 24 hours before cell lysis with the lysis buffer Complete lysis-M (Roche, 04719956001). Total c-Met levels in the cell lysates thus obtained were measured using Human Total HGF R/c-MET ELISA KIT (R&D systems, DYC358) according to the instructions of the manufacturer.

Experiments were performed in triplicate, and mean values of three measurements are presented in FIG. 1A (mean±SD). FIG. 1A shows the ability of antibodies to induce c-Met degradation as expressed as percentages relative to the c-Met level of the IgG treatment group.

As seen in FIG. 1A, NCI-H441 cells were observed to undergo more severe c-Met degradation when treated with the anti-c-Met antibodies L3-1Y and 5D5 than with IgG. In NCIH441 cells rich in Cbl, 5D5 reduced the c-Met level to an extent similar to that of L3-1Y after treatment for 24 hours, but this did not lead to a decrease in cell growth.

1.2. Phosphorylation of c-Met and Downstream Molecule 5D5, a conventional therapeutic anti-c-Met antibody, induces the activation of c-Met (phosphorylation of C-terminal Y1234 or Y1235), which may subsequently cause an adverse effect (agonism), that is, the phosphorylation of downstream molecules Akt and Erk responsible for oncogenesis. Phospho-Akt and phospho-Erk are known as markers for determining agonism.

To examine adverse effects attributed to the agonism, phosphorylation of kinases downstream of c-Met was measured in NCI-H441 and Caki-1 cells treated with the same antibodies as in Example 1.1.

NCI-H441 and Caki-1 cells were seeded at a density of 2×10<sup>5</sup> cells/ml into respective 96-well plates and left for 24 hours before treatment with 5 µg/mL of each of the antibodies for 30 min in the absence of serum. The phosphorylation of the downstream kinases was measured using Western blotting.

The results are shown in FIG. 1B. As may be seen in FIG. 1B, L3-1Y significantly inhibited the phosphorylation of the downstream molecules in both NCI-H441 and Caki-1 cells, compared to the other antibodies, indicating that the antibody L3-1Y effectively blocks the c-Met signaling pathway. Accordingly, little or no adverse effects are detected in the lung cancer cell line NCI-H441 and the kidney cancer cell line Caki-1 treated with L3-1Y, whereas 5D5 causes significant adverse effects. The data shows that an anti-c-Met antibody which targets c-Met in a Cbl-independent manner promises an anticancer effect without side effects.

###### 1.3. c-Met Degradation in MKN45 Cell

Total c-Met levels in MKN45 cells treated with the antibodies were measured using ELISA in the same manner as in Example 1.1, and the results are depicted in FIG. 1C. As is apparent from the data of FIG. 1C, the antibody L3-1Y significantly reduced the intracellular level of c-Met, compared to the positive control 5D5 as well as the negative control IgG. That is, the antibody L3-1Y has potent ability to trigger c-Met degradation.

###### 1.4. Cell Viability—MKN45 Cell

After tumor cells (MKN45) were treated with the antibodies, their viability was measured using a cell proliferation assay. In this context, the cell proliferation assay was performed using CCK-8 (Dojindo Laboratories, Gaithersburg, Md., USA) according to the instructions of the manufacturer.

MKN45 cells were seeded at a density of 1×10<sup>4</sup> cells/ml/well into 96-well plates and treated at 37° C. for 72 hours with or without various concentrations (0.0032, 0.016, 0.008, 0.4, 2, and 10 µg/ml) of IgG or L3-1Y. Subsequently, CCK-8 was aliquoted at a concentration of 10 µl/well to the plates, followed by incubation at 37° C. for an additional one hour. Absorbance at 450 nm of each well was measured on an automatic ELISA reader (Molecular Devices). Cell viability was expressed as percentages of the absorbance value of the non-treated group.

The results are shown in FIG. 1D. As seen in the graph of FIG. 1D, the viability of the tumor cells was significantly reduced upon treatment with the antibody L3-1Y (◆), compared to IgG (○).

#### Example 2

##### Cbl-Dependent c-Met Degradation 1

###### 2.1. Induction of Interaction Between Cbl and c-Met

NCI-H441 cells were seeded at a density of 2×10<sup>5</sup> cells/ml/well into 100 mm plates, and then treated with 5 µg/ml of the anti-c-Met antibody L3-1Y or 5D5 at 37° C. for 30 min in

a serum-free medium. The cells were lysed using a protease mix tablet (Roche) in the lysis buffer Complete lysis-M (Roche, 04719956001) and incubated at 4° C. with immunoprecipitating antibody-conjugated A/G agarose beads (Pierce). These beads were washed four times with a lysis buffer. The proteins bound to the beads were eluted with a sampling buffer (Invitrogen), followed by immunoblot analysis.

The results are given in FIG. 2A. As may be seen in the blots of FIG. 2A, the interaction between Cbl and c-Met was induced by the antibody 5D5, but not by the antibody L3-1Y. Cbl, although serving as a main E3 ligase to induce the quantitative reduction of c-Met, interacts with only activated c-Met and is thus highly apt to cause the adverse effect (agonism). Compared to the antibody 5D5, which induces the interaction of Cbl with c-Met, the antibody L3-1Y is deemed little causative of the adverse effect side effects because it does not induce the interaction.

#### 2.2. c-Met Degradation in EBC-1 and NCI-H441 Cells

EBC-1 or NCI-H441 cells were seeded at a density of 2×10<sup>5</sup> cells/ml, together with 5 µg/ml of the anti-c-Met antibody L3-1Y or 5D5, into 96-well plates and incubated for 4 hours. Then, c-Met degradation was measured using ELISA in the same manner as in Example 1.1.

The results are given in FIG. 2B. As shown in FIG. 2B, the antibody L3-1Y decreased the total c-Met level by 50% or higher in both cells while the antibody 5D5 induced c-Met degradation in NCI-H441 cells to a degree similar to what is induced by L3-1Y, but almost did not in EBC-1 cells.

To examine the cause of the result, Cbl protein levels in EBC-1 and NCI-H441 cells were measured by Western blot analysis using an Cbl antibody (cell signaling). The result is given in the upper panel of FIG. 2C. In addition, as seen in FIG. 2C, Cbl protein was at a relatively high level in NCI-H441 cells, but did not exist in EBC-1 cells. Therefore, the reason why the antibody 5D5 cannot induce c-Met degradation in EBC-1 cells is the absence of Cbl protein in EBC-1 cells. Therefore, the antibody L3-1Y is concluded to trigger Cbl-independent c-Met degradation. In other words, the antibody L3-1Y may exert excellent therapeutic effects on tumors which are not sufficiently sensitive to preexisting anti-c-Met antibodies (e.g., 5D5), such as EBC-1-related tumors, exhibiting the significance that it expands the range of cancers that may be therapeutically treated with anti-c-Met antibodies.

In addition, lung cancer tissues from lung cancer patients (n=14, non-small cell lung cancer (NSCLC) from Oncotest) were analyzed for Cbl protein level by Western blot using the Cbl antibody (cell signaling) in the same manner as above. The results are given in the lower panel of FIG. 2C. As may be seen in FIG. 2C, Cbl levels differ from one patient to another, which indicates that patients, although suffering from the same cancer, are less apt to be therapeutically treated with preexisting anti-c-Met antibodies (e.g., 5D5) if their Cbl protein levels are low. Therefore, if their Cbl protein levels are known or measured, patients may be treated with pertinent antibodies in consideration of personal biological properties, so that more effective personalized therapy may be achieved.

#### 2.3. Effect of c-Met Inhibitor on c-Met Degradation: MKN45 Cell

MKN45 cells were seeded at a density of 2×10<sup>5</sup> cells/ml, together with predetermined concentrations of the anti-c-Met antibody L3-1Y or 5D5, into 96-well plates and incubated for four hours. To each well, 1 µl of PHA-665752 (Selleck Chemical) was added. For controls, 1 µl of DMSO was used, instead of the inhibitor. c-Met degradation was analyzed using ELISA in the same manner as in Example 1.1. The

results are given in FIG. 2E, and show that L3-1Y may trigger c-Met degradation irrespective of whether a c-Met is activated or not.

#### 2.4. Cell Viability—EBC-1 Cell

EBC-1 was seeded at a density of cells/ml/well into 96-well plates and incubated for 72 hours with various concentrations of the antibody 5D5 or L3-1Y (0.0032, 0.016, 0.008, 0.4, 2, and 10 µg/ml). Cell viability was measured in the same manner as in Example 1.4.

The results are given in FIG. 2E. As shown in FIG. 2E, the cell viability was significantly decreased with the antibody L3-1Y (◆), compared to the antibody 5D5 (○).

### Example 3

#### Cbl-Dependent c-Met Degradation 2 (Degradation Pathway)

##### 3.1. c-Met Degradation Mechanism of Anti-c-Met Antibody 1: Ubiquitination Assay

An experiment was made to see whether Anti-c-Met antibody-triggered c-Met degradation takes place through the lysosomal pathway or the proteasome pathway mediated by E3 ligase including Cbl. In this context, poly-ubiquitination was examined by an ubiquitination assay.

Twenty-four hours after EBC-1 or NCI-H441 cells were seeded at a density of 2×10<sup>5</sup> cell/ml into 100 mm plates, they were incubated with 5 µg/ml of the antibody L3-1Y or 5D5 at 37° C. for 30, 60, or 120 min. The cells were separated and treated with a lysis buffer Complete lysis-M (Roche, 04719956001) to afford a protein extract. Ahead of the cell separation, MG132 (C26H41N3O5, Merck) or concanamycin (Merck) was added to inhibit the proteasome pathway or the lysosome pathway, respectively, so as to increase protein levels. Together with anti-c-Met antibody-conjugated NG agarose beads (Pierce), 500 µg of the protein extract was pulled down. The endogenous ubiquitination of c-Met was examined by immunoblotting using an anti-Ub antibody (Santa Cruz).

Photographs of immunoblots are given in FIGS. 3A and 3B (3A: immunoblots of EBC-1 cells, 3B: immunoblots of NCI-H441 cells). As may be seen in FIGS. 3A and 3B, the poly-ubiquitination of c-Met was observed in both the cell lines after treatment with the antibody 5D5, but neither of the cell lines after treatment with the antibody L3-1Y. Thus, the antibody 5D5 may induce the poly-ubiquitination of c-Met, but the antibody L3-1Y cannot, which indicates that the antibody L3-1Y is involved in c-Met degradation through a non-proteasome pathway, that is, a lysosome pathway.

##### 3.2. c-Met Degradation in Cells Transformed with Cbl siRNAs: Cbl Knockdown

Dependency of the anti-c-Met antibody-triggered c-Met degradation on Cbl was examined. For this, Cbl knockdown was achieved by transforming Cbl siRNAs into EBC-1 cells which were then treated with antibodies before measuring c-Met degradation.

Cbl siRNAs (Dharmacon)-transformed EBC-1 cells which were seeded at a density of 2×10<sup>5</sup> cells/ml into plates were incubated at 37° C. for 24 hours with 5 µg/ml of the anti-c-Met antibody L3-1Y. c-Met degradation was measured using ELISA in the same manner as in Example 1.1. For control, 5 µg/ml of IgG was used.

The results are given in FIG. 3C. siCtrl represents a control treated with a control siRNA commercially available from Dharmacon, in comparison with siCbl. As may be seen in FIG. 3C, the total c-Met level in the Cbl siRNA-transformed EBC-1 cells treated with the antibody L3-1Y was reduced to

about 30% of that in the transformed EBC-1 cells treated with the control IgG, indicating a c-Met degradation efficiency of as high as about 70%.

### 3.3. c-Met Mechanism of Anti-c-Met Antibody 2—Treatment with MG132

Apart from Example 3.1, the c-Met degradation mechanism of anti-c-Met antibody was examined. In this regard, c-Met degradation was measured when the proteasome pathway was blocked by the proteasome inhibitor MG132 (C26H41N3O5, Merck).

EBC-1 cells which were seeded at a density of  $2 \times 10^5$  cells/ml into 96-well plates were incubated at 37° C. for 4 hours with the anti-c-Met antibody L3-1Y 5 µg/ml+DMSO 1 µL, or with the antibody L3-1Y 5 µg/ml+MG132 1 µL (10 µM). c-Met degradation was measured using ELISA in the same manner as in Example 1.1. For control, IgG 5 µg/ml+DMSO 1 µL, or IgG 5 µg/ml+MG132 1 µL was used.

The results are given in FIG. 3D. As may be seen in FIG. 3D, the antibody L3-1Y reduced the c-Met level by about 70% in the cells treated without the proteasome inhibitor MG132 and by about 50% in the cells treated with MG132, indicating that L3-1Y-triggered-c-Met degradation is not significantly affected by MG132 treatment. The data demonstrates again that c-Met degradation of the antibody L3-1Y does not take the Cbl-mediated proteasome pathway, but is independent of Cbl.

### 3.4. Cell Viability—HS746T Cell

HS746T cells were seeded at a density of  $5 \times 10^4$  cells/ml/well into 96-well plates and incubated with various concentrations (0.0032, 0.016, 0.008, 0.4, 2, and 10 µg/ml) of the antibody 5D5 or L3-1Y at 37° C. for 72 hours. Cells were measured on the basis of the method used in the example.

HS746T is a stomach cancer cell line in which the site of c-Met for interaction with Cbl is truncated by natural mutation in all c-Met molecules.

The results are given in FIG. 3E. As may be seen in FIG. 3E, tumor cell viability was greatly reduced upon treatment with the antibody L3-1Y (◆), compared to the antibody 5D5 (○).

### 3.5. Apoptosis Induction

Anti-c-Met antibodies were assayed for ability to induce apoptosis.

Apoptotic effects of IgG (control), L3-1Y, and 5D5 on cells were measured in vitro using a Caspase 3/7 Glo® assay system on HS746T cells present at a density of  $5 \times 10^4$  cells/ml/well in 96-well plates.

In brief, EBC-1 cells in an FBS 10%(v/v) RPMI 1640 medium and HS746T cells in an FBS 10%(v/v) DMSO medium were plated at a density of  $5 \times 10^3$  cells/well into respective black 96-well plates (Corning Incorporated), and incubated at 37° C. for 72 hours with various dilutions (0.0032, 0.016, 0.008, 0.4, and 2 µg/ml) of IgG, L3-1Y or 5D5 in a medium supplemented with 10%(v/v) FBS and then at room temperature for 30 min with 100 µL/wells of Caspase 3/7 Glo® (Promega). Luminescence signals were recorded with an Envision 2104 Multi-label Reader (Perkin Elmer). Apoptosis rates after being normalized to CCK-8 assay values are shown in FIG. 3F.

As may be seen in FIG. 3F, the antibody L3-1Y (◆) was found to induce potent apoptosis, whereas the apoptosis induced by 5D5 (▲) was weaker than the control IgG (○).

The apoptotic effects of the antibodies L3-1Y and 5D5 on the lung cancer cell line EBC-1 were measured in the same manner and the results are given in FIG. 3G. As may be seen in FIG. 3G, the antibody L3-1Y induced higher apoptosis in a dose-dependent manner even in the lung cancer cell line

EBC-1, which expresses a low level of Cbl, compared to the preexisting anti-c-Met antibody 5D5.

## Example 4

### LRIG1-Mediated c-Met Degradation

#### 4.1. Induction of Interaction Between LRIG1 and c-Met by Anti-c-Met Antibody: EBC-1 Cell

An examination was made of the ability of anti-c-Met antibodies to induce c-Met to associate with LRIG1 in EBC-1 cells. An LRIG1-c-Met associated protein was separated and purified by co-immunoprecipitation and quantitatively analyzed by immunoblotting. In this regard, cells were treated with an anti-c-Met antibody for periods of time shown in FIG. 4A and harvested. The cells were lysed in a lysis buffer Complete lysis-M (Roche, 04719956001) to afford a protein extract. Together with anti-c-Met antibody-conjugated NG agarose beads (Pierce), 500 µg of the extract was pulled down, followed by immunoblotting with an anti-LRIG1 antibody (Abcam) to detect the association of c-Met with LRIG1. The data obtained above shows that the association of c-Met with LRIG1 is induced two hours after treatment with L3-1Y.

#### 4.2. Induction of Interaction Between LRIG1 and c-Met by Anti-c-Met Antibody: HEK293 Cell

An examination was made of the ability of anti-c-Met antibodies to induce c-Met to associate with LRIG1 in HEK293 cells. An LRIG1-c-Met associated protein was separated and purified by co-immunoprecipitation and quantitatively analyzed by immunoblotting. In this regard, cells were treated with an anti-c-Met antibody for 2 hours and harvested. The cells were lysed in a lysis buffer Complete lysis-M (Roche, 04719956001) to afford a protein extract. Together with anti-c-Met antibody-conjugated NG agarose beads (Pierce), 500 µg of the extract was pulled down, followed by immunoblotting with an anti-LRIG1 antibody (Abcam) to detect the association of c-Met with LRIG1.

The immunoblotting results are shown in FIG. 4B. As is apparent from the data of FIG. 4B, the antibody L3-1Y may induce the association of LRIG1 with c-Met whereas the antibody 5D5 cannot.

#### 4.3. Apoptosis Induction by Anti-c-Met Antibody 1

EBC-1 cells were treated for 72 hours with 1 µg/ml of L3-1Y or 5D5 and transferred to tubes which were spun at 120 rpm at 4° C. for 3 min. The cells were stained for 15 min with 5 µl of AnnexinV (BD Pharmingen) and 2 µl of PI (Propidium Iodide, 50 g/µl) under a dark condition, followed by FACS analysis (FACS CAntoll flow cytometer, Becton, Dickinson and Company). The results are shown in FIG. 4C. The annexin V(+)/PI(-) cell group represents the progress of early apoptosis while the Annexin V(+)/PI(+) cell group underwent later apoptosis. L3-1Y was found to increase both early and late cell apoptosis, compared to 5D5.

#### 4.4. Apoptosis Induction by Anti-c-Met Antibody 2

After L3-1Y or 5D5 EBC-1 was applied at various concentrations (0.0032, 0.016, 0.008, 0.4, 2, and 10 µg/ml) to cells which were seeded at a density of  $5 \times 10^4$  cells/ml/well into 96-well plates, apoptosis rates were measured in vitro using a Caspase 3/7 Glo® assay system in the same manner as in Example 3.5.

The results are shown in FIG. 4D. As may be seen in FIG. 4D, far higher apoptotic effects on EBC-1 cells were obtained with the antibody L3-1Y (◆) than 5D5 (○).

#### 4.5. Apoptosis Induction by Anti-c-Met Antibody 3

To examine the relation of LRIG1 to the apoptotic effect, shown in Example 4.4, of the antibody L3-1Y on EBC-1, EBC-1 cells which were subjected to reverse-transfection

with LRIG1 siRNAs (Dharmacon) for 24 hours were induced to undergo apoptosis in the same manner as in Example 4.4.

Apoptosis rates are depicted in FIG. 4E. In the graph, siCtrl represents a control treated with a control siRNA commercially available from Dharmacon. As may be seen in FIG. 4E, the apoptotic effect of L3-1Y (◆) was significantly reduced in LRIG1-knockdown EBC-1 cells compared to the control, indicating that the ability of L3-1Y to induce the apoptosis of EBC-1 cells is attributed to the formation of the LRIG1-c-Met associated protein.

#### 4.6. c-Met Degradation Mechanism of Anti-c-Met Antibody

In order to examine the c-Met degradation mechanism of anti-c-Met antibodies, c-Met degradation was measured in EBC-1 cells whose lysosome pathway was blocked by treatment with the lysosomal pathway inhibitor concanamycin (Merck).

EBC-1 cells which were seeded at a density of  $2 \times 10^5$  cells/ml into 96-well plates were incubated at 37° C. for 4 hours with the anti-c-Met antibody L3-1Y 5 µg/ml+DMSO 1 µL, the antibody L3-1Y 5 µg/ml+concanamycin 1 µL, the antibody 5D5 5 µg/ml+DMSO 1 µL, or the antibody 5D5 5 µg/ml+concanamycin 1 µL, and c-Met degradation was measured using ELISA in the same manner as in Example 1.1. For control, IgG 5 µg/ml+DMSO 1 µL, or IgG 5 µg/ml+MG132 1 µL, was used.

The results are given in FIG. 4F. As may be seen in FIG. 4F, c-Met degradation in the 5D5-treated cells was almost equivalent to that in the control cells, and was somewhat increased upon the use of DMSO compared to concanamycin, but without significance because of a difference of only 10% or less. In contrast, the antibody L3-1Y did not trigger c-Met degradation in the presence of concanamycin, but increased c-Met degradation by 60% or greater upon DMSO treatment, demonstrating that the c-Met degradation of the antibody L3-1Y takes the lysosomal pathway.

#### 4.7. Immunocytochemistry

Antibody-mediated co-localization of c-Met and lysosome was analyzed by immunocytochemistry. MKN45 or EBC-1 cells at a density of  $2 \times 10^5$  cells/ml were incubated for 4 hours with 1 µg/ml of the anti-c-Met antibody L3-1Y. The cells were fixed with 2% (w/v) paraformaldehyde and blocked for 30 min with 5% (v/v) goat serum (Jackson ImmunoResearch) in PBS-T (0.1% (v/v) Triton X-100 in PBS) before incubation with Alexa 488-conjugated anti-mouse IgG (Invitrogen) at room temperature for 1 hour. Then the cells were washed many times with PBC (Gibco), counterstained with DAPI (4',6'-diamidino-2'-phenylindole dihydrochloride; Vector Labs) and placed in a fluorescent mounting medium. Immunofluorescence images were obtained with a fluorescence microscope (Carl Zeiss) and are given in FIG. 4G. L3-1Y-APC is an antibody labeled with a detectable tag. As seen in FIG. 4G, the antibody L3-1Y was observed in lysosomes, demonstrating that lysosomes are involved in L3-1Y-triggered c-Met degradation.

### Example 5

#### Therapeutic Effect of Anti-c-Met Antibody on Tumor (In Vivo)

##### 5.1. Anti-Tumor Effect in Tumor-Xenografted Model

For use in examining in vivo effects of anti-c-Met antibody on tumor growth, male BALB/c nude mice, 5-6 weeks old, were xenografted with a tumor (all experiments were carried out in Pharmalegacy, China). For at least one week before the transplantation, the mice were acclimated.

Then, the mice were anesthetized with 1-2% isoflurane and xenografted subcutaneously in the right flank with  $5 \times 10^6$  cells of EBC-1 or HS746T. Seven days after the grafting, the tumors measured 50 mm<sup>3</sup> or greater on average. The mice were divided into the following three groups: 5D5 (5 mg/kg I.V. once/week) treated, L3-1Y (5 mg/kg I.V. once/week) treated, and vehicle (PBS 0.2 ml I.V. once/week) treated (control). Each group was composed of 15 mice.

Over a total of five weeks, volumes and weights of the tumors were measured 203 times a week. Tumor volume (V) was calculated according to the following formula:

$$V(\text{mm}^3) = \frac{\text{Long Axis Length (mm)} \times (\text{Small Axis Length (mm)})^2}{2}$$

The results are given in FIG. 5C and Table 3 for EBC-1 and in FIG. 5D and Table 4 for HS746T.

TABLE 3

EBC1	At d28:TV
Vehicle	0.0
L3-1Y (1)	84.6
L3-1Y (2)	87.0
5D5	23.3

TABLE 4

HS746T	At d28:TV
Vehicle	0.0
L3-1Y (1)	Regression
L3-1Y (2)	Regression
5D5	56.4

L3-1Y (1) is an antibody based on hlgG1 with the Th7 hinge (usually referred to just as L3-1Y) while L3-1Y (2) contains the same epitope but has the hlgG2 backbone. FIGS. 5C and 5D are graphs showing tumor growth in mice xenografted with EBC-1 cells (5c) and HS746T cells (5d) over time (n=15) (for comparison, the c-Met small molecule inhibitor CPT-11 and a reference antibody (Reference L) were used). Tumor suppression of each of the antibodies was expressed as percentages of volume reduction compared to the tumor volume on the 28th day of the vehicle-treated group (0%) in Table 3 for EBC-1 and Table 4 for HS746T.

As may be seen in FIGS. 5C and 5D and Tables 3 and 4, the antibody L3-1Y was found to have great anti-tumor activity in vivo, compared to the other antibodies.

##### 5.2. Cell Migration Assay

Cell migration was observed in CIM-Plates of the xCELLigence DP system (Roche). A suspension of  $5 \times 10^4$  cells in 100 µl of a serum-free medium was placed in the upper chamber. The lower part of CIM-plate 16 was filled with a 10% serum medium (migration to chemo-attractant). In the case that HGF was used, it was added at a concentration of 200 ng/ml to the 10% serum medium. Cell migration capability was evaluated by measuring impedance signals only from the cells that passed through an 8 µm pore membrane. The migration of EBC1 (FIG. 5A) was increased by about 10% upon treatment with 5D5, but decreased by 90% or higher upon treatment with L3-1Y. Only L3-1Y reduced the migration of HS746T, as well, whether treated with HGF or not (FIG. 5B).

### Anti-Tumor Effect of Anti-c-Met Antibody on Tumor Resistant to EGFR-Targeted Therapy

#### 6.1. Preparation of EGFR-Targeted Therapy-Resistant Tumor

The human lung cancer cell line HCC827 was treated in vitro for a predetermined period of time with Erlotinib, an EGFR antagonist, to establish HCC827 ER (HCC827 Erlotinib-resistant) cell lines. In detail, HCC827 (ATCC) which was seeded at a density of  $2 \times 10^5$  cells/ml was treated in vitro with a gradual gradient concentration of the EGFR antagonist Erlotinib (Selleck Chemical) from 5 nm to 10  $\mu$ m over 5 months to establish Erlotinib-resistant (ER) cell lines HCC827 ER10 and HCC827 ER15.

Erlotinib resistance was confirmed by a cell viability assay, and the results are shown in FIG. 7. The parent cell line HCC827 died with the treatment of Erlotinib or BIBW2992 (Selleck Chemical), whereas the viability of HCC287-ER (Erlotinib resistant) was not reduced at all by Erlotinib. Apart from a high dose of BIBW2992, the ER cells were not induced to undergo cell death by the EGFR antagonist BIBW2992. As may be seen in FIG. 7, the ER cell lines became resistant to the EGFR antagonist BIBW2992 as well as Erlotinib, indicating that there was a likelihood of resistance to other EGFR antagonists.

HCC827, HCC827 ER10, and HCC827 ER15 cells were analyzed for the expression of p-c-Met, c-Met, EGFR, Cbl, LRIG1, and GAPDH therein by immunoblotting using respective antibodies. In this context, antibodies to p-c-Met, c-Met, Cbl, EGFR, and GAPDH (14C10) were purchased from Cell Signaling and an antibody to LRIG1 was purchased from Abcam.

The immunoblots thus obtained are shown in FIG. 6A. As may be seen in FIG. 6A, the level of c-Met gene was about three-fold increased in both the ER cells, compared to non-resistant HCC82, indicating that constant exposure to an EGFR inhibitor increases c-Met levels and thus elicits resistance.

#### 6.2. Apoptotic Effect of a Combination Dosage of Anti-c-Met Antibody and EGFR Antagonist on Tumor Cell

HCC827 ER15, which expresses c-Met at a high level but Cbl at a relatively low level was used in assay for the apoptotic effect of a combination dosage of an anti-c-Met antibody and an EGFR antagonist.

HCC827 ER15 cells were seeded at a density of  $5 \times 10^4$  cells/ml/well into 96-well plates and incubated with L3-1Y 0.14  $\mu$ g/ml, Erlotinib 10 nm, or L3-1Y 0.14  $\mu$ g/ml+Erlotinib 10 nm at 37° C. for 72 hours. Then, cell viability was measured in the same manner as in Example 1.4.

The results are expressed as percentages of the cell viability (100%) of the control which was neither treated with an anti-c-Met antibody nor an EGFR antagonist in FIG. 6B. As may be seen in FIG. 6B, almost no apoptotic effects were found in the EGFR resistant cells to which the anti-c-Met antibody L3-1Y or the EGFR antagonist Erlotinib were separately administered, but the cell viability was reduced to about 65% when L3-1Y and Erlotinib were administered in combination. That is, a combination dosage of the agents increased the apoptosis of the resistant cells by about 35%.

#### 6.3. Effect of a Combination Dosage of Anti-c-Met Antibody and EGFR Antagonist on c-Met Degradation

An examination was made of the effect of a combination dosage of an anti-c-Met antibody and an EGFR antagonist on c-Met degradation in HCC827 ER15 cells. After HCC827 ER15 cells were treated with a combination of Erlotinib and

the antibody L3-1Y or 5D5, levels of c-Met protein in the cells were measured to examine the effect of c-Met antibodies on c-Met degradation.

HCC827 ER15 which was seeded at a density of  $2 \times 10^5$  cells/ml/well into 96-well plates was incubated with L3-1Y 0.2  $\mu$ g/ml+Erlotinib 100 nm, L3-1Y 1.0  $\mu$ g/ml+Erlotinib 100 nm, 5D5 0.2  $\mu$ g/ml+Erlotinib 100 nm or 5D5 0.1  $\mu$ g/ml+Erlotinib 100 nm at 37° C. for 24 hours, and subjected to cell viability assay in the same manner as in Example 1.1, with Erlotinib 100 nm serving as a control.

Cell viability results are expressed as percentages of the c-Met level in the control (treated with Erlotinib alone, 100%) in FIG. 6C, as measured by ELISA. As may be seen in FIG. 6C, a combination of Erlotinib and L3-1Y was found to trigger c-Met degradation in a dose-dependent manner in the Erlotinib-resistant cell line HCC827 ER15, and elicited significant c-Met degradation, compared to a combination of Erlotinib and 5D5.

#### 6.4. Cbl-Independent Inhibitory Activity Against Growth of EGFR-Targeted Therapy-Resistant Sample

For an anticancer effect assay, an experiment was made in which colonies grown from lung cancer patients (LXFE1422, LXFA526, LXFA1647; samples susceptible to c-Met small molecule inhibitors, from Oncotest)-derived cell lines (using a 3D culture medium (RPMI (Gibco)) for non-small cell lung cancer (NSCLC), at 37° C.) were treated with anti-c-Met antibodies.

Of the lung cancer patients, LXFE1422 was not resistant to Cetuximab, an EGFR-targeting anticancer therapeutic, while both LXFA526 and LXFA1647 patients cannot be treated with Cetuximab due to their resistance.

Lung tissues from the patients were lysed in a lysis buffer Complete lysis-M (Roche, 04719956001) to separate proteins, followed by Western blot analysis. The results are given in FIG. 6D. As may be seen in FIG. 6D, EGFR and Cbl were present at low levels in LXFA526 and LXFA1647 patients, both resistant to Cetuximab.

From the patient samples, the exon 14 coding for the juxtamembrane domain of c-Met was amplified using a one-step RT-PCR kit with the following primers:

(SEQ ID NO: 106)  
Primer F: 5'-TGAAATTGAACAGCGAGCTAAAT-3';  
and

(SEQ ID NO: 107)  
Primer R: 5'-TTGAAATGCACAATCAGGCTAC-3'.

RT-PCR conditions were as follows:

1 cycle of 50° C. 30 min, 95° C. 15 min,  
45 cycles of 94° C. 40 s, 62° C. 40 s, and 72° C. 1 min, and  
1 cycle of 72° C. 10 min.

The RT-PCR products including the exon 14 of the c-Met gene were run on agarose gel by electrophoresis, and the agarose gel electrophoresis photograph is given in FIG. 6E. As may be seen, the splice mutation of c-Met itself was found in none of the three patients.

The anticancer activity of the anti-c-Met antibody L3-1Y was proven in the patient samples in which both EGFR and Cbl were expressed at low levels. Cancer cells from the patients were 3D cultured in Oncotest to evaluate colony forming ability. After treatment with L3-1Y 100  $\mu$ g/ml, the colony forming ability of the cells were evaluated and are expressed as percentages of the number of colonies formed by the control (100  $\mu$ g/ml treated, 100%) in FIG. 6F. As is apparent from the data of FIG. 6F, the antibody had no efficacy on the LXFE1422 patient, but inhibited cancer growth by 44%

(colony formation 56%) for LXFA526, and by 33% (colony formation 67%) for LXFA1647.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein

are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

## SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 114

<210> SEQ ID NO 1

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic (heavy chain CDR1 of AbF46)

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Asp Tyr Tyr Met Ser  
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<210> SEQ ID NO 2

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic (heavy chain CDR2 of AbF46)

<400> SEQUENCE: 2

Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala Ser  
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 3

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic (heavy chain CDR3 of AbF46)

<400> SEQUENCE: 3

Asp Asn Trp Phe Ala Tyr  
1 5

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<210> SEQ ID NO 4  
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<223> OTHER INFORMATION: Xaa is Pro or Ser  
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<223> OTHER INFORMATION: Xaa is Glu or Asp  
  
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Xaa Xaa Tyr Tyr Met Ser  
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<210> SEQ ID NO 5  
<211> LENGTH: 8  
<212> TYPE: PRT  
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<223> OTHER INFORMATION: Xaa is Asn or Lys  
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<223> OTHER INFORMATION: Xaa is Ala or Val  
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<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa is Asn or Thr  
  
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Arg Asn Xaa Xaa Asn Gly Xaa Thr  
1 5

<210> SEQ ID NO 6  
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<223> OTHER INFORMATION: Xaa is Ser or Thr  
  
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Asp Asn Trp Leu Xaa Tyr  
1 5

<210> SEQ ID NO 7  
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<212> TYPE: PRT  
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<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (light chain CDR1 of c-Met antibody)  
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<221> NAME/KEY: MISC\_FEATURE  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: Xaa is His, Arg, Gln or Lys  
<220> FEATURE:  
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<222> LOCATION: (12)..(12)  
<223> OTHER INFORMATION: Xaa is His or Gln  
<220> FEATURE:

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<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (13)..(13)  
 <223> OTHER INFORMATION: Xaa is Lys or Asn

<400> SEQUENCE: 7

Lys Ser Ser Xaa Ser Leu Leu Ala Ser Gly Asn Xaa Xaa Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 8  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
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 <223> OTHER INFORMATION: Synthetic (light chain CDR2 of c-Met antibody)  
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<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (2)..(2)  
 <223> OTHER INFORMATION: Xaa is Ala or Gly  
 <220> FEATURE:

<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (4)..(4)  
 <223> OTHER INFORMATION: Xaa is Thr or Lys  
 <220> FEATURE:

<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (4)..(4)  
 <223> OTHER INFORMATION: Xaa is Ser or Pro  
 <220> FEATURE:

<221> NAME/KEY: misc\_feature  
 <222> LOCATION: (7)..(7)  
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 8

Trp Xaa Ser Xaa Arg Val Xaa  
 1 5

<210> SEQ ID NO 9  
 <211> LENGTH: 9  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (light chain CDR3 of c-Met antibody)  
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<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (1)..(1)  
 <223> OTHER INFORMATION: Xaa is Gly, Ala or Gln  
 <220> FEATURE:

<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (6)..(6)  
 <223> OTHER INFORMATION: Xaa is Arg, His, Ser, Ala, Gly or Lys  
 <220> FEATURE:

<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (8)..(8)  
 <223> OTHER INFORMATION: Xaa is Leu, Tyr, Phe or Met

<400> SEQUENCE: 9

Xaa Gln Ser Tyr Ser Xaa Pro Xaa Thr  
 1 5

<210> SEQ ID NO 10  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (light chain CDR1 of AbF46)

<400> SEQUENCE: 10

Lys Ser Ser Gln Ser Leu Leu Ala Ser Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

-continued

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<210> SEQ ID NO 11  
<211> LENGTH: 7  
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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (light chain CDR2 of AbF46)

<400> SEQUENCE: 11

Trp Ala Ser Thr Arg Val Ser  
1 5

<210> SEQ ID NO 12  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (light chain CDR3 of AbF46)

<400> SEQUENCE: 12

Gln Gln Ser Tyr Ser Ala Pro Leu Thr  
1 5

<210> SEQ ID NO 13  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (CDR-L3 derived from L3-1 clone)

<400> SEQUENCE: 13

Gln Gln Ser Tyr Ser Arg Pro Tyr Thr  
1 5

<210> SEQ ID NO 14  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (CDR-L3 derived from L3-2 clone)

<400> SEQUENCE: 14

Gly Gln Ser Tyr Ser Arg Pro Leu Thr  
1 5

<210> SEQ ID NO 15  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (CDR-L3 derived from L3-3 clone)

<400> SEQUENCE: 15

Ala Gln Ser Tyr Ser His Pro Phe Ser  
1 5

<210> SEQ ID NO 16  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (CDR-L3 derived from L3-5 clone)

<400> SEQUENCE: 16

Gln Gln Ser Tyr Ser Arg Pro Phe Thr  
1 5

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<210> SEQ ID NO 17  
 <211> LENGTH: 117  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (heavy chain variable region of anti  
 c-Met humanized antibody(huAbF46-H4))

<400> SEQUENCE: 17

```

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

<210> SEQ ID NO 18  
 <211> LENGTH: 114  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (light chain variable region of anti  
 c-Met humanized antibody(huAbF46-H4))

<400> SEQUENCE: 18

```

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

<210> SEQ ID NO 19  
 <211> LENGTH: 114  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (light chain variable region of anti  
 c-Met humanized antibody(huAbF46-H4))

<400> SEQUENCE: 19

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

```

Lys Arg

```

<210> SEQ ID NO 20
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (light chain variable region of anti
c-Met humanized antibody(huAbF46-H4))

```

&lt;400&gt; SEQUENCE: 20

```

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

```

Lys Arg

```

<210> SEQ ID NO 21
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (light chain variable region of anti
c-Met humanized antibody(huAbF46-H4))

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&lt;400&gt; SEQUENCE: 21

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

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50	55	60	
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr			
65	70	75	80
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln			
	85	90	95
Ser Tyr Ser Arg Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile			
	100	105	110

Lys Arg

<210> SEQ ID NO 22  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H1 derived from H11-4 clone)  
 <400> SEQUENCE: 22

Pro Glu Tyr Tyr Met Ser  
1 5

<210> SEQ ID NO 23  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H1 derived from YC151 clone)  
 <400> SEQUENCE: 23

Pro Asp Tyr Tyr Met Ser  
1 5

<210> SEQ ID NO 24  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H1 derived from YC193 clone)  
 <400> SEQUENCE: 24

Ser Asp Tyr Tyr Met Ser  
1 5

<210> SEQ ID NO 25  
 <211> LENGTH: 8  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H2 derived from YC244 clone)  
 <400> SEQUENCE: 25

Arg Asn Asn Ala Asn Gly Asn Thr  
1 5

<210> SEQ ID NO 26  
 <211> LENGTH: 8  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H2 derived from YC321 clone)  
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Arg Asn Lys Val Asn Gly Tyr Thr  
1 5

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<210> SEQ ID NO 27  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H3 derived from YC354 clone)

<400> SEQUENCE: 27

Asp Asn Trp Leu Ser Tyr  
 1 5

<210> SEQ ID NO 28  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-H3 derived from YC374 clone)

<400> SEQUENCE: 28

Asp Asn Trp Leu Thr Tyr  
 1 5

<210> SEQ ID NO 29  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 derived from L1-1 clone)

<400> SEQUENCE: 29

Lys Ser Ser His Ser Leu Leu Ala Ser Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 30  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 derived from L1-3 clone)

<400> SEQUENCE: 30

Lys Ser Ser Arg Ser Leu Leu Ser Ser Gly Asn His Lys Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 31  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 derived from L1-4 clone)

<400> SEQUENCE: 31

Lys Ser Ser Lys Ser Leu Leu Ala Ser Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 32  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 derived from L1-12 clone)

<400> SEQUENCE: 32

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Lys Ser Ser Arg Ser Leu Leu Ala Ser Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 33  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 derived from L1-22 clone)

&lt;400&gt; SEQUENCE: 33

Lys Ser Ser His Ser Leu Leu Ala Ser Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

<210> SEQ ID NO 34  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L2 derived from L2-9 clone)

&lt;400&gt; SEQUENCE: 34

Trp Ala Ser Lys Arg Val Ser  
 1 5

<210> SEQ ID NO 35  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L2 derived from L2-12 clone)

&lt;400&gt; SEQUENCE: 35

Trp Gly Ser Thr Arg Val Ser  
 1 5

<210> SEQ ID NO 36  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L2 derived from L2-16 clone)

&lt;400&gt; SEQUENCE: 36

Trp Gly Ser Thr Arg Val Pro  
 1 5

<210> SEQ ID NO 37  
 <211> LENGTH: 9  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L3 derived from L3-32 clone)

&lt;400&gt; SEQUENCE: 37

Gln Gln Ser Tyr Ser Lys Pro Phe Thr  
 1 5

<210> SEQ ID NO 38  
 <211> LENGTH: 1416  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:

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<223> OTHER INFORMATION: Synthetic (nucleotide sequence of heavy chain
of chAbF46)
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: EcoRI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(66)
<223> OTHER INFORMATION: signal sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(417)
<223> OTHER INFORMATION: VH - heavy chain variable region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (418)..(423)
<223> OTHER INFORMATION: NdeI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (418)..(1407)
<223> OTHER INFORMATION: CH - heavy chain constant region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1408)..(1410)
<223> OTHER INFORMATION: TGA - stop sodon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1411)..(1416)
<223> OTHER INFORMATION: XhoI restriction site

<400> SEQUENCE: 38

gaattcgccg ccaccatgga atggagctgg gtttttctcg taacactttt aaatggtatc   60
cagtgtgagg tgaagctggt ggagctctgga ggaggcttgg tacagcctgg gggttctctg   120
agactctcct gtgcaacttc tgggttcacc ttcactgatt actacatgag ctgggtccgc   180
cagcctccag gaaaggcact tgagtggttg ggttttatta gaaacaaagc taatggttac   240
acaacagagt acagtgcac tgtgaagggt cggttcacca tctccagaga taattcccaa   300
agcatcctct atcttcaaat ggacaccctg agagctgagg acagtgccac ttattactgt   360
gcaagagata actggtttgc ttactggggc caagggactc tggtcactgt ctctgcagct   420
agcaccaagg gcccatcggt cttcccctg gcaccctcct ccaagagcac ctctgggggc   480
acagcgccc tgggtgctt ggtcaaggac tacttcccgc aaccgggtgac ggtgtcgtgg   540
aactcaggcg ccttgaccag cggcgtgcac accttcccgc ctgtcctaca gtctcagga   600
ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac   660
atctgcaacg tgaatcacia gccagcaac accaaggtgg acaagaaagt tgagccaaa   720
tcttgtgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg   780
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag   840
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac   900
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc   960
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag  1020
tacaagtgca aggtctcaa caaagccctc ccagcccca tcgagaaaac catctccaaa  1080
gccaaagggc agccccgaga accacaggtg tacaccctgc cccatcccg ggaggagatg  1140
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc  1200
gtggagtggg agagcaatgg cgagccggag aacaactaca agaccacgcc tcccgtgctg  1260
gactccgacg getccttctt cctctacagc aagctcaccg tggacaagag caggtggcag  1320
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaaaca ctacacgcag  1380

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aagagcctct cctgtctcc gggtaaatga ctcgag 1416

<210> SEQ ID NO 39  
 <211> LENGTH: 759  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (nucleotide sequence of light chain  
 of chAbF46)  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (1)..(6)  
 <223> OTHER INFORMATION: EcoRI restriction site  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (7)..(90)  
 <223> OTHER INFORMATION: signal sequence  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (91)..(432)  
 <223> OTHER INFORMATION: VL - light chain variable region  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (430)..(435)  
 <223> OTHER INFORMATION: BsiWI restriction site  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (433)..(750)  
 <223> OTHER INFORMATION: CL - light chain constant region  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (751)..(753)  
 <223> OTHER INFORMATION: stop codon  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (754)..(759)  
 <223> OTHER INFORMATION: XhoI restriction site

<400> SEQUENCE: 39  
 gaattcacta gtgattaatt cgccgccacc atggattcac aggccaggt cctcatgttg 60  
 ctgctgctat cggatctgg tacctgtgga gacattttga tgaccagtc tccatcctcc 120  
 ctgactgtgt cagcaggaga gaaggtcact atgagctgca agtccagtc gagtctttta 180  
 gctagtggca accaaaataa ctacttggcc tggcaccagc agaaaccagg acgatctcct 240  
 aaaatgctga taatttgggc atccactagg gtatctggag tccctgatcg cttcataggc 300  
 agtggatctg ggacggattt cactctgacc atcaacagtg tgcaggctga agatctggct 360  
 gtttattact gtcagcagtc ctacagcgt ccgctcacgt tcggtgctgg gaccaagctg 420  
 gagctgaaac gtacgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag 480  
 ttgaaatctg gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc 540  
 aaagtacagt ggaagtgga taacgcctc caatcgggta actcccagga gagtgtcaca 600  
 gagcaggaca gcaaggacag cacctacagc ctacagcagca cctgacgct gagcaaagca 660  
 gactacgaga aacacaaagt ctacgctgc gaagtcaccc atcagggcct gagctcgccc 720  
 gtcacaaaga gcttcaacag gggagagtgt tgactcgag 759

<210> SEQ ID NO 40  
 <211> LENGTH: 447  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H1-heavy)

<400> SEQUENCE: 40

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

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

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

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala  
   50                                  55                                  60

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

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

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

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys  
   130                                  135                                  140

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

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

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

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

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His  
   210                                  215                                  220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val  
   225                                  230                                  235                                  240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr  
                   245                                  250                                  255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu  
                   260                                  265                                  270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys  
           275                                  280                                  285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser  
   290                                  295                                  300

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

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile  
                   325                                  330                                  335

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

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu  
           355                                  360                                  365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn  
           370                                  375                                  380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser  
   385                                  390                                  395                                  400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg  
                   405                                  410                                  415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu  
                   420                                  425                                  430

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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 435 440 445

<210> SEQ ID NO 41  
 <211> LENGTH: 447  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H3-heavy)

<400> SEQUENCE: 41

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

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Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu  
 355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn  
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser  
 385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg  
 405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu  
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 435 440 445

<210> SEQ ID NO 42  
 <211> LENGTH: 447  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H4-heavy)

<400> SEQUENCE: 42

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

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

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

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala  
 50 55 60

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

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

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

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys  
 130 135 140

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

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

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

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

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His  
 210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val  
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr  
 245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu  
 260 265 270

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Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys  
 275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser  
 290 295 300

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

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile  
 325 330 335

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

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu  
 355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn  
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser  
 385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg  
 405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu  
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 435 440 445

<210> SEQ ID NO 43  
 <211> LENGTH: 220  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H1-light)

<400> SEQUENCE: 43

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

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

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

Pro Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val  
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln  
 85 90 95

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

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp  
 115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn  
 130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu  
 145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp  
 165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr  
 180 185 190

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

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215 220

<210> SEQ ID NO 44  
 <211> LENGTH: 220  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H2-light  
 <400> SEQUENCE: 44

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

Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Ala Ser  
20 25 30

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

Ser Pro Gln Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val  
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys  
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln  
85 90 95

Ser Tyr Ser Ala Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu  
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp  
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn  
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu  
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp  
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr  
180 185 190

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

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
210 215 220

<210> SEQ ID NO 45  
 <211> LENGTH: 220  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of H3-light)  
 <400> SEQUENCE: 45

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

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

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

Pro Pro Lys Leu Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val  
50 55 60

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Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65          70          75          80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
      85          90          95
Ser Tyr Ser Ala Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
      100          105          110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
      115          120          125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
      130          135          140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145          150          155          160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
      165          170          175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
      180          185          190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
      195          200          205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
      210          215          220

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<210> SEQ ID NO 46
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (amino acid sequence of H4-light)

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<400> SEQUENCE: 46

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

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Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu  
210 215

<210> SEQ ID NO 47  
<211> LENGTH: 1350  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of H1-heavy)

<400> SEQUENCE: 47

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctggagggtc cctgagactc 60  
tcctgtgcag cctctggatt caccttcaact gactactaca tgagctgggt ccgccaggct 120  
ccaggggaagg ggtctggagtg gttgggcttt attagaaaca aagctaacgg ttacaccaca 180  
gaatacagtg cgtctgtgaa aggcagatcc accatctcaa gagataattc aaagaactca 240  
ctgtatctgc aaatgaacag cctgaaaacc gaggacacgg ccgtgtatta ctgtgctaga 300  
gataactggt ttgcttactg gggcaagga accctgggtc ccgtctctc ggctagcacc 360  
aagggcccat cggcttccc cctggcacc tcctccaaga gcacctctgg gggcacagcg 420  
gccctgggct gctctgtcaa ggactacttc cccgaaccgg tgacgggtgc gtggaactca 480  
ggcgccctga ccagcggcgt gcacacctc ccggctgtcc tacagtctc aggactctac 540  
tcctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600  
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660  
gacaaaaact acacatgccc accgtgccc gcacctgaac tcctgggggg accgtcagtc 720  
ttctcttcc ccccaaaac caaggacacc ctcatgatct cccggacccc tgaggtcaca 780  
tgctgtgtgg tggacgtgag ccacgaagac cctgagggtc agttcaactg gtacgtggac 840  
ggcgtggagg tgcataatgc caagacaaa cccggggagg agcagtacaa cagcacgtac 900  
cgtgtgtgca gcgtctcag cgtctctgac caggactggc tgaatggcaa ggagtacaag 960  
tgcaaggctc ccaacaaaac cctcccagcc cccatcgaga aaacctctc caaagccaaa 1020  
gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggagga gatgaccaag 1080  
aaccaggtca gctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgcctggag 1140  
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctccctg gctggactcc 1200  
gacggctcct tcttctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260  
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320  
ctctccctgt ctccgggtaa atgactcgag 1350

<210> SEQ ID NO 48  
<211> LENGTH: 1350  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of H3-heavy)

<400> SEQUENCE: 48

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctggagggtc cctgagactc 60  
tcctgtgcag cctctggatt caccttcaact gactactaca tgagctgggt ccgccaggct 120  
ccaggggaagg ggtctggagtg gttgggcttt attagaaaca aagctaacgg ttacaccaca 180  
gaatacagtg cgtctgtgaa aggcagatcc accatctcaa gagataattc aaagaactca 240  
ctgtatctgc aaatgaacag cctgcgtgct gaggacacgg ccgtgtatta ctgtgctaga 300

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gataactggt ttgcttactg gggcaagga accctggtca cgtctctc ggctagcacc 360
aagggeccat cggcttccc cctggcacc tcctccaaga gcacctctgg gggcacageg 420
gcctgggct gctggtcaa ggactacttc ccgaaccgg tgacgggtgc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggtgttc tacagtctc aggactctac 540
tcctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720
ttctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
tgctggtgg tggacgtgag ccacgaagac cctgaggta agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900
cgtgtggtca gcgtctcac cgtcctgac caggactggc tgaatggcaa ggagtacaag 960
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaacctctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggagga gatgaccaag 1080
aaccaggtca gctgacctg cctgggtcaa ggcttctatc ccagcagat cgcctggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgctcccggt gctggactcc 1200
gacggctcct tcttctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa atgactcgag 1350

```

&lt;210&gt; SEQ ID NO 49

&lt;211&gt; LENGTH: 1350

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (nucleotide sequence of H4-heavy)

&lt;400&gt; SEQUENCE: 49

```

gaggttcagc tggaggagtc tggcggggc ctggtgcagc cagggggctc actccgtttg 60
tcctgtcagc cttctggctt caccttcaact gattactaca tgagctgggt gcgtcaggcc 120
ccgggtaagg gcctggaatg gttgggtttt attagaaca aagctaatgg ttacacaaca 180
gagtacagtg catctgtgaa gggctgttc actataagca gagataattc caaaaacaca 240
ctgtacctgc agatgaacag cctgctgctc gaggacactg cgtctatta ttgtgctaga 300
gataactggt ttgcttactg gggccaaggg actctggtca cgtctctc ggctagcacc 360
aagggeccat cggcttccc cctggcacc tcctccaaga gcacctctgg gggcacageg 420
gcctgggct gctggtcaa ggactacttc ccgaaccgg tgacgggtgc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggtgttc tacagtctc aggactctac 540
tcctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720
ttctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780
tgctggtgg tggacgtgag ccacgaagac cctgaggta agttcaactg gtacgtggac 840
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900
cgtgtggtca gcgtctcac cgtcctgac caggactggc tgaatggcaa ggagtacaag 960

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tgcaaggctc ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1080
aaccaggctc gcttgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccggt gctggactcc 1200
gacggctcct tcttctctca cagcaagctc accgtggaca agagcagggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa atgactcgag 1350

```

```

<210> SEQ ID NO 50
<211> LENGTH: 669
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of H1-light)

```

```

<400> SEQUENCE: 50

```

```

gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtctttaa gctagcggca accaaaataa ctacttagct 120
tggcaccagc agaaaccagg acagcctcct aagatgctca ttatttgggc atctaccggg 180
gtatccgggg tcctgaccg attcagtgcc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaatc ctatagtgtc 300
cctctcagct tcggaggcgg taccaagggt gagatcaaac gtacgggtggc tgcaccatct 360
gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420
ctgctgaata acttctatcc cagagagggc aaagtacagt ggaagggtgga taacgcctc 480
caatcgggta actcccagga gagtgtcaca gacagggaca gcaaggacag cacctacagc 540
ctcagcagca cctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600
gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtggt 660
tgactcgag 669

```

```

<210> SEQ ID NO 51
<211> LENGTH: 669
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of H2-light)

```

```

<400> SEQUENCE: 51

```

```

gatattgtga tgaccagac tccactctcc ctgcccgtca ccctggaga gccggcctcc 60
atctcctgca agtccagtc gagtctttaa gctagtgcca accaaaataa ctacttggcc 120
tggcacctgc agaagccagg gcagctctca cagatgctga tcatttgggc atccactagg 180
gtatctggag tcccagacag gttcagtgcc agtgggtcag gcaactgattt cacactgaaa 240
atcagcaggg tggaggctga ggatgttggg gtttattact gccagcagtc ctacagcgtc 300
ccgctcagct tcggacaggg taccaagctg gagctcaaac gtacgggtggc tgcaccatct 360
gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420
ctgctgaata acttctatcc cagagagggc aaagtacagt ggaagggtgga taacgcctc 480
caatcgggta actcccagga gagtgtcaca gacagggaca gcaaggacag cacctacagc 540
ctcagcagca cctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600
gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtggt 660

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 tgactcgag 669

<210> SEQ ID NO 52  
 <211> LENGTH: 669  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (nucleotide sequence of H3-light)

&lt;400&gt; SEQUENCE: 52

```

gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctggcgca gagggccacc 60
atcaactgca agtccagcca gagtctttaa gctagcggca accaaaataa ctacttagct 120
tggtagcagc agaaaccagg acagcctcct aagctgctca ttatttgggc atctaccggg 180
gtatccgggg tcctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaatc ctatagtgtc 300
cctctcacgt tcggaggcgg taccaagggt gagatcaaac gtacgggtggc tgcaccatct 360
gtcttcatct tccgcgcatc tgatgagcag ttgaaatctg gaactgctc tgttgtgtgc 420
ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgcctc 480
caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540
ctcagcagca cctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600
gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gottcaacag gggagagtgt 660
tgactcgag 669
  
```

<210> SEQ ID NO 53  
 <211> LENGTH: 669  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (nucleotide sequence of H4-light)

&lt;400&gt; SEQUENCE: 53

```

gatatccaga tgaccagtc cccgagctcc ctgtccgct ctgtggcgca tagggtcacc 60
atcacctgca agtccagtc gagtctttaa gctagtggca accaaaataa ctacttggcc 120
tggcaccaac agaaaccagg aaaagctccg aaaatgctga ttatttgggc atccactagg 180
gtatctggag tccttctcgc cttctctgga tccgggtctg ggacggattt cactctgacc 240
atcagcagtc tgcagccgga agacttcgca acttattact gtcagcagtc ctacagcgtc 300
ccgctcacgt tcggacaggg taccaagggt gagatcaaac gtacgggtggc tgcaccatct 360
gtcttcatct tccgcgcatc tgatgagcag ttgaaatctg gaactgctc tgttgtgtgc 420
ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgcctc 480
caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540
ctcagcagca cctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600
gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gottcaacag gggagagtgt 660
tgactcgag 669
  
```

<210> SEQ ID NO 54  
 <211> LENGTH: 23  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (linker between VH and VL)

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&lt;400&gt; SEQUENCE: 54

Gly Leu Gly Gly Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 1 5 10 15  
 Gly Ser Ser Gly Val Gly Ser  
 20

&lt;210&gt; SEQ ID NO 55

&lt;211&gt; LENGTH: 1088

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (polynucleotide encoding scFv of huAbF46 antibody)

&lt;400&gt; SEQUENCE: 55

gctagcgctt tagcagaagt tcaattgggt gaatctgggt gtggtttggt tcaaccaggt 60  
 ggttcttga gattgtcttg tgctgcttct ggttttactt tcaccgatta ttacatgtcc 120  
 tgggttagac aagctccagg taaaggtttg gaatggttg gtttcattag aaacaaggct 180  
 aacggttaca ctaccgaata ttctgcttct gttaagggta gattcaccat ttctagagac 240  
 aactctaaga acaccttgta cttgcaaatg aactccttga gagctgaaga tactgctggt 300  
 tattactgcg ctagagataa ttggtttgct tattggggtc aagggtacttt ggttactggt 360  
 tcttctggcc tcgggggcct cggaggagga ggtagtggcg gaggaggctc cggtgatcc 420  
 agcgggtggt gttccgatat tcaaatgacc caatctccat cttctttgct tgcttcagtt 480  
 ggtgatagag ttaccattac ttgtaagtcc tcccaatctt tggtggcttc tggtaatcag 540  
 aacaattact tggcttgca tcaacaaaaa ccaggtaaag ctccaaagat gttgattatt 600  
 tgggcttcta ccagagtttc tgggtttoca tctagatttt ctggttctgg ttcggtact 660  
 gattttactt tgaccatttc atccttgcaa ccagaagatt tcgctactta ctactgtcaa 720  
 caatcttact ctgctccatt gacttttggc caaggtacaa aggtcgaat caagagagaa 780  
 ttcggtaagc ctatccctaa ccctctcctc ggtctcgatt ctacgggtgg tggtgatct 840  
 ggtggtggtg gttctggtg tgggtggtct caggaactga caactatag cgagcaaatc 900  
 ccctcaccaa ctttagaatc gacgocgtac tctttgtcaa cgactactat tttggccaac 960  
 gggaaaggcaa tgcaaggagt ttttgaatat tacaatcag taacgtttgt cagtaattgc 1020  
 ggttctcacc cctcaacaac tagcaaaggc agccccataa acacacagta tgttttttga 1080  
 gtttaaac 1088

&lt;210&gt; SEQ ID NO 56

&lt;211&gt; LENGTH: 5597

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (expression vector including polynucleotide encoding scFv of huAbF46 antibody)

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: misc\_feature

&lt;222&gt; LOCATION: (573)..(578)

&lt;223&gt; OTHER INFORMATION: NheI restriction site

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: misc\_feature

&lt;222&gt; LOCATION: (588)..(938)

&lt;223&gt; OTHER INFORMATION: huAbF46 VH

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: misc\_feature

&lt;222&gt; LOCATION: (939)..(1007)

&lt;223&gt; OTHER INFORMATION: linker

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: misc\_feature

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<222> LOCATION: (1008)..(1349)
<223> OTHER INFORMATION: huAbF46 VL
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1350)..(1355)
<223> OTHER INFORMATION: EcoRI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1356)..(1397)
<223> OTHER INFORMATION: V5 epitope
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1398)..(1442)
<223> OTHER INFORMATION: (G4S)3 linker
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1443)..(1649)
<223> OTHER INFORMATION: Aga2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1650)..(1652)
<223> OTHER INFORMATION: TGA(stop codon)
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1653)..(1660)
<223> OTHER INFORMATION: PmeI restriction site

<400> SEQUENCE: 56

acggattaga agccgccgag cgggtgacag ccctccgaag gaagactctc ctccgtgcg      60
cctcgtcttc accggtcgcy ttctgaaac gcagatgtgc ctgcgccgc actgctccga      120
acaataaaga ttctacaata ctactcttta tggttatgaa gaggaaaaat tggcagtaac      180
ctggccccac aaaccttaa atgaacgaat caaattaaca accataggat gataatgcga      240
ttagtttttt agccttattt ctggggtaat taatcagcga agcgatgatt tttgatctat      300
taacagatat ataaatgcaa aaactgcata accactttaa ctaatacttt caacattttc      360
ggtttgattt acttcttatt caaatgtaat aaaagtatca acaaaaaatt gttaataatac      420
ctctatactt taacgtcaag gagaaaaaac cccggatcgg actactagca gctgtaatac      480
gactcactat agggaatatt aagctaattc tacttcatac attttcaatt aagatgcagt      540
tacttcgctg tttttcaata tttctgttta ttgctagcgt tttagcagaa gttcaattgg      600
ttgaatctgg tgggtggttg gttcaaccag gtgggtcttt gagattgtct tgtgctgctt      660
ctggttttac tttcaccgat tattacatgt cctgggtagt acaagctcca ggtaaagggt      720
tggaaatggt gggtttcatt agaacaagg ctaacggtta cactaccgaa tattctgctt      780
ctgttaaggg tagattcacc atttctagag acaactctaa gaacaccttg tacttgcaaa      840
tgaactcctt gagagctgaa gatactgctg tttattactg cgctagagat aattggtttg      900
cttattgggg tcaaggtact ttggttactg tttcttctgg cctcgggggc ctcgaggagg      960
gaggtagtgg cggaggaggc tccgggtgat ccagcgggtg gggttccgat attcaaatga     1020
cccaatctcc atcttctttg tctgcttcag ttggtgatag agttaccatt acttgaagt     1080
cctccaatc tttgttggtt tctggttaac agaacaatta ctggttgg catcaacaaa     1140
aaccaggtaa agctccaaag atgttgatta tttgggcttc taccagagtt tctggtgttc     1200
catctagatt ttctggttct ggttcgggta ctgattttac tttgaccatt tcatccttgc     1260
aaccagaaga tttcgtact tactactgtc aacaatctta ctctgctcca ttgacttttg     1320
gtcaaggtag aaaggtcgaa atcaagagag aattcggtaa gctatccctt aaccctctcc     1380
tcggtctcga ttctacgggt ggtggtggat ctggtggtgg tggttctggt ggtggtggtt     1440
ctcaggaact gacaactata tgcgagcaaa tcccctcacc aactttagaa tcgacgcctg     1500

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actctttgtc aacgactact attttgcca acgggaaggc aatgcaagga gtttttgaat	1560
attacaaatc agtaacgttt gtcagtaatt gcggttctca cccctcaaca actagcaaag	1620
gcagccccat aaacacacag tatgtttttt gagtttaaac ccgctgatct gataacaaca	1680
gtgtagatgt aacaaaatcg actttgttcc cactgtactt ttagctcgta caaaatacaa	1740
tatacttttc atttctccgt aaacaacatg ttttcccatg taatatcctt ttctattttt	1800
cgttccgtta ccaactttac acatacttta tatagctatt cacttctata cactaaaaaa	1860
ctaagacaat ttaatttttg ctgcctgcca tatttcaatt tgttataaat tctataatt	1920
tatctatta gttagctaaa aaagatgaat gtgaatcgaa tctaagaga attgggcaag	1980
tgcaaaaaca atacttaaat aaatactact cagtaataac ctatttctta gcatttttga	2040
cgaattttgc tattttgtta gagtctttta caccatttgt ctccacacct ccgcttacat	2100
caacaccaat aacgccattt aatctaagcg catcaccaac attttctggc gtcagtccac	2160
cagctaacat aaaatgtaag ctctcggggc tctcttgcct tccaaccag tcagaaatcg	2220
agttccaatc caaaagtcca cctgtcccac ctgcttctga atcaacaag ggaataaacg	2280
aatgaggttt ctgtgaagct gcactgagta gtatgttgca gtcttttggg aatcagagtc	2340
ttttaataac tggcaaacgg aggaactctt ggtattcttg ccacgactca tctccgtgca	2400
gttggacgat atcaatgccg taatcattga ccagagccaa aacatcctcc ttaggttgat	2460
taagaaacac gccaaccaag tatttccggag tgccctgaact atttttatat gcttttacia	2520
gacttgaat tttccttgca ataaccgggt caattgttct ctttctattg ggcacacata	2580
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aagctgcctt tgtgtgctta atcacgtata ctcacgtgct caatagtcac caatgccctc	2760
cctcttggcc ctctcctttt cttttttoga ccgaatttct tgaagacgaa agggcctcgt	2820
gatacgcta tttttatagg ttaatgtcat gataataatg gtttcttagg acggatcgct	2880
tgccgtaac ttacacgcgc ctctgtatctt ttaatgatgg aataatttgg gaatttactc	2940
tgtgtttatt tatttttatg ttttgtattt ggattttaga aagtaataa agaaggtaga	3000
agagttacgg aatgaagaaa aaaaaataa caaaggttta aaaaatttca acaaaaagcg	3060
tactttacat atatatatt tagacaagaa aagcagatta aatagatata cattcgatta	3120
acgataagta aaatgtaaaa tcacaggatt ttcgtgtgtg gtcttctaca cagacaagat	3180
gaaacaattc ggcattaata cctgagagca ggaagagcaa gataaaagggt agtatttgtt	3240
ggcgatcccc cttagagtctt ttacatcttc ggaaaacaaa aactattttt tctttaattt	3300
ctttttttac tttctatttt taatttatat atttatatta aaaaatttaa attataatta	3360
tttttatagc acgtgatgaa aaggaccag gtggcacttt tcggggaaat gtgcgaggaa	3420
cccctatttg tttatttttc taaatacatt caaatatgta tccgctcatg agacaataac	3480
cctgataaat gcttcaataa tattgaaaa ggaagagtat gagtattcaa catttccgtg	3540
tcgcccttat tccctttttt gcggcatttt gccttctgt ttttgcctac ccagaaacgc	3600
tggtgaaagt aaaagatgct gaagatcagt tgggtgcacg agtgggttac atcgaactgg	3660
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gcacttttaa agttctgcta tgtggcgcgg tattatcccc tgttgacgcc gggcaagagc	3780
aactcggctc ccgcatacac tattctcaga atgacttggg tgagtactca ccagtcacag	3840
aaaagcatct tacggatggc atgacagtaa gagaattatg cagtgcctgc ataacctga	3900

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gtgataaacac tgcggccaac ttactttctga caacgatcgg aggaccgaag gagctaaccg 3960
cttttttgca caacatgggg gatcatgtaa ctgccttga tegtgggaa cgggagctga 4020
atgaagccat accaaacgac gagegtgaca ccacgatgcc tgtagcaatg gcaacaacgt 4080
tgcgcaaact attaactggc gaactactta ctctagcttc cgggcaacaa ttaatagact 4140
ggatggaggc ggataaagtt gcaggaccac ttctgcgctc ggccttccg gctggctggt 4200
ttattgtctga taaatctgga gccggtgagc gtgggtctcg cggtatcatt gcagcactgg 4260
ggccagatgg taagcctcc cgtatcgtag ttatctacac gacgggcagt caggcaacta 4320
tggatgaacg aaatagacag atcgcctgaga taggtgcctc actgattaag cattggtaac 4380
tgtcagacca agtttactca tatatacttt agattgattt aaaacttcat ttttaattta 4440
aaaggatcta ggtgaagatc ctttttgata atctcatgac caaaatcctt taactgtgagt 4500
tttcgttcca ctgagcgtca gaccccgtag aaaagatcaa aggatcttct tgagatcctt 4560
tttttctgcg cgtaactctgc tgcttgcaaa caaaaaaacc accgctacca gcggtggttt 4620
gtttgccgga tcaagagcta ccaactcttt ttccgaaggt aactggcttc agcagagcgc 4680
agataccaaa tactgtcctt ctagtgtagc cgtagttagg ccaccacttc aagaactctg 4740
tagcaccgcc tacatacctc gctctgctaa tcctgttacc agtggctgct gccagtggcg 4800
ataagtcgtg tcttaccggg ttgactcaa gacgatagtt accggataag gcgcagcggg 4860
cgggctgaac ggggggttcg tgcacacagc ccagcttggg gcgaacgacc tacaccgaa 4920
tgagatacct acagcgtgag cattgagaaa gcgccacgct tcccgaaggg agaaaggcgg 4980
acaggtatcc ggtaagcggc agggtcggaa caggagagcg cacgaggag cttccagggg 5040
ggaacgcctg gtatctttat agtcctgtcg ggtttcgcca cctctgactt gagcgtcgat 5100
ttttgtgatg ctgcctcagg gggccgagcc tatggaaaaa cgccagcaac gcggcctttt 5160
tacggttcct ggctttttgc tggccttttg ctacatggt ctttctgctg ttatccctg 5220
attctgtgga taaccttatt accgcctttg agtgagctga taccgctcgc cgcagccgaa 5280
cgaccgagcg cagcagagca gtgagcaggg aagcgggaaga gcgcccaata cgcaaaccgc 5340
ctctccccgc gcgttgccg attcattaat gcagctggca cgacaggttt cccgactgga 5400
aagcgggcag tgagcgcaca gcaattaatg tgagttacct cactcattag gcaccccagg 5460
ctttacactt tatgcttccg gctcctatgt tgtgtggaat tgtgagcggg taacaatttc 5520
acacagaaa cagctatgac catgattacg ccaagctcgg aattaaccct cactaaaggg 5580
aacaaaagct ggctagt 5597

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<210> SEQ ID NO 57
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (U6-HC7 hinge)

<400> SEQUENCE: 57

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Glu Pro Lys Ser Cys Asp Cys His Cys Pro Pro Cys Pro
1           5           10

```

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<210> SEQ ID NO 58
<211> LENGTH: 435
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (polynucleotide encoding CDR-L3)

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derived from L3-1 clone)

&lt;400&gt; SEQUENCE: 58

```

gaattcacta gtgattaatt cgccgccacc atggattcac aggccaggt cctcatgttg      60
ctgctgctat cggtatctgg tacctgtgga gatatccaga tgaccagtc cccgagctcc     120
ctgtccgcct ctgtgggcga tagggteacc atcacctgca agtccagtca gagtctttta    180
gctagtggca accaaaataa ctacttggcc tggcaccaac agaaaccagg aaaagctccg     240
aaaatgctga ttatttgggc atccactagg gtatctggag tcccttctcg cttctctgga     300
tccgggtctg ggacggattt cactctgacc atcagcagtc tgcagccgga agacttcgca     360
acttattact gtcagcagtc ctacagcgcg ccgtacacgt tcggacaggg taccaaggtg    420
gagatcaaac gtacg                                                    435

```

&lt;210&gt; SEQ ID NO 59

&lt;211&gt; LENGTH: 435

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (polynucleotide encoding CDR-L3 derived from L3-2 clone)

&lt;400&gt; SEQUENCE: 59

```

gaattcacta gtgattaatt cgccgccacc atggattcac aggccaggt cctcatgttg      60
ctgctgctat cggtatctgg tacctgtgga gatatccaga tgaccagtc cccgagctcc     120
ctgtccgcct ctgtgggcga tagggteacc atcacctgca agtccagtca gagtctttta    180
gctagtggca accaaaataa ctacttggcc tggcaccaac agaaaccagg aaaagctccg     240
aaaatgctga ttatttgggc atccactagg gtatctggag tcccttctcg cttctctgga     300
tccgggtctg ggacggattt cactctgacc atcagcagtc tgcagccgga agacttcgca     360
acttattact gtgggcagtc ctacagcgcg ccgctcacgt tcggacaggg taccaaggtg    420
gagatcaaac gtacg                                                    435

```

&lt;210&gt; SEQ ID NO 60

&lt;211&gt; LENGTH: 435

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (polynucleotide encoding CDR-L3 derived from L3-3 clone)

&lt;400&gt; SEQUENCE: 60

```

gaattcacta gtgattaatt cgccgccacc atggattcac aggccaggt cctcatgttg      60
ctgctgctat cggtatctgg tacctgtgga gatatccaga tgaccagtc cccgagctcc     120
ctgtccgcct ctgtgggcga tagggteacc atcacctgca agtccagtca gagtctttta    180
gctagtggca accaaaataa ctacttggcc tggcaccaac agaaaccagg aaaagctccg     240
aaaatgctga ttatttgggc atccactagg gtatctggag tcccttctcg cttctctgga     300
tccgggtctg ggacggattt cactctgacc atcagcagtc tgcagccgga agacttcgca     360
acttattact gtgcacagtc ctacagccat ccgttctctt tcggacaggg taccaaggtg    420
gagatcaaac gtacg                                                    435

```

&lt;210&gt; SEQ ID NO 61

&lt;211&gt; LENGTH: 435

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

-continued

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (polynucleotide encoding CDR-L3 derived from L3-5 clone)

&lt;400&gt; SEQUENCE: 61

```

gaattcacta gtgattaatt cgccgccacc atggattcac aggcccaggt cctcatgttg      60
ctgctgctat cggtatctgg tacctgtgga gatatccaga tgaccagtc cccgagctcc      120
ctgtccgcct ctgtgggaga tagggtcacc atcacctgca agtcagtcga gagtctttta      180
gctagtggca accaaaataa ctacttggcc tggcaccaac agaaaccagg aaaagctccg      240
aaaatgctga ttatttgggc atccactagg gtatctggag tcccttctcg cttctctgga      300
tccgggtctg ggacggattt cactctgacc atcagcagtc tgcagccgga agacttcgca      360
acttattact gtcagcagtc ctacagccgc ccgtttacgt tcggacaggg taccaaggtg      420
gagatcaaac gtacg                                          435

```

&lt;210&gt; SEQ ID NO 62

&lt;211&gt; LENGTH: 462

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (polypeptide consisting of heavy chain of huAbF46-H4-A1, U6-HC7 hinge and constant region of human IgG1)

&lt;400&gt; SEQUENCE: 62

```

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

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Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe  
 245 250 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro  
 260 265 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val  
 275 280 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr  
 290 295 300

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val  
 305 310 315 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys  
 325 330 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser  
 340 345 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro  
 355 360 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val  
 370 375 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly  
 385 390 395 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp  
 405 410 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp  
 420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His  
 435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 450 455 460

<210> SEQ ID NO 63  
 <211> LENGTH: 1410  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (polynucleotide encoding polypeptide  
 consisting of heavy chain of huAbF46-H4-A1, U6-HC7 hinge and  
 constant region of human IgG1)

<400> SEQUENCE: 63

gaattgcg ccaccatgga atggagctgg gttttctcg taacactttt aaatggtatc 60  
 cagtgtgagg ttcagctggt ggagctctgg ggtggcctgg tgcagccagg gggctcactc 120  
 cgtttgcct gtgcagcttc tggcttcacc ttcactgatt actacatgag ctgggtgcgt 180  
 caggccccgg gtaagggcct ggaatggttg ggttttatta gaaacaaagc taatggttac 240  
 acaacagagt acagtgcac tgtgaaggtt cgtttcacta taagcagaga taattccaaa 300  
 aacacactgt acctgcagat gaacagcctg cgtgctgagg aactgacctg ctattattgt 360  
 gctagagata actggtttgc ttactggggc caagggactc tggtcaccgt ctctcgggct 420  
 agcaccaagg gcccatcggt ctccccctg gcacctcct ccaagagcac ctctgggggc 480  
 acagcgccc tgggctgctt ggtcaaggac tacttccccg aaccgggtgac ggtgctgtgg 540  
 aactcaggcg cctgaccagt cggcgtgac accttccccg ctgtcctaca gtctcagga 600  
 ctctactccc tcagcagcgt ggtgacctg cctccagca gcttgggac ccagacctac 660  
 atctgcaacg tgaatcacia gccagcaac accaaggttg acaagaaagt tgagcccaaa 720  
 agctgagatt gccactgtcc tccatgtcca gcacctgaac tctgggggg accgtcagtc 780

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ttctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca      840
tgcgtggtgg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtacgtggac      900
ggcgtggagg tgcataatgc caagacaaag ccgcgaggagg agcagtacaa cagcacgtac      960
cgtgtgggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag     1020
tgcaagggtct ccaacaaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa     1080
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag     1140
aaccagggtca gctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag     1200
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc     1260
gacggctcct tcttctctca cagcaagctc accgtggaca agagcagggtg gcagcagggg     1320
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc     1380
ctctccctgt ctccgggtaa atgactcgag                                         1410

```

&lt;210&gt; SEQ ID NO 64

&lt;211&gt; LENGTH: 461

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Synthetic (polypeptide consisting of heavy chain of huAbF46-H4-A1, human IgG2 hinge and constant region of human IgG1)

&lt;400&gt; SEQUENCE: 64

```

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

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Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu  
 245 250 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu  
 260 265 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys  
 275 280 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys  
 290 295 300

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu  
 305 310 315 320

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys  
 325 330 335

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys  
 340 345 350

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser  
 355 360 365

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys  
 370 375 380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln  
 385 390 395 400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly  
 405 410 415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln  
 420 425 430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn  
 435 440 445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 450 455 460

&lt;210&gt; SEQ ID NO 65

&lt;211&gt; LENGTH: 1407

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Synthetic (polynucleotide encoding polypeptide  
 consisting of heavy chain of huAbF46-H4-A1, human IgG2 hinge and  
 constant region of human IgG1)

&lt;400&gt; SEQUENCE: 65

gaattcgccg ccaccatgga atggagctgg gtttttctcg taacactttt aaatggtatc 60

cagtgtgagg ttcagctggt ggagtctggc ggtggcctgg tgcagccagg gggctcactc 120

cgtttgcct gtgcagcttc tggettccacc ttcactgatt actacatgag ctgggtgcgt 180

caggccccgg gtaagggocct ggaatggttg ggttttatta gaaacaaagc taatggttac 240

acaacagagt acagtgcac tgtgaagggt cgtttcacta taagcagaga taattccaaa 300

aacacactgt acctgcagat gaacagcctg cgtgctgagg aactgccgt ctattattgt 360

gctagagata actggtttgc ttactggggc caagggactc tggtcaccgt ctctcggt 420

agcaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc 480

acagcgccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgctcgtg 540

aactcaggcg ccttgaccag cggcgtgcac accttccccg ctgtctaca gtctcagga 600

cttactccc tcagcagct ggtgaccgtg ccctccagca gottgggcac ccagacctac 660

atctgcaacg tgaatcaca gccccagca accaaggtgg acaagaaagt tgagaggaag 720

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tgetgtgtgg agtgcccccc ctgccacga cctgaactcc tggggggacc gtcagtcttc 780
ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc 840
gtggtgtgtg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 900
gtggagggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 960
gtggtcagcg tctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 1020
aaggtctcca acaaagccct cccagcccc atcgagaaaa ccatctccaa agccaaaggg 1080
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1140
caggtcagcc tgacctgctt ggtcaaagc ttctatccca gcgacatcgc cgtggagtgg 1200
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctccogtctt ggactccgac 1260
ggctccttct tctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaaac 1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380
tcctgtctc cgggtaaatg actcgag 1407

```

&lt;210&gt; SEQ ID NO 66

&lt;211&gt; LENGTH: 460

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Synthetic (polypeptide consisting of heavy chain of huAbF46-H4-A1, human IgG2 hinge and constant region of human IgG2)

&lt;400&gt; SEQUENCE: 66

```

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

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

<210> SEQ ID NO 67  
 <211> LENGTH: 1404  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (polynucleotide encoding polypeptide consisting of heavy chain of huAbF46-H4-A1, human IgG2 hinge and constant region of human IgG2)

<400> SEQUENCE: 67

gaattcgccg ccaccatgga atggagctgg gtttttctcg taacactttt aaatggtatc	60
cagtgtgagg ttcagctggt ggagtctggc ggtggcctgg tgcagccagg gggctcactc	120
cgtttgcct gtgcagcttc tggcttcacc ttcactgatt actacatgag ctgggtgctg	180
caggcccccg gtaagggcct ggaatggttg ggttttatta gaaacaaagc taatggttac	240
acaacagagt acagtgcac tgatgaagggt cgtttcacta taagcagaga taattccaaa	300
aacacactgt acctgcagat gaacagcctg cgtgctgagg aactgacctg ctattattgt	360
gctagagata actggtttgc ttaactggggc caagggactc tggtcaccgt ctctctggct	420
agcaccaagg gcccatcggg cttecccctg gcgcctgct ccaggagcac ctccgagagc	480
acagcggccc tgggctgctt ggtaaggac tacttcccag aaccgggtgac ggtgctgctg	540
aactcaggcg ctctgaccag cggcgtgcac accttcccag ctgtcctaca gtctctcagga	600
ctctactccc tcagcagctt ggtgacctg cctccagca acttcggcac ccagacctac	660
acctgcaacg tagatcacia gccccagcaac accaaggtgg acaagacagt tgagcgcaaa	720

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tggtgtgtcg agtgcaccac gtgcccagca ccacctgtgg caggaccgtc agtcttctc 780
ttcccccaa aacccaagga caccctcatg atctcccga cccctgaggt cagtgcgctg 840
gtggtggacg tgagccaagc agaccccag gtccagtcca actggtacgt ggacggcgtg 900
gaggtgcata atgccaagc aaagccacgg gaggagcagt tcaacagcac gttccgtgtg 960
gtcagcgctc tcaccgttgt gcaccaggac tggtgaacg gcaaggagta caagtgcaag 1020
gtctccaaca aaggcctccc agccccatc gagaaaacca tctccaaaac caaagggcag 1080
ccccgagaac cacaggtgta caccctgccc ccatcccggg aggagatgac caagaaccag 1140
gtcagcctga cctgctgtgt caaaggcttc taccaccagc acatcgccgt ggagtgggag 1200
agcaatgggc agccggagaa caactacaag accacgcctc ccatgctgga ctccgacggc 1260
tcctttctcc tctacagcaa gtcaccgtg gacaagagca ggtggcagca ggggaacgtc 1320
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc 1380
ctgtctccgg gtaaatgact cgag 1404

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<210> SEQ ID NO 68
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (polypeptide consisting of light
chain of huAbF46-H4-A1 (H36Y) and human kappa constant region)

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<400> SEQUENCE: 68

```

```

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

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225                    230                    235                    240

<210> SEQ ID NO 69  
 <211> LENGTH: 758  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (polynucleotide encoding polypeptide  
 consisting of light chain of huAbF46-H4-A1(H36Y) and human kappa  
 constant region)

<400> SEQUENCE: 69

aattcactag tgattaattc gccccacca tggattcaca ggcccaggtc ctcattgttc     60  
 tgctgctatc ggtatctggt acctgtggag atatccagat gaccagctcc ccgagctccc     120  
 tgtcgcctc tgtggcgat agggtcacca tcacctgcaa gtccagtcag agtccttttag     180  
 ctagtggcaa ccaaaataac tacttggcct ggtaccaaca gaaaccagga aaagctccga     240  
 aaatgctgat tatttgggca tccactaggg tatctggagt cccttctcgc ttctctggat     300  
 ccgggtctgg gacggatttc actctgacca tcagcagtct gcagccggaa gacttcgcaa     360  
 cttattactg tcagcagctc tacagccgcc cgtacacggt cggacagggt accaaggtgg     420  
 agatcaaacg tacggtgggt gcaccatctg tcttcatctt cccgccatct gatgagcagt     480  
 tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc agagaggcca     540  
 aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag agtgtcacag     600  
 agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg agcaaagcag     660  
 actacgagaa acacaaagtc tacgctcgcg aagtcaccca tcagggcctg agctcgcccg     720  
 tcacaaagag cttcaacagg ggagagtgtt gactcgag                             758

<210> SEQ ID NO 70  
 <211> LENGTH: 240  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (polypeptide consisting of light  
 chain of huAbF46-H4-A1 and human kappa constant region)

<400> SEQUENCE: 70

Met Asp Ser Gln Ala Gln Val Leu Met Leu Leu Leu Ser Val Ser  
 1                    5                    10                    15

Gly Thr Cys Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser  
 20                    25                    30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser  
 35                    40                    45

Leu Leu Ala Ser Gly Asn Gln Asn Asn His Leu Ala Trp Tyr Gln Gln  
 50                    55                    60

Lys Pro Gly Lys Ala Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg  
 65                    70                    75                    80

Val Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp  
 85                    90                    95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr  
 100                    105                    110

Tyr Cys Gln Gln Ser Tyr Ser Arg Pro Tyr Thr Phe Gly Gln Gly Thr  
 115                    120                    125

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe  
 130                    135                    140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys



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50              55              60
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser
65              70              75              80

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

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

Val Thr Val Ser Ser
115

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<210> SEQ ID NO 75
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (light chain variable region of anti-
c-Met antibody (AbF46 or huAbF46-H1))

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<400> SEQUENCE: 75

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

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

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

Pro Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val
50             55             60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65             70             75             80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85             90             95

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

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Lys Arg

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<210> SEQ ID NO 76
<211> LENGTH: 1416
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of heavy chain
of anti-c-Met antibody (AbF46 or huAbF46-H1))
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(6)
<223> OTHER INFORMATION: EcoRI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(66)
<223> OTHER INFORMATION: signal sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(417)
<223> OTHER INFORMATION: VH - heavy chain variable region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (418)..(423)
<223> OTHER INFORMATION: NdeI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (418)..(1407)
<223> OTHER INFORMATION: CH - heavy chain constant region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1408)..(1410)

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<223> OTHER INFORMATION: TGA - stop sodon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1411)..(1416)
<223> OTHER INFORMATION: XhoI restriction site

<400> SEQUENCE: 76
gaattcgccg ccaccatgga atggagctgg gtttttctcg taacactttt aaatggatc   60
cagtgtgagg tgaagctggg ggagctctgga ggaggcttgg tacagcctgg gggttctctg   120
agactctcct gtgcaacttc tgggttcacc ttcactgatt actacatgag ctgggtccgc   180
cagcctccag gaaaggcact tgagtgggtg ggttttatta gaaacaaagc taatggttac   240
acaacagagt acagtgcac tgtgaagggt cggttcacca tctccagaga taattcccaa   300
agcatcctct atcttcaaat ggacaccctg agagctgagg acagtgccac ttattactgt   360
gcaagagata actggtttgc ttactggggc caagggactc tggtcactgt ctctgcagct   420
agcaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc   480
acagcggccc tgggctgctt ggtcaaggac tacttccccg aaccgggtgac ggtgtcgtgg   540
aactcaggcg ccttgaccag cggcgtgcac accttccccg ctgtcctaca gtcctcagga   600
cttactccc  toagcagct  ggtgaccgtg cctccagca  gcttgggac  ccagacctac   660
atctgcaacg tgaatcacia gccagcaac  accaaggtgg  acaagaaagt tgagccaaa   720
tcttgtgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg   780
tcagtcttcc tcttcccccc aaaacccaag gacacctca  tgatctcccg gacctctgag   840
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac   900
gtggacggcg tggaggtgca taatgccaa  acaaagccgc  gggaggagca gtacaacagc   960
acgtaccgtg tggtcagcgt cctcaccgct ctgcaccagg actggctgaa tggcaaggag  1020
tacaagtgca aggtctccaa caaagccctc ccagccccca  toagaaaaac catctccaaa  1080
gccaaagggc agccccgaga accacaggtg tacacctgct ccccatcccg ggaggagatg  1140
accaagaacc aggtcagcct gacctgctg  gtcaaaggct tctatcccag cgacatcgcc  1200
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg  1260
gactccgacg gtcctcttt  cctctacagc aagctcaccg tggacaagag caggtggcag  1320
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag  1380
aagagcctct cctgtctccc gggtaaatga ctcgag   1416

<210> SEQ ID NO 77
<211> LENGTH: 759
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (nucleotide sequence of light chain
of anti-c-Met antibody (AbF46 or huAbF46-H1))
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(6)
<223> OTHER INFORMATION: EcoRI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(90)
<223> OTHER INFORMATION: signal sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(432)
<223> OTHER INFORMATION: VL - light chain variable region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (430)..(435)

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<223> OTHER INFORMATION: BsiWI restriction site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (433)..(750)
<223> OTHER INFORMATION: CL - light chain constant region
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (751)..(753)
<223> OTHER INFORMATION: stop codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (754)..(759)
<223> OTHER INFORMATION: XhoI restriction site

<400> SEQUENCE: 77

gaattcacta gtgattaatt cgccgccacc atggattcac aggccaggt cctcatgttg      60
ctgctgctat cggatctctg tacctgtgga gacattttga tgaccagtc tccatcctcc    120
ctgactgtgt cagcaggaga gaaggtcact atgagctgca agtccagtca gagtctttta    180
gctagtggca accaaaataa ctacttggcc tggcaccagc agaaaccagg acgatctcct    240
aaaatgctga taatttgggc atccactagg gtatctggag tccctgatcg cttcataggg    300
agtggatctg ggacggattt cactctgacc atcaacagtg tgcaggctga agatctggct    360
gtttattact gtcagcagtc ctacagcgtc ccgctcacgt tcggtgctgg gaccaagctg    420
gagctgaaac gtacggtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag    480
ttgaaatctg gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagagggc    540
aaagtacagt ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca    600
gagcaggaca gcaaggacag cacctacagc ctacagcagca ccctgacgct gagcaaagca    660
gactacgaga aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc    720
gtcacaaga gcttcaacag gggagagtgt tgactcgag                               759

<210> SEQ ID NO 78
<211> LENGTH: 4170
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (polynucleotide encoding c-Met
protein)

<400> SEQUENCE: 78

atgaagccc ccgctgtgct tgcacctggc atcctcgtgc tcctgtttac cttggtgcag      60
aggagcaatg gggagtgtaa agaggcacta gcaaagtccg agatgaatgt gaatatgaag    120
tatcagcttc ccaacttcac cgcggaaca cccatccaga atgtcattct acatgagcat    180
cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag    240
gttgctgagt acaagactgg gcctgtgctg gaacaccagc attgtttccc atgtcaggac    300
tgcagcagca aagccaattt atcaggaggt gtttgaaag ataacatcaa catggctcta    360
gttgctgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc    420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga ggttcaactgc    480
atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gagcgccctg    540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc    600
ataaattctt cttattttcc agatcatcca ttgcattcga tatcagttag aaggctaaag    660
gaaacgaaag atggttttat gttttgacg gaccagtcct acattgatgt tttacctgag    720
ttcagagatt cttaccccat taagtatgct catgcctttg aaagcaacaa tttattttac    780

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ttcttgacgg tccaaagga aactctagat gctcagactt ttcacacaag aataatcagg	840
ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc	900
acagaaaaga gaaaaagag atccacaaag aaggaagtgt ttaataact tcaggctgcg	960
tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac	1020
attcttttcg ggggtttcgc acaagcaag ccagattctg cogaaccaat ggatcgatct	1080
gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa	1140
aacaatgtga gatgtctcca gcatttttac ggaccaatc atgagcactg ctttaatagg	1200
acacttctga gaaattcatc aggtctgtaa gcgcgccgtg atgaatatcg aacagagttt	1260
accacagctt tgcagcgcgt tgacttattc atgggtcaat tcagcgaagt cctcttaaca	1320
tctatatcca cttcattaa agggacctc accatagcta atcttgggac atcagagggg	1380
cgcttcatgc aggttgggtt ttctogatca ggaccatcaa cccctcatgt gaattttctc	1440
ctggactccc atccagtgtc tccagaagtg attgtggagc atacattaaa ccaaatggc	1500
tacacactgg ttatcactgg gaagaagatc acgaagatcc cattgaatgg cttgggctgc	1560
agacatttcc agtctgcag tcaatgcctc tctgccccac ctttgttca gtgtggctgg	1620
tgcccagaca aatgtgtgcg atcggaggaa tgctgagcg ggacatggac tcaacagatc	1680
tgtctgctg caatctacaa ggttttccca aatagtgcac ccctgaagg agggacaagg	1740
ctgaccatat gtggctggga ctttggattt cggaggaata ataaattga tttaaagaaa	1800
actagagttc tccttgaaa tgagagctgc accttgactt taagtgagag cacgatgaat	1860
acattgaaat gcacagtggc tcctgccatg aataagcatt tcaatatgtc cataattatt	1920
tcaaatggcc acgggacaac acaatacagt acattctcct atgtggatcc tgttaataca	1980
agtatttgcg cgaataacgg tcctatggct ggtggcaact tacttacttt aactggaaat	2040
tacctaaaca gtgggaattc tagacacatt tcaattggtg gaaaaacatg tactttaaaa	2100
agtgtgtcaa acagttattc tgaatgttat accccagccc aaaccatttc aactgagttt	2160
gctgttaaat tgaaaattga cttagccaac cgagagacaa gcattctcag ttaccgtgaa	2220
gatcccattg tctatgaaat tcatccaacc aaatctttta ttagtgttg gagcacaata	2280
acaggtgttg gaaaaacct gaattcagtt agtgtcccga gaatggtcat aatgtgcat	2340
gaagcaggaa ggaactttac agtggcatgt caacatcgct ctaattcaga gataatctgt	2400
tgtaccactc cttcctgca acagctgaat ctgcaactcc cctgaaaaac caaagccttt	2460
ttcatgtag atgggatcct ttccaaatac tttgatctca tttatgtaca taatcctgtg	2520
tttaagcctt ttgaaaagcc agtgatgac tcaatgggca atgaaaatgt actggaatt	2580
aagggaaatg atattgacc tgaagcagtt aaagtgaaag tgttaaaagt tggaaataag	2640
agctgtgaga atatacactt acattctgaa gccgttttat gcacggctcc caatgacctg	2700
ctgaaattga acagcgagct aaatatagag tggaaagcaag caatttcttc aaccgtcctt	2760
ggaaaagtaa tagttcaacc agatcagaat ttcacaggat tgattgctgg tgtgtctca	2820
atatcaacag cactgttatt actacttggg tttttcctgt ggctgaaaaa gagaaagcaa	2880
attaaagatc tgggcagtga attagtctgc tacgatgcaa gagtacacac tctcatttg	2940
gataggcttg taagtccccg aagtgtaagc ccaactacag aatggtttc aatgaatct	3000
gtagactacc gagctacttt tccagaagat cagtttccca attcatctca gaacggttca	3060
tgcgacaag tgcagtatcc tctgacagac atgtcccca tccaaactag tggggactct	3120
gatatatcca gtccattact gcaaaactat gtccacattg acctcagtc tctaaatcca	3180

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gagctggtcc aggcagtgca gcatgtagtg attgggcccga gtagcctgat tgtgcatttc 3240
aatgaagtca taggaagagg gcattttggt tgtgtatata atgggacttt gttggacaat 3300
gatggcaaga aaattcactg tgctgtgaaa tccttgaaca gaatcactga cataggagaa 3360
gtttccaat ttctgaccga gggaaatcctc atgaaagatt ttagtcatcc caatgtcttc 3420
tcgctcctgg gaatctgcct gcgaagtgaa gggctctccgc tgggtgtcct accatacatg 3480
aaacatggag atcttcgaaa ttctcattoga aatgagactc ataatccaac tgtaaaagat 3540
cttattggct ttggctttca agtagccaaa ggcatgaaat atcttgcaag caaaaagttt 3600
gtccacagag acttggtctg aagaaactgt atgctggatg aaaaattcac agtcaaggtt 3660
gctgattttg gtcttgccag agacatgtat gataaagaat actatagtgt acacaacaaa 3720
acaggtgcaa agctgccagt gaagtggatg gctttggaaa gtctgcaaac tcaaaaagttt 3780
accaccaagt cagatgtgtg gtctcttggc gtgctcctct gggagctgat gacaagagga 3840
gccccacctt atcctgacgt aaacaccttt gatataactg tttacttggt gcaagggaga 3900
agactcctac aacccaata ctgccagac cccttatatg aagtaatgct aaaatgctgg 3960
cacccaaag ccgaaatgcg cccatccttt tctgaactgg tgtcccggat atcagcgatc 4020
ttctctactt tcattgggga gcaactatgc catgtgaacg ctacttatgt gaacgtaaaa 4080
tgtgtcgtc cgtatccttc tctgttgta tcagaagata acgctgatga tgaggtggac 4140
acacgaccag cctccttctg ggagacatca 4170

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&lt;210&gt; SEQ ID NO 79

&lt;211&gt; LENGTH: 444

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (SEMA domain of c-Met)

&lt;400&gt; SEQUENCE: 79

```

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

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180					185					190					
Tyr	Val	His	Ala	Phe	Glu	Ser	Asn	Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val
		195					200					205			
Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln	Thr	Phe	His	Thr	Arg	Ile	Ile	Arg
		210					215					220			
Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu	His	Ser	Tyr	Met	Glu	Met	Pro	Leu
		225					230					235			240
Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg	Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu
				245											255
Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala	Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln
				260											270
Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser	Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly
				275											285
Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp	Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser
				290											300
Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys	Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys
				305											320
Ile	Val	Asn	Lys	Asn	Asn	Val	Arg	Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro
				325											335
Asn	His	Glu	His	Cys	Phe	Asn	Arg	Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly
				340											350
Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr	Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu
				355											365
Gln	Arg	Val	Asp	Leu	Phe	Met	Gly	Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr
				370											380
Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly	Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly
				385											400
Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln	Val	Val	Val	Ser	Arg	Ser	Gly	Pro
				405											415
Ser	Thr	Pro	His	Val	Asn	Phe	Leu	Leu	Asp	Ser	His	Pro	Val	Ser	Pro
				420											430
Glu	Val	Ile	Val	Glu	His	Thr	Leu	Asn	Gln	Asn	Gly				
				435											440

&lt;210&gt; SEQ ID NO 80

&lt;211&gt; LENGTH: 451

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (PSI-IPT domain of c-Met)

&lt;400&gt; SEQUENCE: 80

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

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100				105				110							
Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys	Thr	Val	Gly	Pro
		115					120							125	
Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile	Ser	Asn	Gly	His
	130					135					140				
Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp	Pro	Val	Ile	Thr
145					150					155					160
Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly	Thr	Leu	Leu	Thr
				165					170					175	
Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg	His	Ile	Ser	Ile
			180						185					190	
Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn	Ser	Ile	Leu	Glu
		195					200							205	
Cys	Tyr	Thr	Pro	Ala	Gln	Thr	Ile	Ser	Thr	Glu	Phe	Ala	Val	Lys	Leu
	210					215					220				
Lys	Ile	Asp	Leu	Ala	Asn	Arg	Glu	Thr	Ser	Ile	Phe	Ser	Tyr	Arg	Glu
225					230					235					240
Asp	Pro	Ile	Val	Tyr	Glu	Ile	His	Pro	Thr	Lys	Ser	Phe	Ile	Ser	Thr
			245						250					255	
Trp	Trp	Lys	Glu	Pro	Leu	Asn	Ile	Val	Ser	Phe	Leu	Phe	Cys	Phe	Ala
			260						265					270	
Ser	Gly	Gly	Ser	Thr	Ile	Thr	Gly	Val	Gly	Lys	Asn	Leu	Asn	Ser	Val
		275				280							285		
Ser	Val	Pro	Arg	Met	Val	Ile	Asn	Val	His	Glu	Ala	Gly	Arg	Asn	Phe
	290					295					300				
Thr	Val	Ala	Cys	Gln	His	Arg	Ser	Asn	Ser	Glu	Ile	Ile	Cys	Cys	Thr
305					310					315					320
Thr	Pro	Ser	Leu	Gln	Gln	Leu	Asn	Leu	Gln	Leu	Pro	Leu	Lys	Thr	Lys
			325						330					335	
Ala	Phe	Phe	Met	Leu	Asp	Gly	Ile	Leu	Ser	Lys	Tyr	Phe	Asp	Leu	Ile
			340						345					350	
Tyr	Val	His	Asn	Pro	Val	Phe	Lys	Pro	Phe	Glu	Lys	Pro	Val	Met	Ile
		355					360							365	
Ser	Met	Gly	Asn	Glu	Asn	Val	Leu	Glu	Ile	Lys	Gly	Asn	Asp	Ile	Asp
	370					375					380				
Pro	Glu	Ala	Val	Lys	Gly	Glu	Val	Leu	Lys	Val	Gly	Asn	Lys	Ser	Cys
385					390					395					400
Glu	Asn	Ile	His	Leu	His	Ser	Glu	Ala	Val	Leu	Cys	Thr	Val	Pro	Asn
			405						410					415	
Asp	Leu	Leu	Lys	Leu	Asn	Ser	Glu	Leu	Asn	Ile	Glu	Trp	Lys	Gln	Ala
			420						425					430	
Ile	Ser	Ser	Thr	Val	Leu	Gly	Lys	Val	Ile	Val	Gln	Pro	Asp	Gln	Asn
		435				440								445	
Phe	Thr	Gly													
		450													

<210> SEQ ID NO 81  
 <211> LENGTH: 313  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (TyrKc domain of c-Met)

<400> SEQUENCE: 81

Val His Phe Asn Glu Val Ile Gly Arg Gly His Phe Gly Cys Val Tyr

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

<210> SEQ ID NO 82  
 <211> LENGTH: 1332  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (polynucleotide encoding SEMA domain of c-Met)

<400> SEQUENCE: 82  
 ctacatgagc atcacatddd ccttggtgcc actaactaca tttatgtttt aaatgaggaa 60  
 gaccttcaga aggttgctga gtacaagact gggcctgtgc tggaacaccc agattgtttc 120  
 ccatgtcagg actgcagcag caaagccaat ttatcaggag gtgtttggaa agataacatc 180  
 aacatggctc tagttgtoga cacctactat gatgatcaac tcattagctg tggcagcgtc 240  
 aacagaggga cctgccagcg acatgtcttt ccccacaatc atactgctga catacagctg 300

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gaggttcact gcataatttc cccacagata gaagagccca gccagtgtcc tgactgtgtg 360
gtgagcgccc tgggagccaa agtcctttca tctgtaaagg accggttcat caacttcttt 420
gtaggcaata ccataaattc ttcttatttc ccagatcacc cattgcattc gatatacagtg 480
agaaggctaa aggaaacgaa agatggtttt atgtttttga cggaccagtc ctacattgat 540
gttttacctg agttcagaga ttcttaccce attaagtatg tccatgcctt tgaagcaac 600
aattttatth acttcttgag ggtccaaagg gaaactctag atgctcagac ttttcacaca 660
agaataatca ggttctgttc cataaactct ggattgcatt cctacatgga aatgcctctg 720
gagtgtattc tcacagaaaa gagaaaaag agatccacaa agaaggaagt gtttaataata 780
cttcaggctg cgtatgtcag caagcctggg gccagcttg ctagacaaat aggagccagc 840
ctgaatgatg acattctttt cgggggtgttc gcacaaagca agccagattc tgccgaacca 900
atggatcgat ctgccatgtg tgcattcact atcaaatatg tcaacgactt cttcaacaag 960
atcgtcaaca aaaacaatgt gagatgtctc cagcattttt acggacccaa tcatgagcac 1020
tgctttaata ggacacttct gagaattca tcaggctgtg aagcgcgcgc tgatgaatat 1080
cgaacagagt ttaccacagc tttgcagcgc gttgacttat tcatgggtca attcagcgaa 1140
gtcctcttaa catctatata caccttcatt aaaggagacc tcaccatagc taatcttggg 1200
acatcagagg gtcgcttcat gcaggtgtg gtttctcgat caggaccatc aaccctcat 1260
gtgaattttc tcctggactc ccatccagtg tctccagaag tgattgtgga gcatacatta 1320
aaccaaaatg gc 1332

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<210> SEQ ID NO 83
<211> LENGTH: 1299
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (polynucleotide encoding PSI-IPT
domain of c-Met)

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<400> SEQUENCE: 83

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tacacactgg ttatcactgg gaagaagatc acgaagatcc cattgaatgg cttgggctgc 60
agacatttcc agtcctgcag tcaatgcctc tctgccccac cctttgttca gttggctgg 120
tgccacgaca aatgtgtgcg atcggaggaa tgctgagcgc ggacatggac tcaacagatc 180
tgtctgctg caactacaaa ggttttccca aatagtgcac cccttgaagg agggacaagg 240
ctgaccatat gtggctggga ctttgattt cggaggaata ataaattga tttaaagaaa 300
actagagttc tccttgaaa tgagagctgc accttgactt taagtgagag cacgatgaat 360
acattgaaat gcacagttgg tcctgccatg aataagcatt tcaatatgac cataattatt 420
tcaaatggcc acgggacaac acaatacagt acattctcct atgtggatcc tgaataaaca 480
agtatttcgc cgaataacgg tcctatggct ggtggcactt tacttacttt aactggaaat 540
tacctaaaca gtgggaatc tagacacatt tcaattgggt gaaaaacatg tactttaaaa 600
agtgtgtcaa acagttattc tgaatgttat acccagccc aaaccatttc aactgagttt 660
gctgttaaat tgaatttga cttagccaac cgagagacaa gcattctcag ttaccgtgaa 720
gatccattg tctatgaaat tcatccaacc aaatctttta ttagtgggtg gagcacaata 780
acagggtgtg gaaaaaacct gaattcagtt agtgtcccga gaatggatc aaatgtgat 840
gaagcaggaa ggaactttac agtggcatgt caacatcgct ctaattcaga gataatctgt 900
tgtaccactc cttcctgca acagctgaat ctgcaactcc cctgaaaac caaagccttt 960

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ttcatgttag atgggatcct ttccaaatac tttgatctca tttatgtaca taatcctgtg 1020
tttaagcctt ttgaaaagcc agtgatgatc tcaatgggca atgaaaatgt actggaaatt 1080
aagggaatg atattgacct tgaagcagtt aaaggtgaag tgtaaaagt tggaaataag 1140
agctgtgaga atatacactt acattctgaa gccgttttat gcacgggtccc caatgacctg 1200
ctgaaattga acagcgagct aaatatagag tggaagcaag caatttcttc aaccgtcctt 1260
ggaaaagtaa tagttcaacc agatcagaat ttcacagga 1299

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<210> SEQ ID NO 84
<211> LENGTH: 939
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (polynucleotide encoding TyrKc domain
of c-Met)

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<400> SEQUENCE: 84

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gtgcatttca atgaagtcat aggaagaggg cattttgggt gtgtatatca tgggactttg 60
ttggacaatg atggcaagaa aattcactgt gctgtgaaat ccttgaacag aatcactgac 120
ataggagaag tttcccaatt tctgaccgag ggaatcatca tgaagattt tagtcatccc 180
aatgtcctct cgtctctggg aatctgcctg cgaagtgaag ggtctccgct ggtggctcta 240
ccatacatga aacatggaga tcttcgaaat ttcattcgaa atgagactca taatccaact 300
gtaaaagatc ttattggctt tggctttcaa gtagccaaag gcgatgaaata tcttgcaagc 360
aaaaagtttg tccacagaga cttggctgca agaaactgta tgctggatga aaaattcaca 420
gtcaaggttg ctgattttgg tcttgccaga gacatgtatg ataaagaata ctatagtgtg 480
cacaacaaaa caggtgcaaa gctgccagtg aagtggatgg ctttgaaaag tctgcaaaact 540
caaaagttta ccaccaagtc agatgtgtgg tcctttggcg tgctcctctg ggagctgatg 600
acaagaggag cccacacctt tctgacgta aacacctttg atataactgt ttacttggtg 660
caagggagaa gactcctaca acccgaatac tgcccagacc ccttatatga agtaatgcta 720
aaatgctggc accctaagac cgaaatgcgc ccatcctttt ctgaactggt gtcccggata 780
tcagcgatct tctctacttt cattggggag cactatgtcc atgtgaacgc tacttatgtg 840
aacgtaaaat gtgtcgctcc gtatocctct ctgttgtcat cagaagataa cgctgatgat 900
gaggtggaca cagcaccagc ctcttctgg gagacatca 939

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<210> SEQ ID NO 85
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (heavy chain CDR3 of anti-c-Met
antibody)

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<400> SEQUENCE: 85

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Asp Asn Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
1           5           10

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<210> SEQ ID NO 86
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic (light chain CDR3 of anti-c-Met
antibody)

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&lt;400&gt; SEQUENCE: 86

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu  
 1                   5                   10

&lt;210&gt; SEQ ID NO 87

&lt;211&gt; LENGTH: 117

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (heavy chain variable region of monoclonal antibody AbF46)

&lt;400&gt; SEQUENCE: 87

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

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

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

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala  
                  50                   55                   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile  
 65                   70                   75                   80

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

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

Val Thr Val Ser Ala  
                  115

&lt;210&gt; SEQ ID NO 88

&lt;211&gt; LENGTH: 114

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (light chain variable region of anti-c-Met antibody)

&lt;400&gt; SEQUENCE: 88

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Ala Ser  
                  20                   25                   30

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

Ser Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val  
                  50                   55                   60

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

Ile Asn Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln  
                  85                   90                   95

Ser Tyr Ser Ala Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu  
                  100                   105                   110

Lys Arg

&lt;210&gt; SEQ ID NO 89

&lt;211&gt; LENGTH: 17

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (light chain CDR3 of anti-c-Met antibody)

&lt;400&gt; SEQUENCE: 89

Gln Gln Ser Tyr Ser Ala Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu  
 1 5 10 15

Glu

&lt;210&gt; SEQ ID NO 90

&lt;211&gt; LENGTH: 117

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (heavy chain variable region of AT-VH1)

&lt;400&gt; SEQUENCE: 90

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

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

Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu  
 35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala  
 50 55 60

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

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

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

Val Thr Val Ser Ser  
 115

&lt;210&gt; SEQ ID NO 91

&lt;211&gt; LENGTH: 117

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (heavy chain variable region of AT-VH2)

&lt;400&gt; SEQUENCE: 91

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

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

Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu  
 35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala  
 50 55 60

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

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

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

Val Thr Val Ser Ser

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115

<210> SEQ ID NO 92  
 <211> LENGTH: 117  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (heavy chain variable region of AT-VH3)

&lt;400&gt; SEQUENCE: 92

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

<210> SEQ ID NO 93  
 <211> LENGTH: 117  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (heavy chain variable region of AT-VH4)

&lt;400&gt; SEQUENCE: 93

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

<210> SEQ ID NO 94  
 <211> LENGTH: 117  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (heavy chain variable region of AT-

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VH5)

&lt;400&gt; SEQUENCE: 94

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

&lt;210&gt; SEQ ID NO 95

&lt;211&gt; LENGTH: 114

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (light chain variable region of anti c-Met humanized antibody(huAbF46-H4))

&lt;400&gt; SEQUENCE: 95

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

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 113

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic (light chain variable region of AT-Vk1)

&lt;400&gt; SEQUENCE: 96

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



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

Lys

<210> SEQ ID NO 99  
 <211> LENGTH: 113  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (light chain variable region of AT-Vk4)

&lt;400&gt; SEQUENCE: 99

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

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

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

Ala Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val  
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln  
 85 90 95

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

Lys

<210> SEQ ID NO 100  
 <211> LENGTH: 13  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (modified hinge region(U7-HC6))

&lt;400&gt; SEQUENCE: 100

Glu Pro Ser Cys Asp Lys His Cys Cys Pro Pro Cys Pro  
 1 5 10

<210> SEQ ID NO 101  
 <211> LENGTH: 13  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (modified hinge region(U6-HC7))

&lt;400&gt; SEQUENCE: 101

Glu Pro Lys Ser Cys Asp Cys His Cys Pro Pro Cys Pro  
 1 5 10

<210> SEQ ID NO 102  
 <211> LENGTH: 12  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (modified hinge region(U3-HC9))

&lt;400&gt; SEQUENCE: 102

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro  
 1 5 10

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<210> SEQ ID NO 103  
 <211> LENGTH: 15  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (modified hinge region(U6-HC8))  
 <400> SEQUENCE: 103

Glu Pro Arg Asp Cys Gly Cys Lys Pro Cys Pro Pro Cys Pro Ser  
 1 5 10 15

<210> SEQ ID NO 104  
 <211> LENGTH: 13  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (modified hinge region(U8-HC5))  
 <400> SEQUENCE: 104

Glu Lys Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 1 5 10

<210> SEQ ID NO 105  
 <211> LENGTH: 15  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (human hinge region)  
 <400> SEQUENCE: 105

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 1 5 10 15

<210> SEQ ID NO 106  
 <211> LENGTH: 23  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (forward primer for exon 14)  
 <400> SEQUENCE: 106

tgaaattgaa cagcgagcta aat 23

<210> SEQ ID NO 107  
 <211> LENGTH: 22  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (reverse primer for exon 14)  
 <400> SEQUENCE: 107

ttgaaatgca caatcaggct ac 22

<210> SEQ ID NO 108  
 <211> LENGTH: 17  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (CDR-L1 of antibody L3-11Y)  
 <400> SEQUENCE: 108

Lys Ser Ser Gln Ser Leu Leu Ala Trp Gly Asn Gln Asn Asn Tyr Leu  
 1 5 10 15

Ala

-continued

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<210> SEQ ID NO 109  
 <211> LENGTH: 114  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of light chain variable region of antibody L3-11Y)

<400> SEQUENCE: 109

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1             5             10             15
Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Ala Trp
                20             25             30
Gly Asn Gln Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                35             40             45
Ala Pro Lys Met Leu Ile Ile Trp Ala Ser Thr Arg Val Ser Gly Val
                50             55             60
Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65             70             75             80
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                85             90             95
Ser Tyr Ser Arg Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
                100            105            110
Lys Arg
  
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<210> SEQ ID NO 110  
 <211> LENGTH: 220  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic (amino acid sequence of light chain of antibody L3-11Y)

<400> SEQUENCE: 110

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

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
 210 215 220

<210> SEQ ID NO 111  
 <211> LENGTH: 114  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic light chain variable region of anti  
 c-Met antibody

<400> SEQUENCE: 111

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

Lys Arg

<210> SEQ ID NO 112  
 <211> LENGTH: 11241  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Human Cbl gene  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (143)..(2860)

<400> SEQUENCE: 112

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 gggctccgac cctgcccagg cc atg gcc ggc aac gtg aag aag agc 166  
 Met Ala Gly Asn Val Lys Lys Ser  
 1 5  
 tct ggg gcc ggg ggc ggc agc ggc tcc ggg ggc tcg ggt tcg ggt ggc 214  
 Ser Gly Ala Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Gly  
 10 15 20  
 ctg att ggg ctc atg aag gac gcc ttc cag ccg cac cac cac cac cac 262  
 Leu Ile Gly Leu Met Lys Asp Ala Phe Gln Pro His His His His His  
 25 30 35 40  
 cac cac ctc agc ccc cac ccg ccg ggg acg gtg gac aag aag atg gtg 310  
 His His Leu Ser Pro His Pro Gly Thr Val Asp Lys Lys Met Val  
 45 50 55  
 gag aag tgc tgg aag ctc atg gac aag gtg gtg cgg ttg tgt cag aac 358  
 Glu Lys Cys Trp Lys Leu Met Asp Lys Val Val Arg Leu Cys Gln Asn  
 60 65 70  
 cca aag ctg gcg cta aag aat agc cca cct tat atc tta gac ctg cta 406

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Pro	Lys	Leu	Ala	Leu	Lys	Asn	Ser	Pro	Pro	Tyr	Ile	Leu	Asp	Leu	Leu		
		75					80					85					
cca	gat	acc	tac	cag	cat	ctc	cgt	act	atc	ttg	tca	aga	tat	gag	ggg		454
Pro	Asp	Thr	Tyr	Gln	His	Leu	Arg	Thr	Ile	Leu	Ser	Arg	Tyr	Glu	Gly		
	90					95				100							
aag	atg	gag	aca	ctt	gga	gaa	aat	gag	tat	ttt	agg	gtg	ttt	atg	gag		502
Lys	Met	Glu	Thr	Leu	Gly	Glu	Asn	Glu	Tyr	Phe	Arg	Val	Phe	Met	Glu		
105				110					115					120			
aat	ttg	atg	aag	aaa	act	aag	caa	acc	ata	agc	ctc	ttc	aag	gag	gga		550
Asn	Leu	Met	Lys	Lys	Thr	Lys	Gln	Thr	Ile	Ser	Leu	Phe	Lys	Glu	Gly		
			125					130						135			
aaa	gaa	aga	atg	tat	gag	gag	aat	tct	cag	cct	agg	cga	aac	cta	acc		598
Lys	Glu	Arg	Met	Tyr	Glu	Glu	Asn	Ser	Gln	Pro	Arg	Arg	Asn	Leu	Thr		
			140					145					150				
aaa	ctg	tcc	ctc	atc	ttc	agc	cac	atg	ctg	gca	gaa	cta	aaa	gga	atc		646
Lys	Leu	Ser	Leu	Ile	Phe	Ser	His	Met	Leu	Ala	Glu	Leu	Lys	Gly	Ile		
		155					160					165					
ttt	cca	agt	gga	ctc	ttt	cag	gga	gac	aca	ttt	cgg	att	act	aaa	gca		694
Phe	Pro	Ser	Gly	Leu	Phe	Gln	Gly	Asp	Thr	Phe	Arg	Ile	Thr	Lys	Ala		
	170					175					180						
gat	gct	gcg	gaa	ttt	tgg	aga	aaa	gct	ttt	ggg	gaa	aag	aca	ata	gtc		742
Asp	Ala	Ala	Glu	Phe	Trp	Arg	Lys	Ala	Phe	Gly	Glu	Lys	Thr	Ile	Val		
185				190						195				200			
cct	tgg	aag	agc	ttt	cga	cag	gct	cta	cat	gaa	gtg	cat	ccc	atc	agt		790
Pro	Trp	Lys	Ser	Phe	Arg	Gln	Ala	Leu	His	Glu	Val	His	Pro	Ile	Ser		
			205					210						215			
tct	ggg	ctg	gag	gcc	atg	gct	ctg	aaa	tcc	act	att	gat	ctg	acc	tgc		838
Ser	Gly	Leu	Glu	Ala	Met	Ala	Leu	Lys	Ser	Thr	Ile	Asp	Leu	Thr	Cys		
			220					225					230				
aat	gat	tat	att	tcg	ggt	ttt	gaa	ttt	gac	atc	ttt	acc	cga	ctc	ttt		886
Asn	Asp	Tyr	Ile	Ser	Val	Phe	Glu	Phe	Asp	Ile	Phe	Thr	Arg	Leu	Phe		
		235				240						245					
cag	ccc	tgg	tcc	tct	ttg	ctc	agg	aat	tgg	aac	agc	ctt	gct	gta	act		934
Gln	Pro	Trp	Ser	Ser	Leu	Leu	Arg	Asn	Trp	Asn	Ser	Leu	Ala	Val	Thr		
	250					255					260						
cat	cct	ggc	tac	atg	gct	ttt	ttg	acg	tat	gac	gaa	gtg	aaa	gct	cgg		982
His	Pro	Gly	Tyr	Met	Ala	Phe	Leu	Thr	Tyr	Asp	Glu	Val	Lys	Ala	Arg		
265				270					275					280			
ctc	cag	aaa	ttc	att	cac	aaa	cct	ggc	agt	tat	atc	ttc	cgg	ctg	agc		1030
Leu	Gln	Lys	Phe	Ile	His	Lys	Pro	Gly	Ser	Tyr	Ile	Phe	Arg	Leu	Ser		
			285					290						295			
tgt	act	cgt	ctg	ggt	cag	tgg	gct	att	ggg	tat	ggt	act	gct	gat	ggg		1078
Cys	Thr	Arg	Leu	Gly	Gln	Trp	Ala	Ile	Gly	Tyr	Val	Thr	Ala	Asp	Gly		
			300				305						310				
aac	att	ctc	cag	aca	atc	cct	cac	aat	aaa	cct	ctc	ttc	caa	gca	ctg		1126
Asn	Ile	Leu	Gln	Thr	Ile	Pro	His	Asn	Lys	Pro	Leu	Phe	Gln	Ala	Leu		
		315					320					325					
att	gat	ggc	ttc	agg	gaa	ggc	ttc	tat	ttg	ttt	cct	gat	gga	cga	aat		1174
Ile	Asp	Gly	Phe	Arg	Glu	Gly	Phe	Tyr	Leu	Phe	Pro	Asp	Gly	Arg	Asn		
	330					335					340						
cag	aat	cct	gat	ctg	act	ggc	tta	tgt	gaa	cca	act	occ	caa	gac	cat		1222
Gln	Asn	Pro	Asp	Leu	Thr	Gly	Leu	Cys	Glu	Pro	Thr	Pro	Gln	Asp	His		
345				350						355				360			
atc	aaa	gtg	acc	cag	gaa	caa	tat	gaa	tta	tac	tgt	gag	atg	ggc	tcc		1270
Ile	Lys	Val	Thr	Gln	Glu	Gln	Tyr	Glu	Leu	Tyr	Cys	Glu	Met	Gly	Ser		
			365					370						375			
aca	ttc	caa	cta	tgt	aaa	ata	tgt	gct	gaa	aat	gat	aag	gat	gta	aag		1318
Thr	Phe	Gln	Leu	Cys	Lys	Ile	Cys	Ala	Glu	Asn	Asp	Lys	Asp	Val	Lys		
			380					385						390			

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att gag ccc tgt gga cac ctc atg tgc aca tcc tgt ctt aca tcc tgg Ile Glu Pro Cys Gly His Leu Met Cys Thr Ser Cys Leu Thr Ser Trp 395 400 405	1366
cag gaa tca gaa ggt cag ggc tgt cct ttc tgc cga tgt gaa att aaa Gln Glu Ser Glu Gly Gln Gly Cys Pro Phe Cys Arg Cys Glu Ile Lys 410 415 420	1414
ggt act gaa ccc atc gtg gta gat ccg ttt gat cct aga ggg agt ggc Gly Thr Glu Pro Ile Val Val Asp Pro Phe Asp Pro Arg Gly Ser Gly 425 430 435 440	1462
agc ctg ttg agg caa gga gca gag gga gct ccc tcc cca aat tat gat Ser Leu Leu Arg Glu Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp 445 450 455	1510
gat gat gat gat gaa cga gct gat gat act ctc ttc atg atg aag gaa Asp Asp Asp Asp Glu Arg Ala Asp Asp Thr Leu Phe Met Met Lys Glu 460 465 470	1558
ttg gct ggt gcc aag gtg gaa cgg ccg cct tct cca ttc tcc atg gcc Leu Ala Gly Ala Lys Val Glu Arg Pro Pro Ser Pro Phe Ser Met Ala 475 480 485	1606
cca caa gct tcc ctt ccc ccg gtg cca cca cga ctt gac ctt ctg ccg Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Pro 490 495 500	1654
cag cga gta tgt gtt ccc tca agt gct tct gct ctt gga act gct tct Gln Arg Val Cys Val Pro Ser Ser Ala Ser Ala Leu Gly Thr Ala Ser 505 510 515 520	1702
aag gct gct tct ggc tcc ctt cat aaa gac aaa cca ttg cca gta cct Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Val Pro 525 530 535	1750
ccc aca ctt cga gat ctt cca cca cca ccg cct cca gac ccg cca tat Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr 540 545 550	1798
tct gtt gga gca gaa tcc cga cct caa aga cgc ccc ttg cct tgt aca Ser Val Gly Ala Glu Ser Arg Pro Gln Arg Arg Pro Leu Pro Cys Thr 555 560 565	1846
cca ggc gac tgt ccc tcc aga gac aaa ctg ccc cct gtc ccc tct agc Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser 570 575 580	1894
cgc ctt gga gac tca tgg ctg ccc cgg cca atc ccc aaa gta cca gta Arg Leu Gly Asp Ser Trp Leu Pro Arg Pro Ile Pro Lys Val Pro Val 585 590 595 600	1942
tct gcc cca agt tcc agt gat ccc tgg aca gga aga gaa tta acc aac Ser Ala Pro Ser Ser Ser Asp Pro Trp Thr Gly Arg Glu Leu Thr Asn 605 610 615	1990
cgg cac tca ctt cca ttt tca ttg ccc tca caa atg gag ccc aga cca Arg His Ser Leu Pro Phe Ser Leu Pro Ser Leu Met Glu Pro Arg Pro 620 625 630	2038
gat gtg cct agg ctc gga agc acg ttc agt ctg gat acc tcc atg agt Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Ser 635 640 645	2086
atg aat agc agc cca tta gta ggt cca gag tgt gac cac ccc aaa atc Met Asn Ser Ser Pro Leu Val Gly Pro Glu Cys Asp His Pro Lys Ile 650 655 660	2134
aaa cct tcc tca tct gcc aat gcc att tat tct ctg gct gcc aga cct Lys Pro Ser Ser Ser Ala Asn Ala Ile Tyr Ser Leu Ala Ala Arg Pro 665 670 675 680	2182
ctt cct gtg cca aaa ctg cca cct ggg gag caa tgt gag ggt gaa gag Leu Pro Val Pro Lys Leu Pro Pro Gly Glu Gln Cys Glu Gly Glu Glu 685 690 695	2230
gac aca gag tac atg act ccc tct tcc agg cct cta cgg cct ttg gat Asp Thr Glu Tyr Met Thr Pro Ser Ser Arg Pro Leu Arg Pro Leu Asp 700 705 710	2278

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tgt acg tat gaa gca atg tat aat att cag tcc cag gcg cca tct atc Cys Thr Tyr Glu Ala Met Tyr Asn Ile Gln Ser Gln Ala Pro Ser Ile 730 735 740	2374
acc gag agc agc acc ttt ggt gaa ggg aat ttg gcc gca gcc cat gcc Thr Glu Ser Ser Thr Phe Gly Glu Gly Asn Leu Ala Ala Ala His Ala 745 750 755 760	2422
aac act ggt ccc gag gag tca gaa aat gag gat gat ggg tat gat gtc Asn Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val 765 770 775	2470
cca aag cca cct gtg cgg gcc gtg ctg gcc cgc cga act ctc tca gat Pro Lys Pro Pro Val Pro Ala Val Leu Ala Arg Arg Thr Leu Ser Asp 780 785 790	2518
atc tct aat gcc agc tcc tcc ttt ggc tgg ttg tct ctg gat ggt gat Ile Ser Asn Ala Ser Ser Ser Phe Gly Trp Leu Ser Leu Asp Gly Asp 795 800 805	2566
cct aca aca aat gtc act gaa ggt tcc caa gtt ccc gag agg cct cca Pro Thr Thr Asn Val Thr Glu Gly Ser Gln Val Pro Glu Arg Pro Pro 810 815 820	2614
aaa cca ttc ccg cgg aga atc aac tct gaa cgg aaa gct ggc agc tgt Lys Pro Phe Pro Arg Arg Ile Asn Ser Glu Arg Lys Ala Gly Ser Cys 825 830 835 840	2662
cag caa ggt agt ggt cct gcc gcc tct gct gcc acc gcc tca cct cag Gln Gln Gly Ser Gly Pro Ala Ala Ser Ala Ala Thr Ala Ser Pro Gln 845 850 855	2710
ctc tcc agt gag atc gag aac ctc atg agt cag ggg tac tcc tac cag Leu Ser Ser Glu Ile Glu Asn Leu Met Ser Gln Gly Tyr Ser Tyr Gln 860 865 870	2758
gac atc cag aaa gct ttg gtc att gcc cag aac aac atc gag atg gcc Asp Ile Gln Lys Ala Leu Val Ile Ala Gln Asn Asn Ile Glu Met Ala 875 880 885	2806
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ctggttaagg gaggtggggg tcaactgttca tcaactcttaa aatatgtggt ttctctatag 6150  
aaaagtaaaa tgtgtttatg gtcccaaca gtcaactcac aaatttttat aacaaaattt 6210  
ccttgtaaaa actagggacc atctatatat tccctttaag atctagtctt tttttaggt 6270  
gttcagcaat ggtgataaag cagaatattc tctacctca cgtcattaaa gtcagaagat 6330  
tatagacctt ctcaactat aagtcctct tcttgccgtt ggctttctg actctggaat 6390  
gaccactggt cattgaaaa tagttttctg actattggct tggctctaac agtttgtttg 6450  
ttcatccagc aaatgtttat gagtgatgac catgtgccag aaatgtcagg tatgtgtcct 6510  
tcccttggeg ccacatagta gtttactaat gtttggggga ttgtactgg actgtcatag 6570  
cctctgctt tgacctaaa atagctcttc ccagtaagat tgtgcaattt ttattcacag 6630  
ctcttccatg tagacttacc tttcctcata gagctatcct ggtaataaac aggccaagat 6690  
tctcccatta tccctgttg tctcctgtag ctttgataat gctggggaga ttccttggtg 6750  
taagtgtcat ggataccgac tgtttttatg ttggaatttg ttccaacata attagaatct 6810  
gtttggtgag ttgaaagta agttggctca gaggttcaca gtagggcatt aaatgtttaa 6870  
gcaaagcacc tcccacact cccctttcca atctagtgcc ttccttgaac ttttctctga 6930  
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tcaccatgct ctgtactatt tggaaattgt tttccagtct tccaacaacc gttgtggcta 7050  
actatgtttt agaagggtg gaggtgtggg ccctgtcttc gggctcagg acccaagat 7110  
cctttagtca gttgttgggt cttccaagag ccagacatta atacagattg aactccatca 7170  
gtcccctaat tgtcagcctt tacctcctc ccagagcaag gagtttaggg attcctaaagc 7230  
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gtaactcagc ataaactatt actatcactc ctttgaactc agtctccatg agcagtgttt 7350  
tgttgaaat acatagaacg gcttaatgcc tagagggtgg tggatagtga aggacggta 7410  
aggttatatt tttgactgct tagggattct ttggatccaa gaaacagaaa tgttcaagcg 7470  
gaataaagga gggagtggag ttgtgtaag gatgcagggt atttcgcaga acccaggacg 7530  
ggaagtgcct ttggttcttg ggtggagctg gaactgcaga gctttgcacc tagtctcttc 7590  
tcccgttca cagtctgctt atggtatatg tggccccc aaataggcctc tagtctcaa 7650  
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aatttttttt ttttttgaga tggagtctcg ctgtgtcggc caggctggag tgcagtgttg 7770  
cagtctcaac tcaccacaac ctctgcctcc caggttcaag cagttctctg cctcaacctc 7830  
ccgagttagct gggattacag gcgctgcca ccatgccag ctaatgttca tatttttagt 7890  
agagacaggg tttcacctgc ttggctaggg tggctttaa ctcctgacct tcatgatcca 7950  
cccacctcg cctcccaag tgetaagatt acaggcgtga gccaccgccc cgggccata 8010  
cttcgtattc ttaaaaaaaa ctacactcag cccagcacat tgatcaagta tctatctctg 8070  
agcagttggc cttgccaggg agagcagaga tgtggcaggg tccctcagct ggagacaggg 8130  
agcttctcag agaagtggag agagactcca cagacaccct aaaaaggctt ctactcaaga 8190  
agtaaagcca ctactctgct ctttttgctt agtggacagg aaggcacagg agtttgtctg 8250  
ggacatcata gaaattctta ggtttaaact aattctggct attgtctctt ttatttctg 8310  
ttttctctcc ctttgcagt cttcgcctcc aagatttctt cctcctctct tgtgggccag 8370  
cctgtctctg tccagagcta gctgttctc gggtagcctt ccttagcctc cattcagcct 8430

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caggctctttt	gccttctctc	gtgttttattt	agagagcaga	atctaataac	gggttccact	8490
gtagccacta	tccatggact	tctgggtcct	cttcaggttt	gagtgcctga	aaatgttcat	8550
tctctgggct	tgtggcctgt	ctctccact	ctctcctca	ccctctcgt	ccttctctgt	8610
tgagggccgc	tctgcagtaa	tgttctcagg	caagccttc	taggcacctc	agaaactact	8670
ttgccagagc	cagtaagaat	atataatatt	ggagcagttg	ccaggataga	aattaaatat	8730
agattccagt	ttaggataga	gtttttaccg	agagctcttt	agacagtata	cctgtgtctt	8790
ctctggcaat	tgttttcat	ttagtcctat	ataaaagctt	tccttttctg	ttttttttta	8850
aaactatgct	ttgcttgcc	taaactcttt	gatcttatat	ttctctcctc	tcagagcctg	8910
tcctgagttg	taaggtat	catactgctt	tacttaaaag	ttttttaaac	tactagagtc	8970
atgtgataga	cacagaagtt	ccctaataat	ccaaagatgt	ccatcaaggg	aggaaggggtg	9030
ggctcatcaga	ctttgccttt	gatgtttag	actaggctcc	tgagttaagc	agcagagggga	9090
cagcagtgcc	atgtgccttc	actgtgtccc	aggaaatctg	ggttgggttc	agtgggaaat	9150
accagtat	cttggttctg	gaaagtagca	aaagagtagg	agatggggaa	atagggatgg	9210
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ctgttgacag	acagactaag	ctgtgtgggtg	ctcttgccgc	cccttctctg	gtacagagct	9330
tgagaaaaat	gcagccgacc	actccctgtg	ttgtacaga	gcaaagccca	aaagccaacc	9390
tcagatctcc	tgatttggca	gctgaagaaa	tcagcagagt	cctgattgcc	tgattcagtc	9450
ccaaaaatga	atgtcaggcc	ccgccccctc	cccaccaaca	ttgcctctcc	tacattctcc	9510
ttctgcccct	aaatcagaca	ggagggcaga	gaggagtatt	gctcaatgcg	tgctatgtgc	9570
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tgtgtgtcag	ctccctcctc	tctacctacc	tctgaccttc	ttgtgggtga	gggtggccat	9690
gcttatggcc	atcttaaaac	tggagaggca	gagaactact	tatgagtctg	tagaccacgt	9750
gttgtcttcc	atggcctgtt	tctctctctg	tctgggtgag	tgagcctgca	acgcaatgcc	9810
catgagagta	aatgcctcct	gacctaccct	gctcagcact	gttctagtgt	cttggccttg	9870
aaagaaaagc	ctgacttctc	gctgacacat	gtggtagggg	catggcagct	atgaggcacc	9930
tcctacgtct	gttttctggc	tgtggtgact	tgggattttt	aaccttatat	atctttttcc	9990
tttactcaaa	acaaaaaat	ttttagcaca	ctgaaaaaaa	aaaaaagcca	aatgttttgt	10050
gcctttctaa	ggcagcactg	tatcccaggc	tgcatttttag	gacttaatat	gaaataacca	10110
gagtctgagc	tctctacct	tgagtttcat	tagtccttag	tgtctaggag	acaggaaga	10170
atgctctctg	tgactggaga	gggtgacatgc	aggtgcagtg	tgtctggagt	ccctttcccc	10230
tgctgtgaga	cttcagtggg	ggagagaagc	attgtaccct	gggatcattt	ggttgggttc	10290
aatcacaagc	ttagttatca	ggttgcatgc	cttgtctcct	gcaaaagaca	gaatgtttca	10350
caattcccag	gtaaaactctg	gaccattcca	agtgtcctag	ccttctgatg	acattaatta	10410
cctagtgtgtg	tcgaggagta	taggatggac	tctcctgaga	aggggagggt	ggtggccttg	10470
tcttttcttt	ttgctggatc	ctgaactggt	ctagacctcc	tgccccacc	ccccagcccc	10530
catcagatgt	ggctggcctt	tcatttgaag	gcttcagact	taaagcatta	agcagctagt	10590
gcccctctgca	gggcctgggt	tccccagggg	agggcagcaa	ggaacatggg	accagaagcc	10650
tgctctcagt	aatgtgacta	tagtgagcct	tagcaaaagt	ttttctatat	aatgacatct	10710
tacttatctt	ttacccttcc	ctcagttttc	ccctgccttt	aactaataaa	gaattgggag	10770
acagaaat	taaagctctc	cttattcaag	atgttgaaat	tcttagcctg	ggagtgtctg	10830

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agagaacctg atgctttctc cagaatgaag agtcccaatt tgtatatcag tgtaagaag 10890
aaaacaaaac aaacacatag gtgagatgtt cgtggactat tttaaaaatg tgcattaat 10950
ataaaaaatt tatattagca gtatttaac attctcacct gtaaagaata agaaaaacag 11010
aaggtaaata ttottacaga gaatagcaga gctttaagat tcattttcat ttttaagtcca 11070
ttttattttg ccagtgtatt aatgtttaga agtctgtttt actaatgtta tttattaatt 11130
ttttttcatt tccatacaca gttagttaac taaagagctt tttcaagcac ccatgtctgt 11190
aaaaaaaaat ttttaataa agtttctttt gttgtagcag aaaaaaaaaa a 11241

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&lt;210&gt; SEQ ID NO 113

&lt;211&gt; LENGTH: 906

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic

&lt;400&gt; SEQUENCE: 113

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

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Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala  
 290 295 300  
 Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His  
 305 310 315 320  
 Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe  
 325 330 335  
 Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu  
 340 345 350  
 Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr  
 355 360 365  
 Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys  
 370 375 380  
 Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met  
 385 390 395 400  
 Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys  
 405 410 415  
 Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp  
 420 425 430  
 Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu  
 435 440 445  
 Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp  
 450 455 460  
 Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg  
 465 470 475 480  
 Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val  
 485 490 495  
 Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser  
 500 505 510  
 Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His  
 515 520 525  
 Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro  
 530 535 540  
 Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro  
 545 550 555 560  
 Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp  
 565 570 575  
 Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro  
 580 585 590  
 Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro  
 595 600 605  
 Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu  
 610 615 620  
 Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr  
 625 630 635 640  
 Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly  
 645 650 655  
 Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ser Ala Asn Ala  
 660 665 670  
 Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro  
 675 680 685  
 Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Tyr Met Thr Pro Ser  
 690 695 700  
 Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys

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

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&lt;210&gt; SEQ ID NO 114

&lt;211&gt; LENGTH: 1390

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic human c-Met protein

&lt;400&gt; SEQUENCE: 114

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

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165				170				175							
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180											190	
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200							205	
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
		210				215								220	
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
		225				230					235			240	
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
			245							250				255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260							265				270	
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
			275				280							285	
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
		290				295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
		305				310				315				320	
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
			325							330				335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340				345							350	
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360							365	
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
		370				375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
		385				390				395				400	
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
			405							410				415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420							425				430	
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
		435					440							445	
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
		450				455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
						470				475				480	
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
			485							490				495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
			500				505							510	
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520							525	
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
		530				535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
						550				555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
			565							570				575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580				585							590	

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Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu  
 595 600 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys  
 610 615 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile  
 625 630 635 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp  
 645 650 655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly  
 660 665 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg  
 675 680 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn  
 690 695 700

Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe  
 705 710 715 720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe  
 725 730 735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser  
 740 745 750

Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn  
 755 760 765

Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg  
 770 775 780

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

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

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

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

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

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

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

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

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

Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Thr Ala  
 930 935 940

Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg Lys Gln  
 945 950 955 960

Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His  
 965 970 975

Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr  
 980 985 990

Thr Glu Met Val Ser Asn Glu Ser Val Asp Tyr Arg Ala Thr Phe Pro  
 995 1000 1005

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Glu Asp Gln Phe Pro Asn Ser Ser Gln Asn Gly Ser Cys Arg Gln Val  
 1010 1015 1020

Gln Tyr Pro Leu Thr Asp Met Ser Pro Ile Leu Thr Ser Gly Asp Ser  
 1025 1030 1035 1040

Asp Ile Ser Ser Pro Leu Leu Gln Asn Thr Val His Ile Asp Leu Ser  
 1045 1050 1055

Ala Leu Asn Pro Glu Leu Val Gln Ala Val Gln His Val Val Ile Gly  
 1060 1065 1070

Pro Ser Ser Leu Ile Val His Phe Asn Glu Val Ile Gly Arg Gly His  
 1075 1080 1085

Phe Gly Cys Val Tyr His Gly Thr Leu Leu Asp Asn Asp Gly Lys Lys  
 1090 1095 1100

Ile His Cys Ala Val Lys Ser Leu Asn Arg Ile Thr Asp Ile Gly Glu  
 1105 1110 1115 1120

Val Ser Gln Phe Leu Thr Glu Gly Ile Ile Met Lys Asp Phe Ser His  
 1125 1130 1135

Pro Asn Val Leu Ser Leu Leu Gly Ile Cys Leu Arg Ser Glu Gly Ser  
 1140 1145 1150

Pro Leu Val Val Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe  
 1155 1160 1165

Ile Arg Asn Glu Thr His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe  
 1170 1175 1180

Gly Leu Gln Val Ala Lys Gly Met Lys Tyr Leu Ala Ser Lys Lys Phe  
 1185 1190 1195 1200

Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe  
 1205 1210 1215

Thr Val Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr Asp Lys  
 1220 1225 1230

Glu Tyr Tyr Ser Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys  
 1235 1240 1245

Trp Met Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys Ser  
 1250 1255 1260

Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu Met Thr Arg Gly  
 1265 1270 1275 1280

Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe Asp Ile Thr Val Tyr Leu  
 1285 1290 1295

Leu Gln Gly Arg Arg Leu Leu Gln Pro Glu Tyr Cys Pro Asp Pro Leu  
 1300 1305 1310

Tyr Glu Val Met Leu Lys Cys Trp His Pro Lys Ala Glu Met Arg Pro  
 1315 1320 1325

Ser Phe Ser Glu Leu Val Ser Arg Ile Ser Ala Ile Phe Ser Thr Phe  
 1330 1335 1340

Ile Gly Glu His Tyr Val His Val Asn Ala Thr Tyr Val Asn Val Lys  
 1345 1350 1355 1360

Cys Val Ala Pro Tyr Pro Ser Leu Leu Ser Ser Glu Asp Asn Ala Asp  
 1365 1370 1375

Asp Glu Val Asp Thr Arg Pro Ala Ser Phe Trp Glu Thr Ser  
 1380 1385 1390

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What is claimed is:

1. A method of identifying a subject suitable for treatment with an anti-c-Met antibody or antigen binding fragment thereof that specifically binds to an epitope within a SEMA domain of a c-Met protein, the method comprising:

(1) determining a Cbl concentration, a Cbl mutation, and/or a mutation of a site of c-Met for interaction with Cbl in a cell sample from a subject;

(2) determining that the subject is suitable for treatment with the anti-c-Met antibody when Cbl is present at a low level or absent in the cell sample or when Cbl or c-Met contains a mutation that inhibits interaction between Cbl and c-Met; and

(3) administering the anti-c-Met antibody or antigen-binding fragment thereof to the subject determined to be suitable for treatment, wherein the anti-c-Met antibody or antigen-binding fragment thereof comprises SEQ ID NOs: 1-3, 10, 11, and 13, specifically binds to an epitope having 5 to 19 consecutive amino acids of SEQ ID NO: 71 that includes the amino sequence of SEQ ID NO: 73 (EEPSQ), and promotes LRIG1-mediated c-Met degradation.

2. The method of claim 1, wherein Cbl concentration is determined by immunohistochemical analysis, and a stain intensity of '-' or '+1' indicates that Cbl is present at a low level or absent, respectively, in the cell sample.

3. The method of claim 1, wherein the Cbl mutation is a deletion or substitution of 51 or more consecutive nucleotides within nucleotides 1169-1414 of the nucleotide sequence of GenBank Accession Number NM\_005188 (SEQ ID NO: 112), or a deletion or substitution of 17 or more consecutive amino acids within amino acids 343-424 of the amino acid sequence of GenBank Accession Number NP\_005179 (SEQ ID NO: 113).

4. The method of claim 1, wherein the mutation of a site of c-Met (SEQ ID NO: 114) for interaction with Cbl is a deletion or a substitution of tyrosine at position 1003 (Y1003) with an

amino acid other than tyrosine, or a deletion or a substitution of 141 or more consecutive nucleotides within exon 14 of the c-Met gene with other nucleotides, or a deletion or a substitution of 46 or more consecutive amino acids within a polypeptide encoded by exon 14 of the c-Met gene with other amino acids.

5. The method of claim 1, further comprising determining the presence of LRIG1 in the cell sample.

6. The method of claim 5, further comprising determining the cell sample or the subject to be suitable for treatment with the anti-c-Met antibody when LRIG1 is present.

7. The method of claim 6, wherein LRIG1 concentration is determined by immunohistochemical analysis, and a stain intensity of '+2' or '+3' indicates that LRIG1 is present in the cell sample.

8. The method of claim 1, wherein the anti-c-Met antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 17 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 111.

9. The method of claim 1, wherein the anti-c-Met antibody or antigen binding fragment thereof comprises a heavy chain comprising the amino acid residues from the 18th to 460th positions of SEQ ID NO: 66 and a light chain comprising the amino acid residues from the 21st to 240th positions of SEQ ID NO: 68.

10. The method of claim 1, wherein the anti-c-Met antibody or antigen binding fragment thereof is an antibody of mouse origin, a mouse-human chimeric antibody, a humanized antibody, or a human antibody.

11. The method of claim 1, wherein the anti-c-Met antibody or antigen binding fragment thereof is an antibody of mouse origin, a mouse-human chimeric antibody, a humanized antibody, or a human antibody.

12. The method of claim 1, wherein the cell sample is a sample of cancer cells.

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专利名称(译)	使用Cbl作为生物标志物来鉴定适合用抗c-Met抗体治疗的受试者		
公开(公告)号	<a href="#">US9213031</a>	公开(公告)日	2015-12-15
申请号	US13/949012	申请日	2013-07-23
[标]申请(专利权)人(译)	三星电子株式会社		
申请(专利权)人(译)	SAMSUNG ELECTRONICS CO. , LTD.		
当前申请(专利权)人(译)	SAMSUNG ELECTRONICS CO. , LTD.		
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发明人	LEE, JI MIN KIM, KYUNG AH KIM, BO GYOU OH, YOUNG MI LEE, SAET BYOUL JEONG, YUN JU		
IPC分类号	C12Q1/68 G01N33/53 C07K16/30 G01N33/574 C07K16/28 A61K39/395 A61K39/00		
CPC分类号	G01N33/57492 A61K39/39558 C07K16/2863 C07K16/30 C12Q1/6886 A61K2039/505 C07K2317/24 C07K2317/565 C07K2317/622 C07K2317/73 C07K2317/76 C12Q2600/106 C12Q2600/156 G01N2800/52 A61K2300/00		
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优先权	1020120080145 2012-07-23 KR 1020120102395 2012-09-14 KR		
其他公开文献	US20140105901A1		
外部链接	<a href="#">Espacenet</a> <a href="#">USPTO</a>		

摘要(译)

一种鉴定细胞样品或适于用抗c-Met抗体或其抗原结合片段治疗的受试者的方法, 其通过测定Cbl浓度, Cbl特异性结合c-Met蛋白的SEMA结构域内的表位。c-Met位点的突变和/或突变, 用于与来自受试者的细胞样品中的Cbl相互作用, 以及相关的组合物和方法。

