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(54) **Title**: ANTI-MST1R ANTIBODIES AND USES THEREOF

(57) **Abstract**: The present disclosure provides recombinant antigen-binding regions and antibodies and functional fragments containing such antigen-binding regions that are specific for MST1R, which plays an integral role in various disorders or conditions, such as cancer. These antibodies, accordingly, can be used to treat these and other disorders and conditions. Antibodies of the disclosure also can be used in the diagnostics field, as well as for further investigating the role of MST1R in the progression of disorders associated with tumors. The disclosure also provides nucleic acid sequences encoding the foregoing antibodies, vectors containing the same, pharmaceutical compositions and kits with instructions for use.

DESCRIPTION

Title of Invention

ANTI-MST1R ANTIBODIES AND USES THEREOF

Background

[0001]

MST1R (macrophage stimulating 1 receptor; human MST1R is shown in GenBank accession No; NM_002447.2), also described as RON or CDw136, is a c-Met related tyrosine kinase found on cells of epithelial origin. The 1400 amino acid single chain precursor is cleaved into a disulfide-linked heterodimer consisting of an extracellular 40kDa α-chain and a 150kDa β-chain, which includes the intracellular tyrosine kinase domain. Similar to c-Met, MST1R induces invasive cell growth, migration, cell dissociation and matrix invasion. [Wang, et al., *Carcinogenesis* 24, 1291-1300, 2003; Lee, et al., *Clin Cancer Res* 11, 2222-2228, 2005]. Both tyrosine kinases are overexpressed on a variety of malignant tumors, such as breast, lung or prostate cancer [O'Toole, et al., *Cancer Res* 66, 9162-9170, 2006]. MSP, macrophage stimulatory protein, is the only ligand to MST1R known so far. MSP binding triggers autophosphorylation of the MST1R tyrosine kinase domain. Thereby activated MST1R transduces a variety of different pathway cascades. [Wang, et al., *Carcinogenesis* 24, 1291-1300, 2003; O'Toole, et al., *Cancer Res* 66, 9162-9170, 2006]. Generation of biologically active, truncated MST1R variants through mRNA splicing has also been reported [Wang, et al., *Carcinogenesis* 24, 1291-1300, 2003]. For example, MST1R⊿160 variant was found in some of colorectal carcinoma samples, and its overexpression without ligand mediated tumor formation in nude mice [Zhou et al., *Oncogene* 22, 186-197, 2003]. Anti-MST1R antibodies like IMC-41A10 block the ligand-receptor interaction and are potent inhibitors of receptor and downstream signaling, cell migration and tumorigenesis [O'Toole, et al., *Cancer Res* 66, 9162-9170, 2006].

[0002]

In conclusion, antibodies blocking MST1R activity are of potential therapeutic relevance in human cancer.

Summary

[0003]

It is an object to provide human and humanized antibodies against MST1R.

[0004]

It is another object to provide antibodies that are safe for human administration.

[0005]

It is also an object to provide methods for treating disease or and/or conditions associated with MST1R up-regulation by using one or more antibodies of the invention. These and other objects are more fully described herein.

[0006]

In one embodiment, an isolated antibody or functional fragment that contains an antigen-binding region is specific for MST1R.

[0007]

Such an antibody or functional fragment thereof may contain an antigen-binding region that contains an H-CDR3 (heavy chain CDR3) region having the amino acid sequence of SEQ ID NO: 1 or 4; the antigen-binding region may further include an H-CDR2 (heavy chain CDR2) region having the amino acid sequence of SEQ ID NO: 2 or 5; and the antigen-binding region also may contain an H-CDR1 (heavy chain CDR1) region having the amino acid sequence of SEQ ID NO: 3 or 6. Such an antibody or functional fragment thereof may contain an antigen-binding region that contains an L-CDR3 (light chain CDR3) region having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11 or 12; the antigen-binding region may further include an L-CDR1 (light chain CDR1) region having the amino acid sequence of SEQ ID NO: 13 or 15; and the antigen-binding region also may contain an L-CDR2 (light chain CDR2) region having the amino acid sequence of SEQ ID NO: 14 or 16.

[0008]

Antibodies (and functional fragments thereof) described herein may contain an antigen-binding region that is specific for an epitope of MST1R, which epitope contains one or more amino acid

residues of amino acid having the amino acid sequence of SEQ ID NO: 17. For certain antibodies, the epitope may be linear, whereas for others, it may be conformational (*i.e.*, discontinuous). An antibody or functional fragment thereof having one or more of these properties may contain an antigen-binding region that contains an H-CDR3 region having the amino acid sequence of SEQ ID NO: 1 or 4; the antigen-binding region may further include an H-CDR2 region having the amino acid sequence of SEQ ID NO: 2 or 5; and the antigen-binding region also may contain an H-CDR1 region having the amino acid sequence of SEQ ID NO: 3 or 6. Such a MST1R -specific antibody of the invention may contain an antigen-binding region that contains an L-CDR3 region having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11 or 12; the antigen-binding region may further include an L-CDR1 region shown in SEQ ID NO: 13 or 15; and the antigen-binding region also may contain an L-CDR2 region having the amino acid sequence of SEQ ID NO: 14 or 16.

[0009]

Peptide variants of the sequences disclosed herein are also embraced by various embodiments of the disclosure. Accordingly, the embodiments include anti-MST1R antibodies having a heavy chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions having the amino acid sequence of SEQ ID NO: 1, 2, 3, 4, 5 or 6; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions having the amino acid sequence of SEQ ID NO: 1, 2, 3, 4, 5 or 6. Further included are anti-MST1R antibodies having a light chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16.

[0010]

An antibody disclosed herein may be an IgG (*e.g.*, IgG_1), while an antibody fragment may be a Fab or scFv, for example. An inventive antibody fragment, accordingly, may be, or may contain, an antigen-binding region that behaves in one or more ways as described herein.

[0011]

Another embodiment also relates to isolated nucleic acid sequences, each of which can encode an antigen-binding region of a human antibody or functional fragment thereof that is specific for an epitope of MST1R. Such a nucleic acid sequence may encode a variable heavy chain of an antibody and include a sequence selected from the group consisting of SEQ ID NOS: 18, 20 or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 18 or 20. The nucleic acid might encode a variable light chain of an isolated antibody or functional fragment thereof, and may contain a sequence selected from the group consisting of SEQ ID NOS: 22, 24, 26, 28, 30, 32, or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 22, 24, 26, 28, 30 or 32.

[0012]

Nucleic acids described herein are suitable for recombinant production. Thus, vectors and host cells containing a nucleic acid sequence disclosed herein are also further embodiments.

[0013]

Compositions described herein may be used for therapeutic or prophylactic applications. These embodiments, therefore, include a pharmaceutical composition containing an inventive antibody (or functional antibody fragment) and a pharmaceutically acceptable carrier or excipient thereof. In a related aspect, another embodiment includes methods for treating a disorder or condition associated with the undesired presence of MST1R or MST1R expressing cells. Such method contains the steps of administering to a subject in need thereof an effective amount of the pharmaceutical composition that contains an inventive antibody as described or contemplated herein.

[0014]

Yet other embodiments relate to isolated epitopes of MST1R, either in linear or conformational form, and their use for the isolation of an antibody or functional fragment thereof, which antibody of antibody fragment comprises an antigen-binding region that is specific for said epitope. In this regard, a conformational epitope may contain one or more amino acid residues in SEQ ID NO: 17. An epitope of MST1R can be used, for example, for the isolation of antibodies or functional fragments thereof (each of which antibodies or antibody fragments comprises an

antigen-binding region that is specific for such epitope), comprising the steps of contacting said epitope of MST1R with an antibody library and isolating the antibody(ies) or functional fragment(s) thereof.

[0015]

In another embodiment, the disclosure provides an isolated epitope of MST1R, which consists essentially of an amino acid sequence in SEQ ID NO: 17. As used herein, such an epitope "consists essentially of" one of the immediately preceding amino acid sequences plus additional features, provided that the additional features do not materially affect the basic and novel characteristics of the epitope.

[0016]

The disclosure is also directed to a kit having (i) an isolated epitope of MST1R comprising one or more amino acid residues of the amino acid sequence in SEQ ID NO: 17; (ii) an antibody library; and (iii) instructions for using the antibody library to isolate one or more members of such library that binds specifically to such epitope.

(DETAILED DESCRIPTION)

[0017]

The present disclosure is based on the discovery of novel antibodies that are specific to or have a high affinity for MST1R and can deliver a therapeutic benefit to a subject. The antibodies disclosed herein, which may be human or humanized, can be used in many contexts, which are more fully described herein.

[0018]

A "human" antibody or functional human antibody fragment is hereby defined as one that is not chimeric (*e.g.*, not "humanized") and not from (either in whole or in part) a non-human species. A human antibody or functional antibody fragment can be derived from a human or can be a synthetic human antibody. A "synthetic human antibody" is defined herein as an antibody having a sequence derived, in whole or in part, *in silico* from synthetic sequences that are based on the analysis of known human antibody sequences. *In silico* design of a human antibody sequence or fragment thereof can be achieved, for example, by analyzing a database of human

antibody or antibody fragment sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Another example of a human antibody or functional antibody fragment, is one that is encoded by a nucleic acid isolated from a library of antibody sequences of human origin (*i.e.*, such library being based on antibodies taken from a human natural source).

[0019]

A "humanized antibody" or functional humanized antibody fragment is defined herein as one that is (i) derived from a non-human source (*e.g.*, a transgenic mouse which bears a heterologous immune system), which antibody is based on a human germline sequence; or (ii) chimeric, wherein the variable domain is derived from a non-human origin and the constant domain is derived from a human origin or (iii) complementarity determining regions (CDR)-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

[0020]

As used herein, an antibody "binds specifically to," is "specific to/for" or "specifically recognizes" an antigen (here, MST1R) if such antibody is able to discriminate between such antigen and one or more reference antigen(s), since binding specificity is not an absolute, but a relative property. In its most general form (and when no defined reference is mentioned), "specific binding" is referring to the ability of the antibody to discriminate between the antigen of interest and an unrelated antigen, as determined, for example, in accordance with one of the following methods. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans. For example, a standard ELISA assay can be carried out. The scoring may be carried out by standard color development (e.g. secondary antibody with horseradish peroxide and tetramethyl benzidine with hydrogenperoxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (=negative reaction) may be 0.1 OD; typical positive reaction may be 1 OD. This means the difference positive/negative can be more than 10-fold. Typically, determination of binding specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

[0021]

However, "specific binding" also may refer to the ability of an antibody to discriminate between the target antigen and one or more closely related antigen(s), which are used as reference points, e.g. between target MST1R and target semaphorin. Additionally, "specific binding" may relate to the ability of an antibody to discriminate between different parts of its target antigen, e.g. different domains or regions of MST1R, such as epitopes in the N-terminal or in the C-terminal region of target MST1R, or between one or more key amino acid residues or stretches of amino acid residues of target MST1R.

[0022]

Also, as used herein, an "immunoglobulin" (Ig) hereby is defined as a protein belonging to the class IgG, IgM, IgE, IgA, or IgD (or any subclass thereof), and includes all conventionally known antibodies and functional fragments thereof. A "functional fragment" of an antibody/immunoglobulin hereby is defined as a fragment of an antibody/immunoglobulin (e.g., a variable region of an IgG) that retains the antigen-binding region. An "antigen-binding region" of an antibody typically is found in one or more hypervariable region(s) of an antibody, i.e., the CDR-1, -2, and/or –3 regions; however, the variable "framework" regions can also play an important role in antigen binding, such as by providing a scaffold for the CDRs. In various embodiments, the "antigen-binding region" comprises at least amino acid residues 4 to 103 of the variable light (VL) chain and 5 to 109 of the variable heavy (VH) chain, amino acid residues 3 to 107 of VL and 4 to 111 of VH, and are the complete VL and VH chains (amino acid positions 1 to 109 of VL and 1 to 113 of VH; numbering according to WO 97/08320). A exemplary class of immunoglobulins for use in the embodiments described herein is IgG. "Functional fragments" of the invention include the domain of a $F(ab')_2$ fragment, a Fab fragment and scFv. The $F(ab')_2$ or Fab may be engineered to minimize or completely remove the intermolecular disulphide interactions that occur between the CH1 and CL domains.

[0023]

An antibody described herein may be derived from a recombinant antibody library that is based on amino acid sequences that have been designed in silico and encoded by nucleic acids that are synthetically created. *In silico* design of an antibody sequence is achieved, for example, by analyzing a database of human sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Methods for designing and obtaining *in silico*-created sequences are

described, for example, in Knappik et al., *J. Mol. Biol.* 296: 57-86, 2000; Krebs et al., *J. Immunol. Methods*. 254:67-84, 2001; and U.S. Patent No. 6,300,064 issued to Knappik et al., which hereby are incorporated by reference in their entirety.

(Antibodies Described Herein)

[0024]

Throughout this disclosure, reference is made to the following representative antibodies: "antibody nos." or "LACS" or "MOR" X. MOR X represents an antibody having a variable heavy region corresponding to SEQ ID NO: 18 or 20 (DNA)/SEQ ID NO: 19 or 21 (protein) and a variable light region selected from the group consisting of SEQ ID NOs: 22, 24, 26, 28, 30 and 32 (DNA)/SEQ ID NOs: 23, 25, 27, 29, 31 and 33 (protein).

[0025]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 18 (DNA)/SEQ ID: NO: 19 (protein) and a variable light chain corresponding to SEQ ID NO: 22 (DNA)/SEQ ID NO: 23 (protein).

[0026]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 20 (DNA)/SEQ ID: NO: 21 (protein) and a variable light chain corresponding to SEQ ID NO: 24 (DNA)/SEQ ID NO: 25 (protein).

[0027]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 18 (DNA)/SEQ ID: NO: 19 (protein) and a variable light chain corresponding to SEQ ID NO: 26 (DNA)/SEQ ID NO: 27 (protein).

[0028]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 18 (DNA)/SEQ ID: NO: 19 (protein) and a variable light chain corresponding to SEQ ID NO: 28 (DNA)/SEQ ID NO: 29 (protein).

[0029]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 18 (DNA)/SEQ ID: NO: 19 (protein) and a variable light chain corresponding to SEQ ID NO: 30(DNA)/SEQ ID NO: 31 (protein).

[0030]

In one example, the disclosure provides an antibody having a variable heavy region corresponding to SEQ ID NO: 18 (DNA)/SEQ ID: NO: 19 (protein) and a variable light chain corresponding to SEQ ID NO: 32 (DNA)/SEQ ID NO: 33 (protein).

[0031]

In another aspect, the disclosure provides following antibodies.

[0032]

In one example, the disclosure provides an antibody containing an antigen-binding region that contains an H-CDR3 (heavy chain CDR3) region having the amino acid sequence of SEQ ID NO: 1 or 4; the antigen-binding region may further include an H-CDR2 (heavy chain CDR2) region having the amino acid sequence of SEQ ID NO: 2 or 5; and the antigen-binding region also may contain an H-CDR1 (heavy chain CDR1) region having the amino acid sequence of SEQ ID NO: 3 or 6. Such an antibody thereof may contain an antigen-binding region that contains an L-CDR3 (light chain CDR3) region having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11 or 12; the antigen-binding region may further include an L-CDR1 (light chain CDR1) region having the amino acid sequence of SEQ ID NO: 13 or 15; and the antigen-binding region also may contain an L-CDR2 (light chain CDR2) region having the amino acid sequence of SEQ ID NO: 14 or 16.

[0033]

The disclosure also provides an antibody containing the antigen-binding region (i) H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2 and H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, (ii) H-CDR3 region having the amino acid sequence of SEQ ID NO: 4, H-CDR2 region having the amino acid sequence of SEQ ID NO: 5 and H-CDR1 region having the amino acid sequence of SEQ ID NO: 6.

[0034]

One embodiment also provides an antibody containing an antigen-binding region selected from the group consisting of (i) L-CDR3 region having the amino acid sequence of SEQ ID NO: 7, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (ii) L-CDR3 region having the amino acid sequence of SEQ ID NO: 8, L-CDR1 region having the amino acid sequence of SEQ ID NO: 15 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 16, (iii) L-CDR3 region having the amino acid sequence of SEQ ID NO: 9, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (iv) L-CDR3 region having the amino acid sequence of SEQ ID NO: 10, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (v) L-CDR3 region having the amino acid sequence of SEQ ID NO: 11, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, or (vi) L-CDR3 region having the amino acid sequence of SEQ ID NO: 12, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14.

[0035]

Another embodiment provides an antibody containing an antigen-binding region selected from the group consisting of (i) H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2, H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, L-CDR3 region having the amino acid sequence of SEQ ID NO: 7, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (ii) H-CDR3 region having the amino acid sequence of SEQ ID NO: 4, H-CDR2 region having the amino acid sequence of SEQ ID NO: 5, H-CDR1 region having the amino acid sequence of SEQ ID NO: 6, L-CDR3 region having the amino acid sequence of SEQ ID NO: 8, L-CDR1 region having the amino acid sequence of SEQ ID NO: 15 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 16,, (iii) H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2, H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, L-CDR3 region having the amino acid sequence of SEQ ID NO: 9, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (iv) H-CDR3 region having the amino acid

sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2, H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, L-CDR3 region having the amino acid sequence of SEQ ID NO: 10, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, (v) H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2, H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, L-CDR3 region having the amino acid sequence of SEQ ID NO: 11, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14, and (vi) H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, H-CDR2 region having the amino acid sequence of SEQ ID NO: 2, H-CDR1 region having the amino acid sequence of SEQ ID NO: 3, L-CDR3 region having the amino acid sequence of SEQ ID NO: 12, L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and L-CDR2 region having the amino acid sequence of SEQ ID NO: 14,

[0036]

In another aspect, the disclosure provides the following antibodies.

[0037]

One embodiment also provides an antibody comprising (i) a heavy chain having an amino acid sequence of SEQ ID NO: 49 or 51; and (ii) a light chain having an amino acid sequence selected from the group of SEQ ID NOs: 53, 55, 57, 59, 61 and 63.

[0038]

Yet another embodiment provides an antibody selected from the group of (i) a heavy chain having an amino acid sequence of SEQ ID NO: 49 and a light chain having an amino acid sequence of SEQ ID NO: 53 (named as "MOR07919"), (ii) a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 55 (named as "MOR07692"), (iii) a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 57 (named as "MOR07923"), (iv) a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 59 (named as "MOR07924"), (v) a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ

ID NO: 61 (named as "MOR07925"), (vi) a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 63 named as "MOR07926").

[0039]

In one aspect, the disclosure provides antibodies having an antigen-binding region that can bind specifically to or has a high affinity for one or more regions of target MST1R, having the amino acid sequence of SEQ ID NO: 17. An antibody is said to have a "high affinity" for an antigen if the affinity measurement is at least 100 nM (monovalent affinity of Fab fragment) as a K_D. An antibody or antigen-binding region described herein can, for example, bind to MST1R with an affinity of about less than 100 nM, less than about 60 nM, or less than about 30 nM. Further embodiments include antibodies that bind to MST1R with an affinity of less than about 10 nM or less than about 3 nM. In particular, isolated human or humanized antibodies or functional fragments thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, where the antibody or functional fragment thereof has an affinity against the partial peptide of MST1R as a K_D of less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 0.5 nM or less than about 0.1 nM as determined by surface plasmon resonance. While, the affinity against the partial peptide of MST1R as a K_D less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 0.5 nM or less than 0.1 nM as determined by Solution Equilibrium Titration. For instance, the affinity of an antibody, described herein, against MST1R may be about 0.98 nM or 0.02 nM (monovalent affinity of Fab fragment).

Table 1 provides a summary of affinities of representative antibodies disclosed herein, as determined by surface plasmon resonance (Biacore) and Solution Equilibrium Titration (SET):

[0040]

[Table 1]

TABLE 1: Antibody Affinities

Antibody (Fab)	BIACORE (Fab) K_D [nM]	SET (Fab) K_D [nM]
MOR07692	0.80	0.25
MOR07919	0.98	0.27
MOR07923	0.07	0.02
MOR07924	0.20	0.03
MOR07925	0.02	0.01
MOR07926	0.13	0.04

[0041]

With reference to Table 1, the affinity of MOR X antibodies was measured by surface plasmon resonance (Biacore) on immobilized recombinant human MST1R. The Biacore studies were performed on directly immobilized antigen. The Fab format of MORs X exhibit a monovalent affinity range between about 0.02 and 0.98 nM on immobilized MST1R protein with Fab MOR07925 showing the highest affinity, followed by Fabs MOR07923 and MOR07926. In addition, the Fab format of MORs X exhibit affinity range between about 0.01 and 0.27 nM with Fab MOR07925 showing the highest affinity, followed by Fabs MOR07923 and MOR07924 in SET studies.

[0042]

Another feature of antibodies described herein is their specificity for an area within the N-terminal region of MST1R. For example, MOR X disclosed herein can bind specifically to the N-terminal region of MST1R.

[0043]

The type of epitope to which an antibody as described herein binds may be linear (i.e. one consecutive stretch of amino acids) or conformational (i.e. multiple stretches of amino acids). In order to determine whether the epitope of a particular antibody is linear or conformational, the skilled practitioner can analyze the binding of antibodies to overlapping peptides (e.g., 13-mer peptides with an overlap of 11 amino acids) covering different domains of MST1R. ELISA analysis was performed using a recombinant MST1R partial peptide, having the amino acid sequence of SEQ ID NO: 17. Since MOR X was not applicable to immunoblot analysis in order to detect denatured form of the same recombinant MST1R protein, then MOR X must have conformational epitopes within amino acids residues of SEQ ID NO: 17.

[0044]

An antibody disclosed herein is species cross-reactive with humans and at least one other species, which may be, for example, a monkey or a mouse. An antibody that is cross reactive with at least cynomolgus monkey, for example, can provide greater flexibility and benefits over known anti-target MST1R antibodies, for purposes of conducting *in vivo* studies in multiple species with the same antibody.

[0045]

In one embodiment, the described antibody not only is able to bind to MST1R, but also is able to inhibit activation of the MST1R. Inhibition of the receptor leads to suppression of intrinsic kinase activity of the receptor and down-regulates signal transduction. Such down regulation can occur for example by limiting ligand binding to MST1R, changing conformation of MST1R, or internalization of MST1R. More specifically, the antibody disclosed herein can mediate its therapeutic effect by MST1R via antibody-effector functions.

[0046]

Yet another embodiment relates to the inhibition of ligand-dependent MST1R phosphorylation activity of MST1R by antibodies described herein. The disclosed antibody IC50 value of at least 100 ng/ml, at least 50 ng/ml, at least 20 ng/ml, at least 10 ng /ml or at least 5 ng/ml in MSP-dependent MST1R signal transduction assay system such as an "Elk1 luciferase assay".

[0047]

Another antibody described herein also inhibits ligand-independent MST1R activation

[0048]

A further antibody disclosed herein also inhibits ERK phosphorylation in response to MST1R ligand MSP.

[0049]

Yet another antibody described herein also suppresses MSP-promoted proliferation of tumor cells that express MST1R.

(Peptide Variants)

[0050]

Antibodies described throughout the disclosure are not limited to the specific peptide sequences provided herein. Rather, variants of these polypeptides are also embodied. With reference to the instant disclosure and conventionally available technologies and references, the skilled practitioner will be able to prepare, test and utilize functional variants of the antibodies disclosed herein, while appreciating these variants having the ability to suppress both/either ligand - dependent and/or -independent activation of MST1R fall within the scope of the present invention.

[0051]

A variant can include, for example, an antibody that has at least one altered complementarity determining region (CDR) (hyper-variable) and/or framework (FR) (variable) domain/position, vis-à-vis a peptide sequence disclosed herein. To better illustrate this concept, a brief description of antibody structure follows.

[0052]

An antibody is composed of two peptide chains, each containing one (light chain) or three (heavy chain) constant domains and a variable region (VL, VH), the latter of which is in each case made up of four FR regions and three interspaced CDRs. The antigen-binding site is formed by one or more CDRs, yet the FR regions provide the structural framework for the CDRs and, hence, play an important role in antigen binding. By altering one or more amino acid residues in a CDR or

FR region, the skilled worker routinely can generate mutated or diversified antibody sequences, which can be screened against the antigen, for new or improved properties, for example.

[0053]

FIG. 1 (VH) and FIG. 2: (VL) delineate the CDR and FR regions (according to Kabat definition) for certain antibodies disclosed herein and compare amino acids at a given position to each other and to corresponding HuCAL "master gene" sequences (as described in U.S. Patent No. 6,300,064):

[0054]

The skilled practitioner can use the data in FIG. 1 and FIG. 2 to design peptide variants that are within the scope of the embodiments disclosed herein. In one embodiment, variants are constructed by changing amino acids within one or more CDR regions; a variant might also have one or more altered framework regions. With reference to a comparison of the novel antibodies to each other, candidate residues that can be changed include residues of the variable light and residues of the variable heavy chains of MORs X. Alterations also may be made in the framework regions. For example, a peptide FR domain might be altered where there is a deviation in a residue compared to a germline sequence.

[0055]

With reference to a comparison of the novel antibodies to the corresponding consensus or "master gene" sequence, candidate residues that can be changed including residues of the variable light chain of MOR X, such as residues of VLλ3 and including residues of the variable heavy chain of MOR X, such as residues of VH3. Alternatively, the skilled worker could make the same analysis by comparing the amino acid sequences disclosed herein to known sequences of the same class of such antibodies, using, for example, the procedure described by Knappik *et al.* (*J. Mol. Biol.* 296, 57-86, 2000) and U.S. Patent No. 6,300,064 issued to Knappik *et al.*

[0056]

Furthermore, variants may be obtained by using one MOR X as a starting point for optimization by diversifying one or more amino acid residues in the MOR X sequence, preferably amino acid residues in one or more CDRs, and by screening the resulting collection of antibody variants for variants with improved properties. Diversification of one or more amino acid residues in the

CDR-3 of VL, the CDR-3 of VH, the CDR-1 of VL and/or the CDR-2 of VH may be accomplished by synthesizing a collection of DNA molecules using trinucleotide mutagenesis (TRIM) technology (Virnekäs, B., Ge, L., Plückthun, A., Schneider, K.C., Wellnhofer, G., and Moroney S.E. (1994) "Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis." *Nucl. Acids Res.* 22, 5600.).

(Conservative Amino Acid Variants)

[0057]

Polypeptide variants may be made that conserve the overall molecular structure of an antibody peptide sequence described herein. Given the properties of the individual amino acids, some rational substitutions will be recognized by the skilled worker. Amino acid substitutions, *i.e.*, "conservative substitutions," may be made, for instance, on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved.

[0058]

For example, (a) nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; (b) polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; (c) positively charged (basic) amino acids include arginine, lysine, and histidine; and (d) negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Substitutions typically may be made within groups (a)-(d). In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices. Similarly, certain amino acids, such as alanine, cysteine, leucine, methionine, glutamic acid, glutamine, histidine and lysine are more commonly found in α-helices, while valine, isoleucine, phenylalanine, tyrosine, tryptophan and threonine are more commonly found in β-pleated sheets. Glycine, serine, aspartic acid, asparagine, and proline are commonly found in turns. Some preferred substitutions may be made among the following groups: (i) S and T; (ii) P and G; and (iii) A, V, L and I. Given the known genetic code, and recombinant and synthetic DNA techniques, the skilled practitioner readily can construct DNAs encoding the conservative amino acid variants.

[0059]

As used herein, "sequence identity" between two polypeptide sequences, indicates the percentage of amino acids that are identical between the sequences. "Sequence homology" indicates the percentage of amino acids that either is identical or that represents conservative amino acid substitutions. Polypeptide sequences of the invention have a sequence identity in the CDR regions of at least 60%, at least 70% or 80%, at least 90% or at least 95%. Embodied antibodies also have a sequence homology in the CDR regions of at least 80%, at least 90% or at least 95%.

(DNA Molecules)

[0060]

The present disclosure also relates to the DNA molecules that encode an antibody described herein. These sequences include, but are not limited to, those DNA molecules set forth in FIGs. 3A, 3B, and 4A to 4F.

[0061]

DNA molecules of the disclosure are not limited to the sequences disclosed herein, but also include variants thereof. DNA variants within the various embodiments may be described by reference to their physical properties in hybridization. The skilled practitioner will recognize that DNA can be used to identify its complement and, since DNA is double stranded, its equivalent or homolog, using nucleic acid hybridization techniques. It also will be recognized that hybridization can occur with less than 100% complementarity. However, given appropriate choice of conditions, hybridization techniques can be used to differentiate among DNA sequences based on their structural relatedness to a particular probe. For guidance regarding such conditions see, Sambrook et al., 1989 (Sambrook, J., E.F. Fritsch, and T. Maniatis (1989) *Molecular Cloning: A laboratory manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, USA) and Ausubel et al., 1995 (Ausubel, F.M., R. Brent, R.E. Kingston, D.D. Moore, J.G. Sedman, J.A. Smith, & K. Struhl. eds. (1995). *Current Protocols in Molecular Biology*. New York: John Wiley and Sons).

[0062]

Structural similarity between two polynucleotide sequences can be expressed as a function of "stringency" of the conditions under which the two sequences will hybridize with one

another. As used herein, the term "stringency" refers to the extent that the conditions disfavor hybridization. Stringent conditions strongly disfavor hybridization, and only the most structurally related molecules will hybridize to one another under such conditions. Conversely, non-stringent conditions favor hybridization of molecules displaying a lesser degree of structural relatedness. Hybridization stringency, therefore, directly correlates with the structural relationships of two nucleic acid sequences. The following relationships are useful in correlating hybridization and relatedness (where T_m is the melting temperature of a nucleic acid duplex):

[0063]

a. $T_m = 69.3 + 0.41(G+C)\%$

[0064]

b. The T_m of a duplex DNA decreases by 1℃ with every increase of 1% in the number of mismatched base pairs.

[0065]

c. $(T_m)_{\mu 2} - (T_m)_{\mu 1} = 18.5 \log_{10} \mu 2/\mu 1$
where $\mu 1$ and $\mu 2$ are the ionic strengths of two solutions.

[0066]

Hybridization stringency is a function of many factors, including overall DNA concentration, ionic strength, temperature, probe size and the presence of agents which disrupt hydrogen bonding. Factors promoting hybridization include high DNA concentrations, high ionic strengths, low temperatures, longer probe size and the absence of agents that disrupt hydrogen bonding. Hybridization typically is performed in two phases: the "binding" phase and the "washing" phase.

[0067]

First, in the binding phase, the probe is bound to the target under conditions favoring hybridization. Stringency is usually controlled at this stage by altering the temperature. For high stringency, the temperature is usually between 65℃ and 70℃, unless short (< 20 nt) oligonucleotide probes are used. A representative hybridization solution comprises 6 X SSC, 0.5% SDS, 5 X Denhardt's solution and 100 μg of non-specific carrier DNA. See Ausubel *et al.*,

section 2.9, supplement 27 (1994). Of course, many different, yet functionally equivalent, buffer conditions are known. Where the degree of relatedness is lower, a lower temperature may be chosen. Low stringency binding temperatures are between about 25℃ and 40℃. Medium stringency is between at least about 40℃ to less than about 65℃. High stringency is at least about 65℃.

[0068]

Second, the excess probe is removed by washing. It is at this phase that more stringent conditions usually are applied. Hence, it is this "washing" stage that is most important in determining relatedness via hybridization. Washing solutions typically contain lower salt concentrations. One exemplary medium stringency solution contains 2 X SSC and 0.1% SDS. A high stringency wash solution contains the equivalent (in ionic strength) of less than about 0.2 X SSC, with a preferred stringent solution containing about 0.1 X SSC. The temperatures associated with various stringencies are the same as discussed above for "binding." The washing solution also typically is replaced a number of times during washing. For example, typical high stringency washing conditions comprise washing twice for 30 minutes at 55℃and three times for 15 minutes at 60℃.

[0069]

Accordingly, the present disclosure includes nucleic acid molecules that hybridize to the molecules of set forth in FIGs. 3A, 3B, and 4A to 4F under high stringency binding and washing conditions, where such nucleic molecules encode an antibody or functional fragment thereof having properties as described herein. Embodied molecules (from an mRNA perspective) are those that have at least 75% or 80% (preferably at least 85%, more preferably at least 90% and most preferably at least 95%) homology or sequence identity with one of the DNA molecules described herein. In one particular example of a variant of the disclosure, nucleic acid position 7 in SEQ ID NO: 18 or 20 can be substituted from a C to a G, thereby changing the codon from CAA to GAA.

(Functionally Equivalent Variants)

[0070]

Yet another class of DNA variants within the scope of the invention may be described with reference to the product they encode (see the peptides listed in FIGs. 3C, 3D, and 4G to 4L). These functionally equivalent genes are characterized by the fact that they encode the same peptide sequences found in FIGs. 3C, 3D, and 4G to 4L due to the degeneracy of the genetic code. The amino acid sequence in FIG. 3C is also shown as SEQ ID NO: 19. The amino acid sequence in FIG. 3D is also shown as SEQ ID: NO:21. The amino acid sequence in FIG. 4G is also shown as SEQ ID: NO:23. The amino acid sequence in FIG. 4H is also shown as SEQ ID: NO:25. The amino acid sequence in FIG. 4I is also shown as SEQ ID: NO: 27. The amino acid sequence in FIG. 4J is also shown as SEQ ID: NO: 29. The amino acid sequence in FIG. 4K is also shown as SEQ ID: NO: 31. The amino acid sequence in FIG. 4L is also shown as SEQ ID: NO: 33.

[0071]

It is recognized that variants of DNA molecules provided herein can be constructed in several different ways. For example, they may be constructed as completely synthetic DNAs. Methods of efficiently synthesizing oligonucleotides in the range of 20 to about 150 nucleotides are widely available. See Ausubel et al., section 2.11, Supplement 21 (1993). Overlapping oligonucleotides may be synthesized and assembled in a fashion first reported by Khorana et al., *J. Mol. Biol.* 72:209-217 (1971); see also Ausubel et al., supra, Section 8.2. Synthetic DNAs preferably are designed with convenient restriction sites engineered at the 5' and 3' ends of the gene to facilitate cloning into an appropriate vector.

[0072]

As indicated, a method of generating variants is to start with one of the DNAs disclosed herein and then to conduct site-directed mutagenesis. *See* Ausubel et al., *supra,* chapter 8, Supplement 37 (1997). In a typical method, a target DNA is cloned into a single-stranded DNA bacteriophage vehicle. Single-stranded DNA is isolated and hybridized with an oligonucleotide containing the desired nucleotide alteration(s). The complementary strand is synthesized and the double stranded phage is introduced into a host. Some of the resulting progeny will contain the desired mutant, which can be confirmed using DNA sequencing. In addition, various methods are available that increase the probability that the progeny phage will be the desired

mutant. These methods are well known to those in the field and kits are commercially available for generating such mutants.

(Recombinant DNA constructs and expression)

[0073]

The present disclosure further provides recombinant DNA constructs comprising one or more of the nucleotide sequences described herein. These recombinant constructs are used in connection with a vector, such as a plasmid, phagemid, phage or viral vector, into which a DNA molecule encoding any disclosed antibody is inserted.

[0074]

The encoded gene may be produced by techniques described in Sambrook et al., 1989, and Ausubel et al., 1989. Alternatively, the DNA sequences may be chemically synthesized using, for example, synthesizers. See, for example, the techniques described in *Oligonucleotide Synthesis* (1984, Gait, ed., IRL Press, Oxford), which is incorporated by reference herein in its entirety. Recombinant constructs of the disclosure are comprised with expression vectors that are capable of expressing the RNA and/or protein products of the encoded DNA(s). The vector may further comprise regulatory sequences, including a promoter operably linked to the open reading frame (ORF). The vector may further comprise a selectable marker sequence. Specific initiation and bacterial secretory signals also may be required for efficient translation of inserted target gene coding sequences.

[0075]

The present disclosure further provides host cells containing at least one of the DNAs described herein. The host cell can be virtually any cell for which expression vectors are available. It may be, for example, a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, and may be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, lipofection, DEAE, dextran mediated transfection, electroporation or phage infection.

(Bacterial Expression)

[0076]

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and, if desirable, to provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*.

[0077]

Bacterial vectors may be, for example, bacteriophage-, plasmid- or phagemid-based. These vectors can contain a selectable marker and bacterial origin of replication derived from commercially available plasmids typically containing elements of the well known cloning vector pBR322 (ATCC Accession No. 37017). Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is de-repressed/induced by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

[0078]

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the protein being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of antibodies or to screen peptide libraries, for example, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable.

(Therapeutic Methods)

[0079]

Therapeutic methods involve administering to a subject in need of treatment a therapeutically effective amount of an antibody contemplated by the disclosure. A "therapeutically effective"

amount hereby is defined as the amount of an antibody that is of sufficient quantity to deplete MST1R -positive cells in a treated area of a subject—either as a single dose or according to a multiple dose regimen, alone or in combination with other agents, which leads to the alleviation of an adverse condition, yet which amount is toxicologically tolerable. The subject may be a human or non-human animal (*e.g.*, rabbit, rat, mouse, monkey or other lower-order primate).

[0080]

An antibody of the disclosure might be co-administered with known medicaments, and in some instances the antibody might itself be modified. For example, an antibody could be conjugated to an immunotoxin or a radio labeled antibody to potentially further increase efficacy.

[0081]

The antibodies described herein can be used as a therapeutic or a diagnostic tool in a variety of situations where MST1R is undesirably expressed or found. Disorders and conditions particularly suitable for treatment with an antibody of the disclosure are MST1R- expressing malignant tumors and neoplasma, for example, breast, lung, colon, bladder, skin, pancreatic, glioma, lymphoma, prostate, thyroid, ovary, gastric, liver, stomach and on the like.

[0082]

To treat any of the foregoing disorders, pharmaceutical compositions for use in accordance with the present disclosure may be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. Any antibody described herein can be administered by any suitable means, which can vary, depending on the type of disorder being treated. Possible administration routes include parenteral (e.g., intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous), intrapulmonary and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. In addition, any disclosed antibody may be administered by pulse infusion, with, e.g., declining doses of the antibody. The dosing can be administered by injections, such as for example, intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. The amount to be administered will depend on a variety of factors such as the clinical symptoms, weight of the individual, whether other drugs are administered. The skilled practitioner will recognize that the route of administration will vary depending on the disorder or condition to be treated and will

understand which route would be most appropriate for the individual based on the specific factors for each individual.

[0083]

Determining a therapeutically effective amount of the novel polypeptide, according to this invention, largely will depend on particular patient characteristics, route of administration, and the nature of the disorder being treated. General guidance can be found, for example, in the publications of the *International Conference on Harmonisation* and in *Remington's Pharmaceutical Sciences*, chapters 27 and 28, pp. 484-528 (18th ed., Alfonso R. Gennaro, ED., Easton, PA.: Mack Pub. Co., 1990). More specifically, determining a therapeutically effective amount will depend on such factors as toxicity and efficacy of the medicament. Toxicity may be determined using methods well known in the art and found in the foregoing references. Efficacy may be determined utilizing the same guidance in conjunction with the methods described below in the Examples.

(Diagnostic Methods)

[0084]

MST1R is highly expressed on cancer cells in certain malignancies; thus, an anti-MST1R antibody of the disclosure may be employed in order to image or visualize a site or location of possible MST1R in a patient. In this regard, an antibody can be detectably labeled, through the use of radioisotopes, affinity labels (such as biotin, avidin, etc.), fluorescent labels, paramagnetic atoms, etc. Procedures for accomplishing such labeling are well known to the art. Clinical applications of antibodies in diagnostic imaging are reviewed by Grossman, H.B., *Urol. Clin. North Amer.* 13:465-474 (1986)), Unger, E.C. et al., *Invest. Radiol.* 20:693-700 (1985)), and Khaw, B. A. et al., *Science* 209:295-297 (1980)).

[0085]

The detection of foci of such detectably labeled antibodies might be indicative of MST1R, for example. In one embodiment, this examination is done by removing samples of tissue or blood and incubating such samples in the presence of the detectably labeled antibodies. In a one embodiment, this technique is done in a non-invasive manner through the use of magnetic

imaging, fluorography, etc. Such a diagnostic test may be employed in monitoring the success of treatment of diseases, where presence or absence of a MST1R-positive cell is a relevant indicator.

(Therapeutic And Diagnostic Compositions)

[0086]

The antibodies of the present disclosure can be formulated according to known methods to prepare pharmaceutically useful compositions, where an antibody described herein (including any functional fragment thereof) is combined in a mixture with a pharmaceutically acceptable carrier vehicle. Suitable vehicles and their formulation are described, for example, in *REMINGTON'S PHARMACEUTICAL SCIENCES* (18th ed., Alfonso R. Gennaro, ED., Easton, PA.: Mack Pub. Co., 1990). In order to form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain an effective amount of one or more of the antibodies of the present disclosure, together with a suitable amount of carrier vehicle.

[0087]

Preparations may be suitably formulated to give controlled-release of the active compound. Controlled-release preparations may be achieved through the use of polymers to complex or absorb anti-MST1R antibody. The controlled delivery may be exercised by selecting appropriate macromolecules (for example polyesters, polyamino acids, polyvinyl, pyrrolidone, ethylenevinyl-acetate, methylcellulose, carboxymethylcellulose, or protamine, sulfate) and the concentration of macromolecules as well as the methods of incorporation in order to control release. Another possible method to control the duration of action by controlled release preparations is to incorporate anti-MST1R antibody into particles of a polymeric material such as polyesters, polyamino acids, hydrogels, poly(lactic acid) or ethylene vinylacetate copolymers. Alternatively, instead of incorporating these agents into polymeric particles, it is possible to entrap these materials in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatine-microcapsules and poly(methylmethacylate) microcapsules, respectively, or in colloidal drug delivery systems, for example, liposomes, albumin microspheres, microemulsions, nanoparticles,

and nanocapsules or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* (1980).

[0088]

The compounds may be formulated for parenteral administration by injection, *e.g.,* by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.,* in ampules, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.,* sterile pyrogen-free water, before use.

[0089]

The compositions may, if desired, be presented in a pack or dispenser device, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Moreover, the pack or dispenser device and compositions may be presented in a kit for commercial distribution.

[0090]

The various embodiments of the invention may further be understood by reference to the following working examples, which are intended to illustrate and, hence, not limit the scope of the inventive disclosure.

Brief Description of Drawings

[0091]

[Fig. 1]

FIG. 1 provides amino acid sequences of various novel antibody variable heavy regions, and which delineates the CDR and framework (FR) regions. The VH3 sequence (SEQ ID NO: 80) is aligned with the MOR07692, MOR07923, MOR07924, MOR07925, MOR07926 variable heavy region sequence (SEQ ID NO: 19), and the VH5 sequence (SEQ ID NO: 81) is aligned with MOR07919 variable heavy region sequence (SEQ ID NO: 21).

[0092]

[Fig. 2]

FIG. 2: FIG. 2A and FIG. 2B provide amino acid sequences of various novel antibody variable light regions, and which delineates the CDR and framework (FR) regions. The VLκ3 sequence (VLk3; SEQ ID NO: 82) is aligned with the MOR07692 (SEQ ID NO: 23), MOR07923 (SEQ ID NO: 27), MOR07924 (SEQ ID NO: 29), MOR07925 (SEQ ID NO: 31), MOR07926 (SEQ ID NO: 33) variable light region sequences, and the VLλ3 sequence (VLl3; SEQ ID NO: 83) is aligned with MOR07919 variable light region sequence (SEQ ID NO: 25).

[0093]

[Fig. 3]

FIG. 3: FIG. 3A (MOR07692, MOR07923, MOR07924, MOR07925, MOR07926; SEQ ID NO: 18) and FIG. 3B (MOR07919; SEQ ID NO: 20) provide nucleic acid sequences of various novel antibody variable heavy regions. FIG. 3C (MOR07692, MOR07923, MOR07924, MOR07925, MOR07926; SEQ ID NO: 19) and FIG. 3D (MOR07919; SEQ ID NO: 21) provide amino acid sequences of various novel antibody variable heavy regions. CDR regions H-CDR1, H-CDR2 and H-CDR3 are designated from N- to C-terminus in boldface and underlined.

[0094]

[Fig. 4]

FIG. 4: FIG. 4A (MOR07692; SEQ ID NO: 22), FIG. 4B (MOR07919; SEQ ID NO: 24), FIG. 4C (MOR07923; SEQ ID NO: 26), FIG. 4D (MOR07924; SEQ ID NO: 28), FIG. 4E (MOR07925; SEQ ID NO: 30) and FIG. 4F (MOR07926; SEQ ID NO: 32) provide nucleic acid sequences of various novel antibody variable light regions. FIG. 4G (MOR07692; SEQ ID NO: 23), FIG. 4H (MOR07919; SEQ ID NO: 25), FIG. 4I (MOR07923; SEQ ID NO: 27), FIG. 4J (MOR07924; SEQ ID NO: 29), FIG. 4K (MOR07925; SEQ ID NO: 31), and FIG. 4L (MOR07926; SEQ ID NO: 33) provide amino acid sequences of various novel antibody variable light regions. CDR regions L-CDR1, L-CDR2 and L-CDR3 are designated from N- to C-terminus in boldface and underlined.

[0095]

[Fig. 5]

FIG. 5 provides amino acid sequences of variable heavy regions of various consensus-based Human Combinatorial Antibody Library (HuCAL®) antibody master gene sequences. CDR regions H-CDR1, H-CDR2 and H-CDR3 are underlined as designated from N- to C-terminus. The upper line is MOR07919 (SEQ ID NO: 21) while the lower line is MOR07692/7923/7924/7925/7926 (SEQ ID NO: 19).

[0096]

[Fig. 6]

FIG. 6 provides amino acid sequences of variable light regions of various consensus-based HuCAL antibody master gene sequences. CDR regions L-CDR1, L-CDR2 and L-CDR3 are underlined as designated from N- to C-terminus. The two sets of lines from top to bottom are as follows: MOR07919 (SEQ ID NO: 25); MOR07692 (SEQ ID NO: 23); MOR07923 (SEQ ID NO: 27); MOR07924 (SEQ ID NO: 29); MOR07925 (SEQ ID NO: 31); MOR07926 (SEQ ID NO: 33), respectively.

[0097]

[Fig. 7]

FIG. 7: FIG. 7A and FIG. 7B provide the nucleic acid and the amino acid sequence of various novel antibody heavy chains (FIG. 7A: MOR07919; FIG. 7B: MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926; respectively) as expressed from pMORPH®2_h_IgG1f. CDR regions are in boldface and underlined. Amino acid sequence of VH leader and heavy chain constant region is indicated in italics or italics and boldface, respectively. Restriction sites and priming sites of sequencing primers are designated above or below the sequence. The nucleic acid sequence of FIG. 7A is represented by SEQ ID NO: 64, while the amino acid sequence is SEQ ID NO: 65. The nucleic acid sequence of FIG. 7B is represented by SEQ ID NO: 66, while the amino acid sequence is SEQ ID NO: 67.

[0098]

[Fig. 8]

FIG. 8 provides the nucleic acid sequence (SEQ ID NO: 68) and the amino acid sequence (SEQ ID NO: 69) of a novel antibody lambda light chain (MOR07919) as expressed from pMORPH®2_h_Ig_lambda2. CDR regions are in boldface and underlined. Amino acid sequence of VL leader and lambda light chain constant region is indicated in italics or italics and boldface, respectively. Restriction sites and priming sites of sequencing primers are designated above or below the sequence.

[0099]

[Fig. 9]

FIG. 9: FIG. 9A to FIG. 9E provide the nucleic acid and the amino acid sequence of various novel antibody kappa light chains as expressed from pMORPH®2_h_Ig_kappa. CDR regions are in boldface and underlined. Amino acid sequence of VL leader and kappa light chain constant region is indicated in italics or italics and boldface, respectively. Restriction sites and priming sites of sequencing primers are designated above or below the sequence. The nucleic acid sequence of FIG. 9A is represented by SEQ ID NO: 70, while the amino acid sequence is SEQ ID NO: 71 (MOR07692). The nucleic acid sequence of FIG. 9B is represented by SEQ ID NO: 72, while the amino acid sequence is SEQ ID NO: 73 (MOR07923). The nucleic acid sequence of FIG. 9C is represented by SEQ ID NO: 74, while the amino acid sequence is SEQ ID NO: 75 (MOR07924). The nucleic acid sequence of FIG. 9D is represented by SEQ ID NO: 76, while the amino acid sequence is SEQ ID NO: 77 (MOR07925). The nucleic acid sequence of FIG. 9E is represented by SEQ ID NO: 78, while the amino acid sequence is SEQ ID NO: 79 (MOR07926).

[0100]

[Fig. 10]

FIG. 10 provides a FACS analysis demonstrating crossreactivity of isolated antibodies (MorphoSys IgG1- 2 μg/ml) to MST1R orthologs.

[0101]

[Fig. 11]

FIG. 11 shows binding activity of MOR07692, MOR07919, MOR07923, MOR07924, MOR07925 and MOR07926 to the 25-571 portion of human MST1R compared to PBS

control. Using the t-test analysis for n=3, the p values are as follows: MOR07692: 4.56E-07; MOR07919: 1.43E-05; MOR07923: 2.10E-05; MOR07924: 1.42E-06; MOR07925: 9.74E-07; and MOR07926: 1.53E-06.

[0102]

[Fig. 12]

FIG. 12 shows inhibitory Elk1 trans reporter activity in the absence of ligand. Using the t-test analysis and an antibody concentration of 5 μg/ml, the p values are as follows: MOR07692: 5.39E-06; MOR07919: 3.19E-04; and MOR07925: 3.78E-05.

[0103]

[Fig. 13]

FIG. 13 shows inhibition of 200 ng/ml MSP-induced phosphorylation by MOR07692 compared to hIgG control at various time points (min) at an absorbance of 450 nm with a 570 nm reference) At the 5 min time point, the p value is 5.43E-05, while at the 15 min time point, the p value is 4.76E-06.

[0104]

[Fig. 14]

FIG. 14 is a western blot illustrating inhibition of 100 ng/ml MSP-induced phosphorylation of ERK by 1 μg/ml MOR07692 compared to no antibody and hIgG controls in the presence or absence of 1 μg/ml cross-linked antibody.

[0105]

[Fig. 15]

FIG. 15 shows inhibitory activity of the specified antibodies or without antibody control on MSP-induced cell proliferation (%) in the presence or absence of 100 ng/ml MSP. For the various antibodies, the p values are as follows: MOR07692: 0.0001; MOR07919: 0.2037; MOR07923: 0.0106; MOR07924: 0.0203; MOR07925: 0.0042; and MOR07926: 0.0044.

[0106]

[Fig. 16]

FIG. 16 shows inhibition of MSP-induced migration by indicated anti-MST1R antibodies.

[0107]

[Fig. 17]

FIG. 17 shows potential of indicted anti-MST1R antibodies to induce internalization.

Examples

(Cell culture and transient transfection)

[0108]

Human embryonic kidney (HEK) 293FreeStyle™ cells were grown in Freestyle 293 Medium (Invitrogen). 293α was a stable transfectant obtained by transfection with integrinαv and integrinβ3 expression vectors into HEK293 cells. HEK293 and 293α cells were propagated in DMEM containing 10% FCS. PC3 and T47D were cultured in RPMI containing 10% FCS. For pannings, screenings and functional assays, HEK 293FreeStyle™ cells were transfected with plasmid DNAs using 293fectin (Invitrogen). 293T and 293α cells were transfected with plasmid DNAs using Lipofectamine 2000 (Invitrogen) according to the supplier's instructions.

(Flow cytometry ("FACS"))

[0109]

Cells (5 x 10^5 cells/well) were incubated with Fab or IgG antibodies at the indicated concentrations in 50 μl FACS buffer (PBS, 5% FCS) for 60 min at 4℃ in round bottom 96-well culture plates (Corning). Cells were washed twice and then incubated with Fluorescein Isothiocyanate (FITC) conjugated detection antibody for 30 min at 4℃. Cells were washed again, resuspended in 0.3 ml FACS buffer and then analyzed by flow cytometry in a Cytomics FC500 (Beckman Coulter, Inc.). Data were analysed via FlowJo software (Tomy digital biology Co., Ltd.). Polyclonal goat anti-hMSP R IgG (R&D systems) or anti-FLAG M2 antibody

(Sigma) was used as a positive control and MOR03207 (anti-lysozyme) antibody was used as a negative control.

(Surface plasmon resonance)

[0110]

The kinetic constants k_{on} and k_{off} were determined with serial dilutions of the respective Fab binding to covalently immobilized MST1R-Fc fusion protein (R&D systems) using the BIAcore 3000 instrument (Biacore). For covalent antigen immobilization standard EDC-NHS amine coupling chemistry was used. For direct coupling of MST1R-Fc fusion protein CM5 senor chips (Biacore) were coated with ~600-700 RU in 10 mM acetate buffer, pH 4.5. For the reference flow cell a respective amount of HSA (human serum albumin) was used. Kinetic measurements were done in PBS (136 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 1.76 mM KH_2PO_4 pH 7.4) at a flow rate of 20 µl/min using Fab concentration range from 15.6-500 nM. Injection time for each concentration was 1 min, followed by 3 min dissociation phase. For regeneration 5 µl 10 mM HCl was used. All sensograms were globally fitted using BIA evaluation software 3.2 (Biacore).

(Solution Equilibrium Titration (SET))

[0111]

Affinity determination in solution was basically performed as described in the literature (Friguet, B., Chaffotte, A. F., Djavadi-Ohaniance, L., and Goldberg, M. E. (1985) *J Immunol Methods* 77, 305-319.). In order to improve the sensitivity and accuracy of the SET method, the method was modified from classical ELISA to ECL based technology (Haenel, C., Satzger, M., Ducata, D. D., Ostendorp, R., and Brocks, B. (2005) *Anal Biochem* 339, 182-184).

Example 1

(ANTIBODY GENERATION FROM HuCAL LIBRARIES)

[0112]

For the generation of therapeutic antibodies against MST1R, selections with the MorphoSys HuCAL GOLD phage display library were carried out. HuCAL GOLD® is a Fab library based on the HuCAL® concept (Knappik et al. (*J. Mol. Biol.*, 296, 57-86,. 2000); Krebs et al., *J. Immunol. Methods*, 254, 67-84, 2001; Rothe et al., *J. Mol. Biol.*, 376(4):1182-200, 2008), in which all six CDRs are diversified, and which employs the CysDisplay™ technology for linking Fab fragments to the phage surface (WO 01/05950).

(A. Phagemid Rescue, Phage Amplification And Purification)

[0113]

HuCAL GOLD® phagemid library was amplified in 2x YT medium containing 34 µg/ml chloramphenicol and 1% glucose (2x YT-CG). After helper phage infection (VCSM13) at an OD_{600nm} of 0.5 (30 min at 37°Cwithout shaking; 30 min at 37°C shaking at 250 rpm), cells were spun down (4120 g; 5 min; 4°C), resuspended in 2x YT/ 34 µg/ml chloramphenicol / 50 µg/ml kanamycin / 0.25 mM IPTG and grown overnight at 22°C. Phages were PEG-precipitated from the supernatant, resuspended in PBS/ 20% glycerol and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1 cells were infected with eluted phages and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol (LB-CG). After overnight incubation at 30°C, colonies were scraped off, and used to inoculate 2xYT-CG until an OD_{600nm} of 0.5 was reached and VCSM13 helper phages added for infection as described above.

(B. Pannings with HuCAL GOLD®)

[0114]

For the selections HuCAL GOLD® antibody-phages were divided into six pools comprising different combinations of VH master genes (pool 1: VH1/3/5 κ, pool 2: VH1/3/5 λ, pool 3: VH2/4/6 κ, pool 4: VH2/4/6 λ, pool 5: VH1-6 κ, pool 6: VH1-6 λ). These pools were individually subjected to 3 rounds of whole cell panning on MST1R expression vector-transfected HEK 293FreeStyle™ cells followed by pH-elution and a post-adsorption step on MST1R-negative HEK 293FreeStyle™ cells for depletion of irrelevant antibody-phages. Finally, the remaining antibody phages were used to infect *E. coli* TG1 cells which were then plated on

agar plates and incubated overnight at 30°C. The next day, the bacterial colonies were scraped off the plates, phages were rescued and amplified as described above. The second and the third round of selections were performed as the initial one. In addition to standard pannings, the LCDR3- RapMAT®technology was applied to potentially identify clones with higher affinities. RapMAT® represents a built-in affinity maturation process for the rapid selection of high affinity antibodies. This technology is based on the modular design of the HuCAL GOLD® Fab library. For the RapMAT® method two rounds of standard panning were performed with separate pools of lambda and kappa libraries. The selected 2nd round Fab pools were diversified via exchange of the LCDR3 with LCDR3 library cassettes. The resulting Fab libraries were subjected to two further rounds of pannings under stringent conditions.

(C. Subcloning And Expression Of Soluble Fab Fragments)

[0115]

The Fab encoding inserts of the selected HuCAL GOLD® phagemids were subcloned into the expression vector pMORPH®x9_Fab_FS (Rauchenberger et al., *J. Biol. Chem.* 278(40):38194-205, 2003) to facilitate rapid expression of soluble Fab. For this purpose, the Fab encoding insert (ompA-VLCL and phoA-Fd) of the selected clones was cut out of the plasmid DNA with *Xba*I and *Eco*RI, and cloned into the *Xba*I / *Eco*RI cut vector pMORPH®x9_ FS. Fabs expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tag® II) for detection and purification.

(D. Expression of HuCAL GOLD® Fab Antibodies in *E. coli* and Purification)

[0116]

Expression of Fab fragments encoded by pMORPH®x9_Fab_FS in *E. coli* TG-1 cells was carried out in shaker flask cultures using 750 ml of 2x YT medium supplemented with 34 µg/ml chloramphenicol. Cultures were shaken at 30°C until the OD600nm reached 0.5. Expression was induced by addition of 0.75 mM IPTG for 20 hr at 30°C. Bacteria were harvested by centrifugation and the periplasmic fraction prepared using 30-35ml BBS. Fabs were purified via Strep-tag® II using Step-Tactin sepharose columns. Purity of the samples was analyzed together with calibration standards by SDS-PAGE in denatured, reduced state and by size exclusion

chromatography (SEC) in native state. Protein concentrations were determined by UV-spectrophotometry (Krebs et al., *J. Immunol. Methods* 254, 67-84, 2001).

Example 2

(CLONING, EXPRESSION AND PURIFICATION OF HuCAL® IgG1)

[0117]

In order to express full length IgG1, variable domain fragments of heavy (VH) and light chains (VL) were subcloned from Fab expression vector into pMORPH®2_hIg vectors. Restriction enzymes *Mfe*I and *Blp*I were used for subcloning of VH fragments. Restriction enzymes *Eco*RV and *Bsi*WI or *Hpa*I were used for subcloning of VL kappa or VL lambda fragments, respectively. After digestion, VH and VL fragments were isolated from preparative agarose gel and ligated into the respective IgG expression vectors (VH fragment into pMORPH®2_h_IgG1f; Vkappa fragment into pMORPH®2_h_Igκ; Vlambda fragment into pMORPH®2_h_Igλ2). The resulting IgG expression plasmids were characterized by restriction analysis and sequencing. Transient expression of full length human IgG was performed in HKB11 cells, which were transfected with IgG heavy and light chain expression vectors. IgGs were purified from cell culture supernatants by affinity chromatography *via* Protein A Sepharose column. Further down stream processing included a buffer exchange by gel filtration and sterile filtration of purified IgG. Quality control revealed a purity of >90 % by reducing SDS-PAGE and >90 % monomeric IgG as determined by analytical size exclusion chromatography.

Example 3

(ELISA SCREENING OF HuCAL® Fab CLONES AND HuCAL® IgG1)

[0118]

Wells of a 384-well MaxiSorp™ microtiter plate were coated with 0.5 µg/ml recombinant MST1R-Fc fusion protein diluted in PBS. The plate was incubated overnight at 4℃. Next day, the wells were washed 3 times with PBST (0.05% Tween20 in PBS) and then blocked with MPBST (5% milk powder in PBST) for 30 min at room temperature on a microtiter plate shaker. The wells were washed 3 times with PBST before adding the primary antibody,

i.e. preblocked BEL extracts of HuCAL® Fab clones or purified HuCAL® antibodies and control antibodies. The plate was incubated for 2 hr at room temperature on a microtiter plate shaker and then washed 3 times with PBST. For detection of HuCAL® antibodies, goat anti-human IgG alkaline phosphatase (Dianova, diluted 1:5,000 in 0.5% milkpowder in PBST) was added and the plate incubated for 1h at room temperature on a microtiter plate shaker. Subsequently, the plate was washed 5 times with TBST (0.05% Tween20 in TBS). Attophos (AttoPhos Substrate Set, Roche) was added (diluted 1:10 in TBS) and fluorescence was measured in a TECAN microtiter plate reader (emission: 535nm, excitation: 430nm).

Example 4

(CROSS-REACTIVITY ANALYSIS BY FACS)

[0119]

FACS-analysis of MST1R ortholog-expressing cells: Human MST1R (cDNA nucleotide sequence is shown as GenBank Accession No: NM_002447.2), cynomolgus monkey MST1R and mouse MST1R (cDNA nucleotide sequence is shown as GeneBank Accession No: NM_009074.1) expression vector containing N-terminal Flag tag (pFLAG-myc-CMV-19, Sigma) were constructed. cDNA encoding cynomolgus monkey MST1R was amplified by PCR using cynomolgus monkey stomach cDNA as a template with forward and reverse primers having nucleotide sequences of SEQ ID NO: 34 and 35, respectively. By sequencing analysis of PCR product, the cynomolgus MST1R ORF nucleotide sequence was identified as shown in SEQ ID NO: 36. The corresponding amino acid sequence was shown in SEQ ID NO: 37. Then human, cynomolgus monkey and mouse MST1R ORF cDNA, excluding signal peptide regions, were amplified using respective forward and reverse primers having nucleotide sequences of SEQ ID NO: 38 and 39 (human), 40 and 41 (cynomolgus monkey), and 42 and 43 (mouse) with appropriate cloning sites and then cloned into pFLAG-myc-CMV-19. An amplified human MST1R fragment encodes amino acids corresponding to GenBank Accession No: NP_002438.2 (SEQ ID NO: 45). A Mouse MST1R fragment encodes amino acids corresponding to GenBank Accession No: NP_033100.1 (SEQ ID NO: 47) except for those amino acid differences at positions: 688 (Leu to Pro), 713 (Ile to Val), 714 (Ala to Gly) and 719 (Ala to Val). These expression vectors were transfected into HEK293T cells. For FACS-analysis, cells were

incubated with 2 μg/ml primary antibodies followed by incubation with FITC-labeled secondary antibody as described above. In FIG. 10, anti-Flag antibody confirmed expression of each (human, cynomolgus monkey and mouse MST1R) protein. MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 showed binding to both human and monkey MST1R. On the other hand, MOR07919 also exhibited binding to mouse MST1R besides human and monkey MST1R.

[0120]

The nucleotide sequence of these antibodies was decided by DNA sequencer. The nucleotide sequence of variable heavy chain of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 was decided as shown in FIG. 3A and SEQ ID NO: 18. The nucleotide sequence of variable heavy chain of MOR07919 is shown in FIG. 3B and SEQ ID NO: 20. The amino acid sequence of variable heavy chain of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 was decided as shown in FIG. 3C and SEQ ID NO: 19. The amino acid sequence of variable heavy chain of MOR07919 is shown in FIG. 3D and SEQ ID NO: 21.

[0121]

The nucleotide sequence of variable light chain of MOR07692 is shown in FIG. 4A and SEQ ID NO: 22. The amino acid sequence of variable light chain of MOR07692 is shown in FIG 4G and SEQ ID NO: 23. The nucleotide sequence of variable light chain of MOR07919 is shown in FIG. 4B and SEQ ID NO: 24. The amino acid sequence of variable light chain of MOR07919 is shown in FIG. 4H and SEQ ID NO: 25. The nucleotide sequence of variable light chain of MOR07923 is shown in FIG. 4C and SEQ ID NO: 26. The amino acid sequence of variable light chain of MOR07923 is shown in FIG. 4I and SEQ ID NO: 27. The nucleotide sequence of variable light chain of MOR07924 is shown in FIG. 4D and SEQ ID NO: 28. The amino acid sequence of variable light chain of MOR07924 is shown in FIG. 4J and SEQ ID NO: 29. The nucleotide sequence of variable light chain of MOR07925 is shown in FIG. 4E and SEQ ID NO: 30. The amino acid sequence of variable light chain of MOR07925 is shown in FIG. 4K and SEQ ID NO: 31. The nucleotide sequence of variable light chain of MOR07926 is shown in FIG. 4F and SEQ ID NO: 32. The amino acid sequence of variable light chain of MOR07926 is shown in FIG. 4L and SEQ ID NO: 33.

[0122]

The amino acid sequence of variable heavy chain CDR3 (H-CDR3) of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 is shown in SEQ ID NO: 1. The amino acid sequence of variable heavy chain CDR3 (H-CDR3) of MOR07919 is shown in SEQ ID NO: 4.

[0123]

The amino acid sequence of variable heavy chain CDR2 (H-CDR2) of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 is shown in SEQ ID NO: 2. The amino acid sequence of variable heavy chain CDR2 (H-CDR2) of MOR07919 is shown in SEQ ID NO: 5.

[0124]

The amino acid sequence of variable heavy chain CDR1 (H-CDR1) of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 is shown in SEQ ID NO: 3. The amino acid sequence of variable heavy chain CDR1 (H-CDR1) of MOR07919 is shown in SEQ ID NO: 6.

[0125]

The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07692, is shown in SEQ ID NO: 7. The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07919 is shown in SEQ ID NO: 8. The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07923 is shown in SEQ ID NO: 9. The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07924 is shown in SEQ ID NO: 10. The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07925 is shown in SEQ ID NO: 11 The amino acid sequence of variable light chain CDR3 (L-CDR3) of MOR07926 is shown in SEQ ID NO: 12.

[0126]

The amino acid sequence of variable light chain CDR2 (L-CDR2) of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 is shown in SEQ ID NO: 14. The amino acid sequence of variable light chain CDR2 (L-CDR2) of MOR07919 is shown in SEQ ID NO: 16.

[0127]

The amino acid sequence of variable light chain CDR1 (L-CDR1) of MOR07692, MOR07923, MOR07924, MOR07925 and MOR07926 is shown in SEQ ID NO: 13. The amino acid sequence of variable light chain CDR1 (L-CDR1) of MOR07919 is shown in SEQ ID NO: 15.

[0128]

The nucleotide sequence of heavy chain of MOR07692 is shown in SEQ ID: NO: 50. The amino acid sequence of heavy chain of MOR07692 is shown in SEQ ID NO: 51. The nucleotide sequence of light chain of MOR07692 is shown in SEQ ID: NO: 54. The amino acid sequence of light chain of MOR07692 is shown in SEQ ID NO: 55.

[0129]

The nucleotide sequence of heavy chain of MOR07923 is shown in SEQ ID: NO: 50. The amino acid sequence of heavy chain of MOR07923 is shown in SEQ ID NO: 51. The nucleotide sequence of light chain of MOR07923 is shown in SEQ ID: NO: 56. The amino acid sequence of light chain of MOR07923 is shown in SEQ ID NO: 57.

[0130]

The nucleotide sequence of heavy chain of MOR07924 is shown in SEQ ID: NO: 50. The amino acid sequence of heavy chain of MOR07924 is shown in SEQ ID NO: 51. The nucleotide sequence of light chain of MOR07924 is shown in SEQ ID: NO: 58. The amino acid sequence of light chain of MOR07924 is shown in SEQ ID NO: 59.

[0131]

The nucleotide sequence of heavy chain of MOR07925 is shown in SEQ ID: NO: 50. The amino acid sequence of heavy chain of MOR07925 is shown in SEQ ID NO: 51. The nucleotide sequence of light chain of MOR07925 is shown in SEQ ID: NO: 60. The amino acid sequence of light chain of MOR07925 is shown in SEQ ID NO: 61.

[0132]

The nucleotide sequence of heavy chain of MOR07926 is shown in SEQ ID: NO: 50. The amino acid sequence of heavy chain of MOR07926 is shown in SEQ ID NO: 51. The nucleotide sequence of light chain of MOR07926 is shown in SEQ ID: NO: 62. The amino acid sequence of light chain of MOR07926 is shown in SEQ ID NO: 63

[0133]

The nucleotide sequence of heavy chain of MOR07919 is shown in SEQ ID: NO: 48. The amino acid sequence of heavy chain of MOR07919 is shown in SEQ ID NO: 49. The nucleotide

sequence of light chain of MOR07919 is shown in SEQ ID: NO: 52. The amino acid sequence of light chain of MOR07919 is shown in SEQ ID NO: 53.

Example 5

(BINDING ACTIVITY ANALYSIS BY ELISA)

[0134]

Wells of a 96-well MaxiSorp™ microtiter plate were coated with 1 μg/ml recombinant MST1R-Fc fusion protein (containing 25-571 amino acid sequence of human MST1R, R&D) diluted in PBS. The plate was incubated overnight at 4℃. Next day, the wells were washed once with PBS-FCS buffer (5% FCS in PBS) and then blocked with PBS-FCS buffer for 1 hr at room temperature. After removal of the PBS-FCS buffer 4 μg/ml primary antibody was added to the MST1R-Fc coated wells and incubated for 1 hr at room temperature. After washing once with PBS-FCS buffer, the secondary antibody was added and allowed to incubate for 1hr at room temperature. After washing 3 times with PBS-FCS buffer, substrate of HRP (0.4 mg/ml *o*-Phenylenediamine Dihydrochloride and 0.006% Hydrogen peroxide in substrate buffer (50 mM tri-sodium citrate dehydrate, 100mM di- sodium Hydorogen Phosphate, pH4.5)) was added. After yellow color developed, 1 M HCl was further added to stop reaction. Absorbance at 490 nm was measured in EnVision microtiter plate reader. In FIG. 11, all of the obtained antibodies (MOR07692, MOR07919, MOR07923, MOR07924, MOR07925 and MOR07926) showed binding to 25-571 portion of human MST1R. Each antibody was applicable for immunoprecipitation of non-reduced and non-denatured MST1R, but not for Western blotting to detect reduced and denatured MST1R (data not shown). It indicates that these antibodies recognize native conformation within amino acids residues in SEQ ID NO: 17.

Example 6

(BIOLOGICAL ASSAYS)

(A. Elk1 Luciferase Reporter Gene Assay)

[0135]

Functionality of antibodies was tested via Elk1 luciferase reporter gene assay. The principle of the assay is based on the co-transfection of 293α cells with several vectors. MST1R is integrated into the cell membrane and becomes activated (phosphorylated) to transduce signal to ERK (extracellullar signal-regulated kinase) when it is overexpressed or stimulated with MSP. To test functionality of antibodies, Elk1 luciferase reporter gene assay was established as follows: First we constructed pFR-Luc2CP vector. To construct pFR-Luc2CP, pFR-Luc vector (Stratagene) was digested with *Hind*III, treated with T4 DNA polymerase for blunting, and digested with *Bam*HI to obtain about 140 bp fragment containing the 5 x GAL4 binding element and TATA box. pGL4.12[*luc2CP*] (Promega) was digested with *Eco*ICRI/*Bgl*II, dephosphorylated, and ligated with the above fragment to generate pFR-Luc2CP. Then, 293α cells were transiently co-transfectd with pcDNA-DEST40 MST1R, pcDNA-DEST40, pFA2-Elk1(Stratagene), pFR-Luc2CP and pGL4.74 [hRluc/TK] (Promega) using a Lipofectamine 2000 (Invitrogen) transfection procedure and seeded onto white 96-well cell culture plates. The next day after transfection, the cells were preincubated with the antibodies for 1 hr and then the ligand (human MSP) was added to the wells. After 6 hr incubation, cell lysates were prepared and the firefly luciferase activity (specific signal) and the Renilla luciferase activity (signal for normalization) were measured using the Dual-luciferase reporter assay system (Promega). The firefly/Renilla ratio was calculated to normalize the data of each well. Table 2 shows IC_{50} values in the presence of 100 ng/ml MSP ligand. MOR07692, MOR07919, MOR07923, MOR07924, MOR07925 and MOR07926 showed low IC_{50} value ranging between 4 and 100 ng/ml. As shown in FIG. 12, overexpression of MST1R by itself induced ligand-independent activation of MST1R. MOR07925, MOR07919 and MOR07692 also suppressed this type of activation of MST1R.

[0136]

[Table 2]

Table 2: IC_{50} value of Elk1 luciferase reporter gene assay

Clone ID	Reporter assay IC50 (ng/ml)
MOR07692	4.4
MOR07919	87.6
MOR07923	9
MOR07924	15.7
MOR07925	5.9
MOR07926	11.4

(B. ELISA for Detection of Phosphorylation of MST1R)

[0137]

The change in phosphorylation status of MST1R after treatment with ligand and/or antibody was determined by ELISA system. After overnight incubation of PC3 cells (1 x 10^6) on 6 cm-diameter dishes, cells were washed with PBS, and incubated with 0.1% BSA-RPMI medium. After overnight incubation, cells were treated with 1 μg/ml MOR07692 antibody for 1hr at 37℃, and then stimulated with 200 ng/ml of recombinant MSP (R&D systems) for 0 min to 15 min. Then cell lysates were prepared and phosphorylated forms of MST1R were measured by Human Phospho-MSP R/Ron ELISA system (R&D systems) according to the supplier's instruction. MOR07692 showed complete inhibition of MST1R phosphorylation promoted by addition of MSP ligand as shown in FIG. 13.

(C. Western blotting for activated ERK)

[0138]

The change in phosphorylation status of ERK after treatment with ligand and/or antibody was determined by Western blotting. After overnight cultivation of PC3 cells (2×10^5) on 12 wells plate, cells were washed with PBS, and incubated with 0.1% BSA-RPMI medium. After overnight incubation, cells were treated with 1 μg/ml MOR07692 antibody with or without 1 μg/ml goat affinity purified antibody to human IgG-Fc (Cappel) for 1hr at 37℃. After the incubation, 100 ng/ml of recombinant MSP (R&D systems) was added, and further incubated for 30 min. Then cells were lysed with RIPA buffer containing complete mini (Roche) and phosphatase inhibitor (Nakarai tesque). Lysates were cleared from cellular debris by centrifugation, and protein concentrations were determined using BCA protein assay (PIERCE). Lysates were resuspended in buffer containing β-mercaproethanol and denatured at 99℃ for 5 minutes. Protein (10 μg/lane) was resolved by SDS-PAGE on 5-20% gels. Proteins were blotted onto PVDF membrane (BioRad). Membranes were blocked with Blockace (Yukijirushi), for 1 hr at room temperature and incubated overnight at 4℃ with polyclonal antibodies against ERK or phospho-ERK antibody. After washing, membranes were incubated with secondary anti-rabbit horseradish peroxidase-conjugated antibody (Amersham). Immunoreactive bands were visualized on X-ray films using ECL plus substrate (GE Healthcare). FIG. 14 represented ERK phosphorylation in response to ligand MSP. The increase was almost completely inhibited by the addition of MOR07692 in the presence and absence of cross link antibody to human IgG-Fc.

(D. Cell Proliferation assay)

[0139]

T-47D cells (5000 cells/well) suspended in RPMI medium containing 2% charcoal/dextran-treated FCS (Hyclone) were seeded onto 96-well plates. Cells were incubated with 1 μg/ml antibodies for 1 hr at 37℃, and then stimulated with 100 ng/ml recombinant MSP. After 5 days incubation, cellular ATP was measured by CellTiter-Glo luminescent cell viability assay kit (Promega), according to the supplier's instruction. As shown in FIG. 15, MOR07692,

MOR07923, MOR07924, MOR07925 and MOR07926 clearly suppressed MSP-promoted proliferation of T-47D cells. MOR07919 had a weaker inhibitory activity than other antibodies.

(E. Migration Assay)

[0140]

BxPC-3 cells (5 x 10^4 cells/well) suspended in RPMI medium containing 10% FCS were seeded onto 96-well Oris™ Cell Migration Assay plates (Platypus Technologies, LLC.). After overnight cultivation, the stoppers were removed from test wells and medium was replaced with 2% charcoal/dextran-treated FCS (Hyclone). Cells were incubated with 10 μg/ml antibodies for 1 hr at 37℃, and then stimulated with 300 ng/ml recombinant MSP. After 24 hr incubation, migrated cells were observed using bright field microscopy (Nikon) and then their images were analyzed by Image J software to calculate cell-free area. As shown in FIG 16, MOR07919, MOR07692 and MOR07925 clearly suppressed MSP-promoted cell migration of BxPC-3 cells. MOR07692 and MOR07925 had stronger inhibitory activity compared to MOR07919.

(F. Internalization assay)

[0141]

In order to evaluate the ability of antibodies to internalize, Hum-ZAP secondary conjugate (affinity-purified goat anti-human IgG-saporin provided by ADVANCED TARGETING SYSTEMS) was used as the secondary antibody to cause protein synthesis inhibition and, ultimately, cell death after internalization into cells. PC3 cells (2000 cells/well) suspended in RPMI medium containing 10% FCS were seeded onto 96-well flat clear bottom white culture plates. The next day, the cells were preincubated with antibodies for 1 hr at 4℃. After removal of the medium containing the antibodies, 0.5 μg/ml Hum-ZAP secondary conjugate was added to the wells. The plates were incubated for 1 hr at 4℃ and then for 3 days at 37℃. The cellular ATP was measured as readout for cell viability by CellTiter-Glo luminescent cell viability assay kit (Promega), according to the supplier's instruction. As shown in FIG. 17, viability of PC3 cells was greatly reduced by the treatment with MOR07692, MOR07919, MOR07923, MOR07924, MOR07925 and MOR07926, suggesting the potential of these antibodies to internalize.

[0142]

The contents of all patents, patent applications, published PCT applications and articles, books, references, reference manuals and abstracts cited herein are hereby incorporated by reference in their entirety to more fully describe the state of the art to which the invention pertains.

[0143]

As various changes can be made in the above-described subject matter without departing from the scope and spirit of the present invention, it is intended that all subject matter contained in the above description, or defined in the appended claims, be interpreted as descriptive and illustrative of the present invention. Many modifications and variations of the present invention are possible in light of the above teachings.

CLAIMS

[Claim 1]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof inhibits ligand -dependent and/or -independent phosphorylation of MST1R.

[Claim 2]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof inhibits ligand -dependent and -independent phosphorylation of MST1R.

[Claim 3]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof inhibits ligand -dependent and/or -independent phosphorylation of MST1R, in addition to inhibiting phosphorylation of ERK and/or Akt.

[Claim 4]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof inhibits ligand -dependent

and -independent phosphorylation of MST1R, in addition to inhibiting phosphorylation of ERK and/or Akt.

[Claim 5]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof has an affinity against said partial peptide of MST1R as a K_D of less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 0.5 nM or less than about 0.1 nM as determined by surface plasmon resonance.

[Claim 6]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof has an affinity against said partial peptide of MST1R as a K_D less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 0.5 nM or less than 0.1 nM as determined by Solution Equilibrium Titration.

[Claim 7]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof suppresses MSP-promoted cell proliferation of tumor cells that express MST1R.

[Claim 8]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of

SEQ ID NO: 17, wherein said antibody or functional fragment thereof suppresses MSP-promoted cell migration of tumor cells that express MST1R.

[Claim 9]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof internalizes MST1R.

[Claim 10]

An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17, wherein said antibody or functional fragment thereof is cross-reactive with human and at least one other species.

[Claim 11]

The isolated human or humanized antibody or functional fragment thereof according to claim 10, wherein said other species is a mouse or a monkey.

[Claim 12]

The isolated antigen-binding region of an antibody or functional fragment thereof according to any one of claims 1 to 11.

[Claim 13]

The isolated antigen-binding region according to claim 12, which comprises an H-CDR3 region having the amino acid sequence of SEQ ID NO: 1 or 4.

[Claim 14]

The isolated antigen-binding region according to claim 13, further comprising an H-CDR2 region having the amino acid sequence of SEQ ID NO: 2 or 5.

[Claim 15]

The isolated antigen-binding region according to claim 14, further comprising an H-CDR1 region having the amino acid sequence of SEQ ID NO: 3 or 6.

[Claim 16]

The isolated antigen-binding region according to claim 15, wherein (i) the H-CDR3 region having the amino acid sequence of SEQ ID NO: 1, the H-CDR2 region having the amino acid sequence of SEQ ID NO: 2 and the H-CDR1 region having the amino acid sequence of SEQ ID NO: 3; or (ii) the H-CDR3 region having the amino acid sequence of SEQ ID NO: 4, the H-CDR2 region having the amino acid sequence of SEQ ID NO: 5 and the H-CDR1 region having the amino acid sequence of SEQ ID NO: 6.

[Claim 17]

The isolated antigen-binding region according to claim 12, comprising a variable heavy chain having the amino acid sequence of SEQ ID NO: 19 or 21.

[Claim 18]

The isolated antigen-binding region according to claim 12, comprising an L-CDR3 region having the amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 8, 9, 10, 11 and 12.

[Claim 19]

The isolated antigen-binding region according to claim 18, comprising an L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 or 15.

[Claim 20]

The isolated antigen-binding region according to claim 19, comprising an L-CDR2 region having the amino acid sequence of SEQ ID NO: 14 or 16.

[Claim 21]

The isolated antigen-binding region according to claim 20, wherein the antigen-binding region is (i) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 7, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 14; (ii) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 8, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 15 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 16; (iii) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 9, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 14; (iv) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 10, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 14; (v) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 11, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 14; or (vi) the L-CDR3 region having the amino acid sequence of SEQ ID NO: 12, the L-CDR1 region having the amino acid sequence of SEQ ID NO: 13 and the L-CDR2 region having the amino acid sequence of SEQ ID NO: 14.

[Claim 22]

The isolated antigen-binding region according to claim 12, comprising a variable light chain having the amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 25, 27, 29, 31 and 33.

[Claim 23]

The isolated antigen-binding region according to claim 12, comprising a heavy chain amino acid sequence of (i) SEQ ID NO: 49 or 51; or (ii) a sequence having at least 80 percent sequence identity in the CDR regions with the CDR regions of SEQ ID 49 or 51.

[Claim 24]

The isolated antigen-binding region according to claim 12, comprising a light chain amino acid sequence of (i) SEQ ID NO: 53, 55, 57, 59, 61 or 63; or (ii) a sequence having at least 80 percent sequence identity in the CDR regions with the CDR regions of SEQ ID NO: 53, 55, 57, 59, 61 or 63.

[Claim 25]

The isolated antibody to according to any one of claims 1 to 11, wherein the isolated antibody is an IgG.

[Claim 26]

The isolated antibody to according to claim 25, wherein the isolated antibody is an IgG1.

[Claim 27]

The isolated antibody or functional fragment thereof according to any one of claims 1 to 13, wherein the isolated antibody or functional fragment thereof comprises a variable heavy chain of SEQ ID NO: 19 or 21.

[Claim 28]

The isolated antibody or functional fragment thereof according to any one of claims 1 to 11, wherein the isolated antibody or functional fragment thereof comprises a variable light chain having the amino acid sequence of SEQ ID NO: 23, 25, 27, 29, 31 or 33.

[Claim 29]

The antibody or functional fragment thereof according to any one of claims 1 to 11, comprising an H-CDR3 region having the amino acid sequence of SEQ ID NO: 1 or 4.

[Claim 30]

The antibody or functional fragment thereof according to claim 29, comprising an H-CDR2 region having the amino acid sequence of SEQ ID NO: 2 or 5.

[Claim 31]

The antibody or functional fragment thereof according to claim 30, comprising an H-CDR1 region having the amino acid sequence of SEQ ID NO: 3 or 6.

[Claim 32]

The isolated antibody or functional fragment thereof according to any one of claims 1 to 11, wherein said antigen-binding region comprises an L-CDR3 region of SEQ ID NO: 7, 8, 9, 10, 11 or 12.

[Claim 33]

The isolated antibody or functional fragment thereof according to claim 32, wherein said antigen-binding region comprises an L-CDR1 region of SEQ ID NO: 13 or 15.

[Claim 34]

The isolated antibody or functional fragment thereof according to claim 33, wherein said antigen-binding region further comprises an L-CDR2 region of SEQ ID NO: 14 or 16.

[Claim 35]

The isolated antibody or functional fragment thereof according to any one of claims 1 to 11, comprising a heavy chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 49 and 51; and (ii) a sequence having at least 80 percent sequence identity in the CDR regions with the CDR regions of SEQ ID NOs: 49 and 51.

[Claim 36]

The isolated antibody or functional fragment thereof according to any one of claims 1 to 11, which comprises a light chain amino acid sequence selected from the group consisting of (i) SEQ ID NOs: 53, 55, 57, 59, 61 and 63; and (ii) a sequence having at least 80 percent sequence identity in the CDR regions with the CDR regions of SEQ ID NOs: 53, 55, 57, 59, 61 and 63.

[Claim 37]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 49 and a light chain having an amino acid sequence of SEQ ID NO: 53.

[Claim 38]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 55.

[Claim 39]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 57.

[Claim 40]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 59.

[Claim 41]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 61.

[Claim 42]

An antibody having a heavy chain having an amino acid sequence of SEQ ID NO: 51 and a light chain having an amino acid sequence of SEQ ID NO: 63.

[Claim 43]

The isolated functional fragment according to any one of claims 1 to 11, which is a Fab or scFv antibody fragment.

[Claim 44]

A variable heavy chain of an isolated antibody or functional fragment thereof that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 18 or 20, or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 18 or 20, wherein said antibody or functional fragment thereof is specific for an epitope of MST1R.

[Claim 45]

A variable light chain of an isolated antibody or functional fragment thereof that is encoded by (i) a nucleic acid sequence comprising selected from the group consisting of SEQ ID NOs: 22, 24, 26, 28, 30 and 32, or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of selected from the group consisting of SEQ ID NOs: 22, 24, 26, 28, 30 and 32, wherein said antibody or functional fragment thereof is specific for an epitope of MST1R.

[Claim 46]

An isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody or functional fragment thereof that is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17.

[Claim 47]

A nucleic acid sequence encoding a variable heavy chain of an isolated antibody or functional fragment thereof, comprising (i) a sequence of SEQ ID NO: 18 or 20 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 18 or 20, wherein said antibody or functional fragment thereof is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17.

[Claim 48]

A nucleic acid sequence encoding a variable light chain of an isolated antibody or functional fragment thereof, comprising (i) a sequence selected from the group consisting of SEQ ID NOs: 22, 24, 26, 28, 30 and 32 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand selected from the group consisting of SEQ ID NOs: 22, 24, 26, 28, 30 and 32, wherein said antibody or functional fragment thereof is specific for a partial peptide of MST1R, having an amino acid sequence of SEQ ID NO: 17.

[Claim 49]

A vector comprising the nucleic acid sequence according to any one of claims 46 to 48.

[Claim 50]

An isolated cell comprising the vector according to claim 49.

[Claim 51]

The isolated cell according to claim 50, wherein said cell is bacterial.

[Claim 52]

The isolated cell according to claim 50, wherein said cell is mammalian.

[Claim 53]

A pharmaceutical composition comprising an antibody or functional fragment according to any one of claims 1 to 11 or 25 to 45, and a pharmaceutically acceptable carrier or excipient thereof.

[Claim 54]

A method for treating a disorder or condition associated with the undesired presence of MST1R, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition according to claim 53.

[Claim 55]

The method according to claim 54, wherein said disorder or condition is caused by MST1R phosphorylation.

[Claim 56]

The method according to claim 55, wherein said disorder or condition is a malignant tumor and/or neoplasm.

[Claim 57]

The method according to claim 56, wherein said disorder or condition is: breast cancer, lung cancer, colon cancer, bladder cancer, skin cancer, pancreatic cancer, glioma, lymphoma, prostate cancer, thyroid cancer, ovary cancer, gastric cancer, liver cancer or stomach cancer.

[Claim 58]

A method for targeting MST1R+ cells in a subject or a cell sample, comprising the step of contacting said MST1R+ cells and an antibody or functional fragment thereof according to any one of claims 1 to 11 or 25 to 45.

[Claim 59]

A human antibody according to any one of claims 1 to 11 or 25 to 45, wherein the human antibody is a synthetic human antibody.

[Claim 60]

The isolated antigen-binding region according to any one of claims 17 or 22 to 24, wherein said sequence identity is at least 80%.

[Claim 61]

The isolated antibody or functional fragment thereof according to any one of claims 35 to 42, wherein said sequence identity is at least 80%.

[Claim 62]

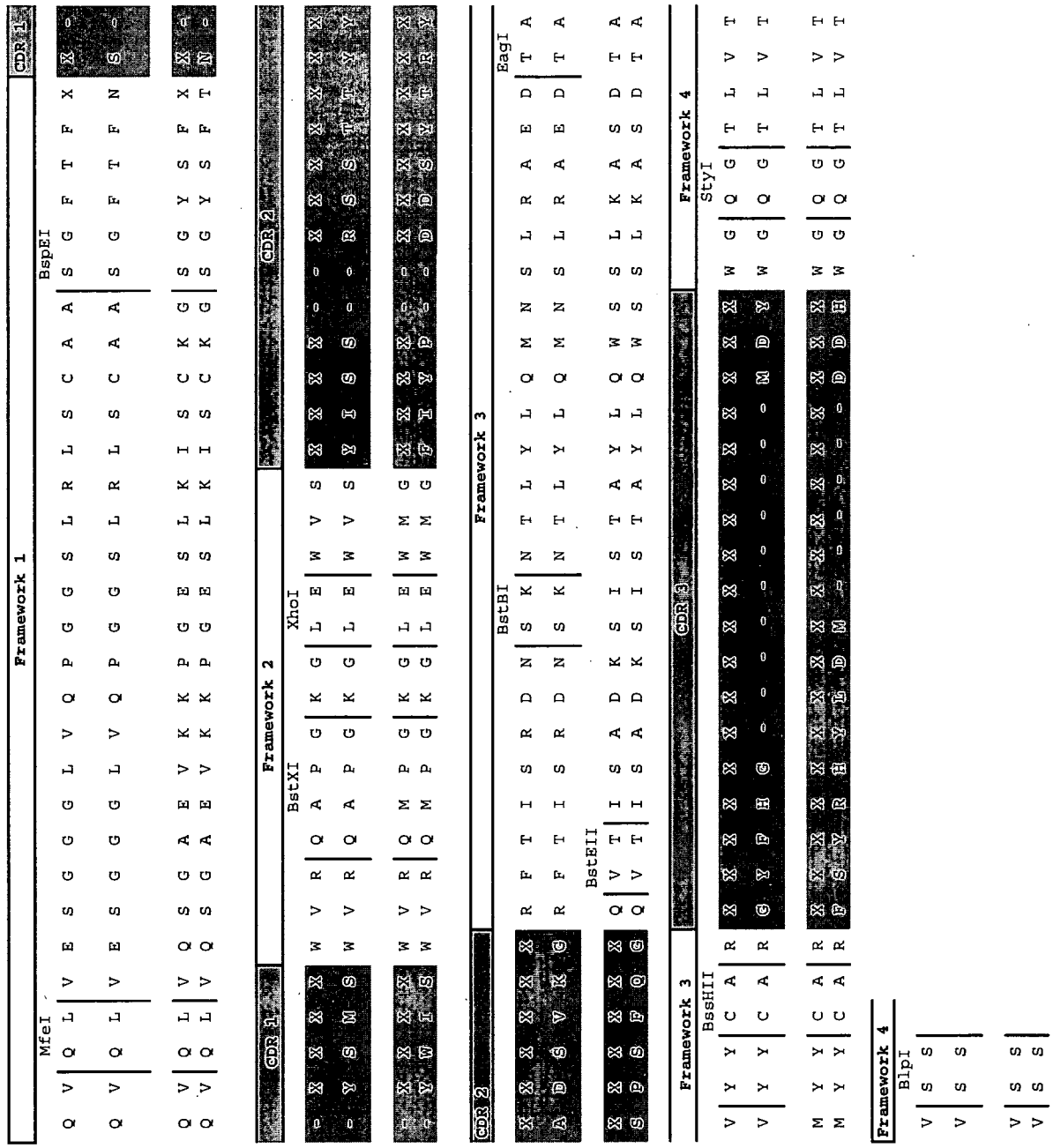
A method for producing an antibody by using the vector of claim 49.

[Claim 63]

A method for producing an antibody by culturing the isolated cell of any one of claims 50 to 52.

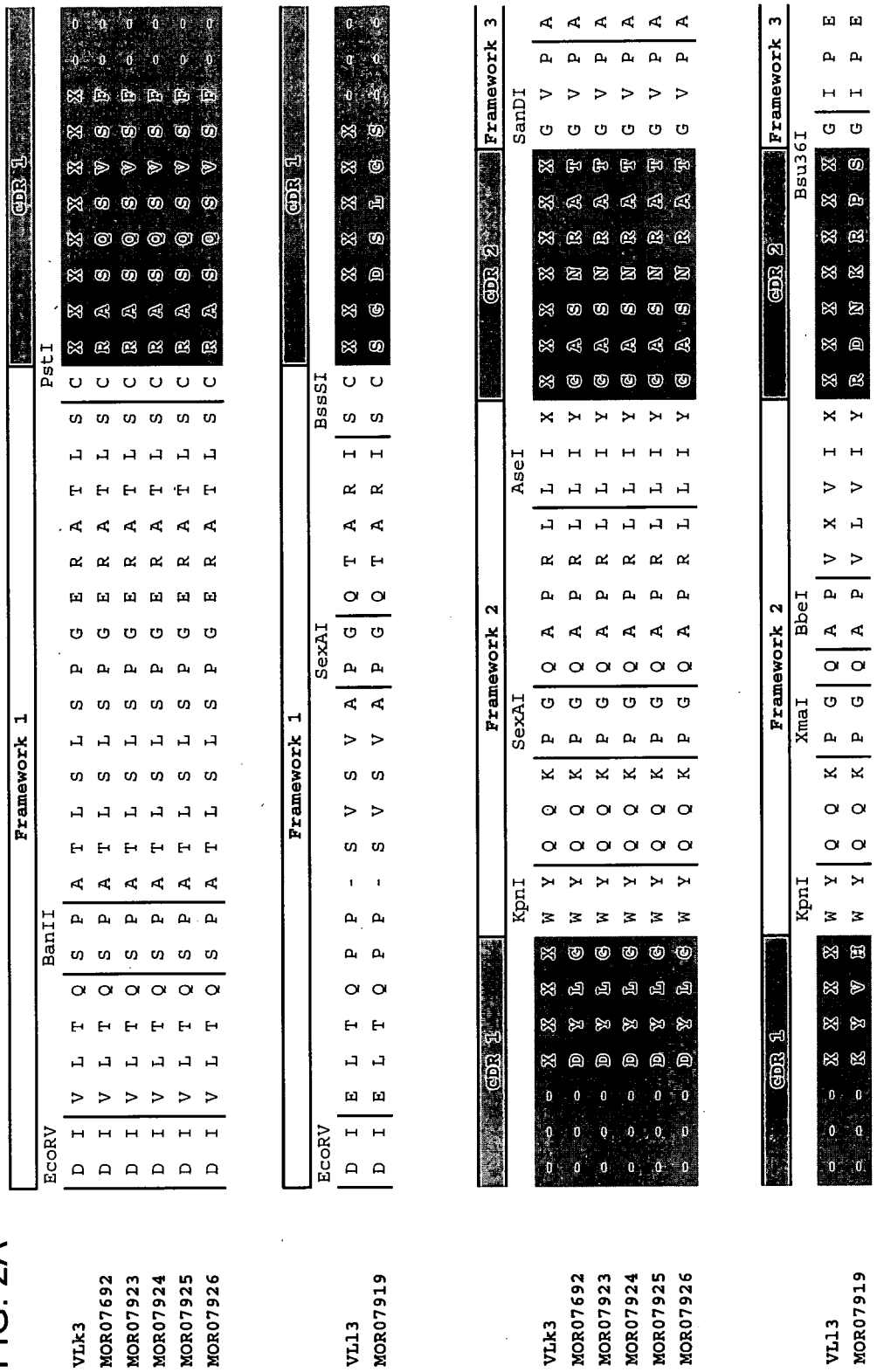
[Fig. 1]

FIG. 1


Framework 1
CDR 1
Framework 2
CDR 2
Framework 3
Framework 4
MfeI
BspEI
BstXI
XhoI
BstBI
EagI
BstEII
BsshII
StyI
BlpI
VH3
MOR07692, 7923, 7924, 7925, 7926
VH5
MOR07919

[Fig. 2A]

FIG. 2A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CDR 1
EcoRV
BanII
PstI
VLk3
MOR07692
MOR07923
MOR07924
MOR07925
MOR07926
VL13
MOR07919
BssSI
SexAI
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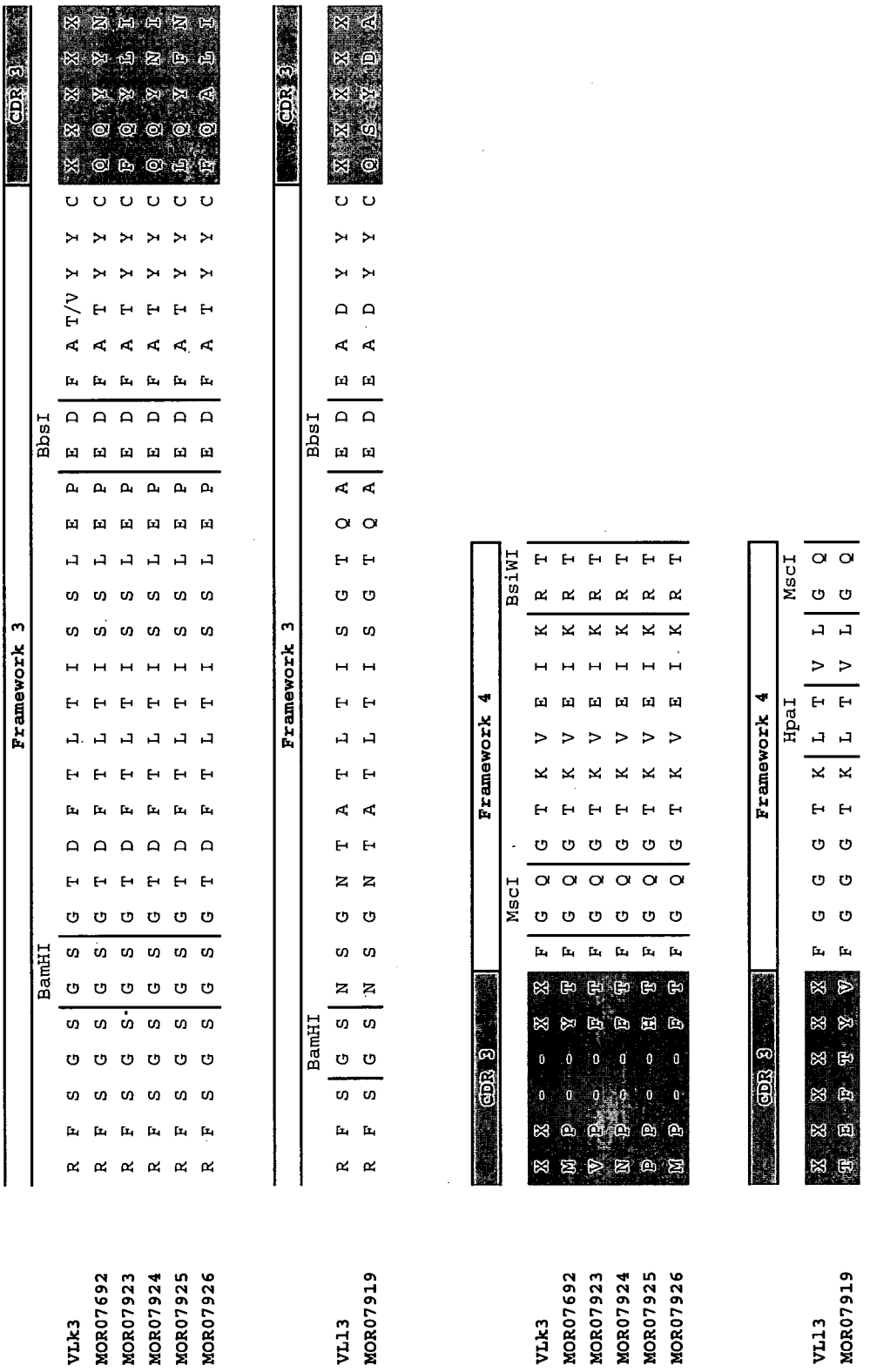
Framework 2
Framework 3
KpnI
SexAI
AseI
SanDI
XmaI
BbeI
Bsu36I

[Fig. 2B]


Framework 3
CDR 3
BamHI
BbsI
VLk3
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MOR07923
MOR07924
MOR07925
MOR07926
VL13
MOR07919
Framework 4
MscI
BsiWI
HpaI

FIG. 2B

[Fig. 3A]

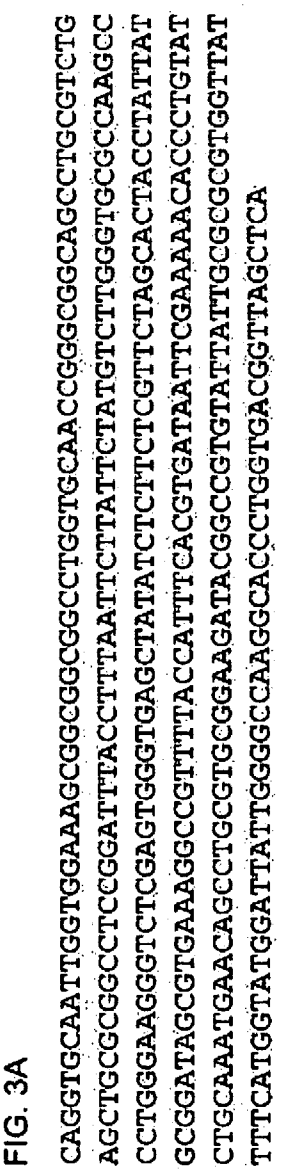


FIG. 3A
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTG
AGCTGCCGCGGCGCCTCCGGATTTACCTTTAATTCTTATTCTATGTCTTGGGTGCGCCAAGCC
CCTGGGAAGGGTCTCGAGTGGGTGAGCTATATCTCTTCTCGTTCTAGCACTACCTATTAT
GCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTAT
CTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGTGGTTAT
TTTCATGGTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

[Fig. 3B]

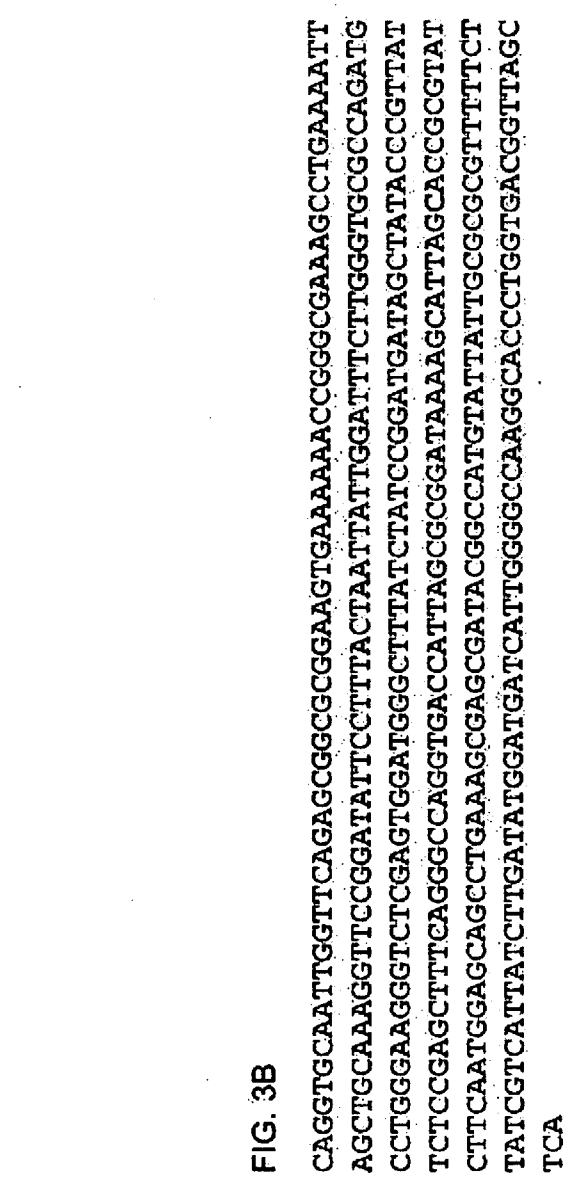


FIG. 3B
CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATT
AGCTGCAAAGGTTCCGGATATTCCTTTACTAATTATTGGATTTCTTGGGTGCGCCAGATG
CCTGGGAAGGGTCTCGAGTGGATGGGCTTTATCTATCCGGATGATAGCTATACCCGTTAT
TCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTAT
CTTCAATGGAGCAGCCTGAAAGCGATACGGCCATGTATTATTGCGCGCGTTTTTCT
TATCGTCATTATCTTGATATGGATGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGC
TCA

[Fig. 3C]

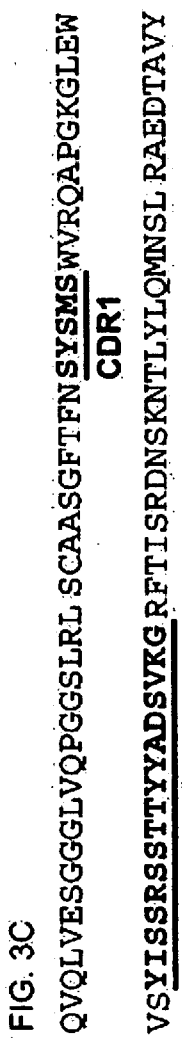


FIG. 3C
QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYSMSWVRQAPGKGLEW
CDR1
VSYISSRSSTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
CDR2
YCARGYFHGMDYWGQGTLVTVSS
CDR3

[Fig. 3D]

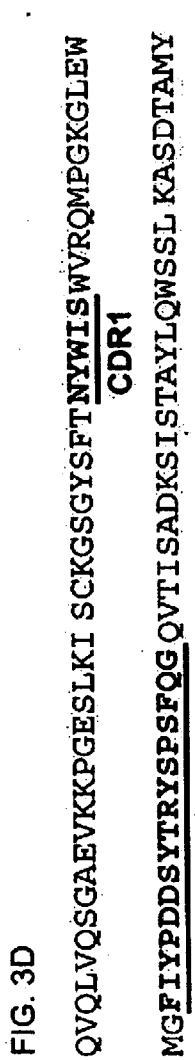


FIG. 3D
QVQLVQSGAEVKKPGESLKI SCKGSGYSFTNYWISWVRQMPGKGLEW
CDR1
MGFIYPDDSYTRYSPSFQG QVTISADKSISTAYLQWSSL KASDTAMY
CDR2
YCARFSYRHYLDMDDH WGQGTLVTVSS
CDR3

[Fig. 4A]

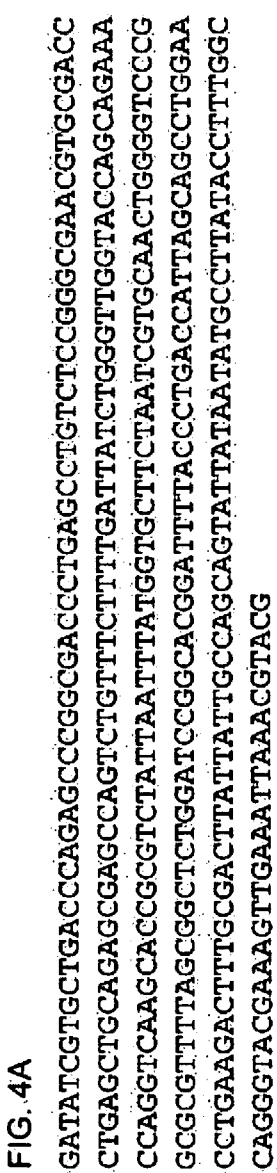
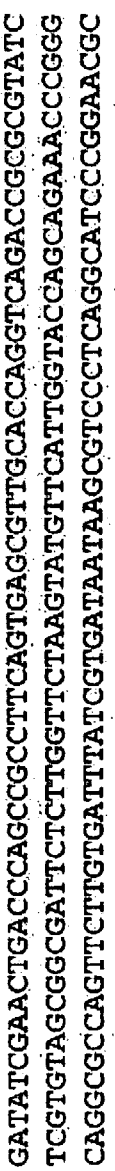


FIG. 4A
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACC
CTGAGCTGCAGAGCGAGCCAGTCTGTTTCTTTTTGATTATCTGGGTTGGTACCAGCAGAAA
CCAGGTCAAGCACCGCGTCTATTAATTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCG
GCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAA
CCTGAAGACTTTGCGACTTATTATTGCCAGCAGTATTATAATATGCCTTATACCTTTGGC
CAGGGTACGAAAGTTGAAATTAAACGTACG

[Fig. 4B]

FIG. 4B


GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATC
TCGTGTAGCGGCGATTCTCTTGGTTCTAAGTATGTTCATTGGTACCAGCAGAAACCCGGG
CAGGCGCCAGTTCTTGTGATTTATCGTGATAATAAGCGTCCCTCAGGCATCCCGGAACGC
TTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAA
GACGAAGCGGATTATTATTGCCAGTCTTATGATGCTACTGAGTTTACTTATGTGTTTGGC
GGCGGCACGAAGTTAACCGTTCTTGGCCAG

[Fig. 4C]

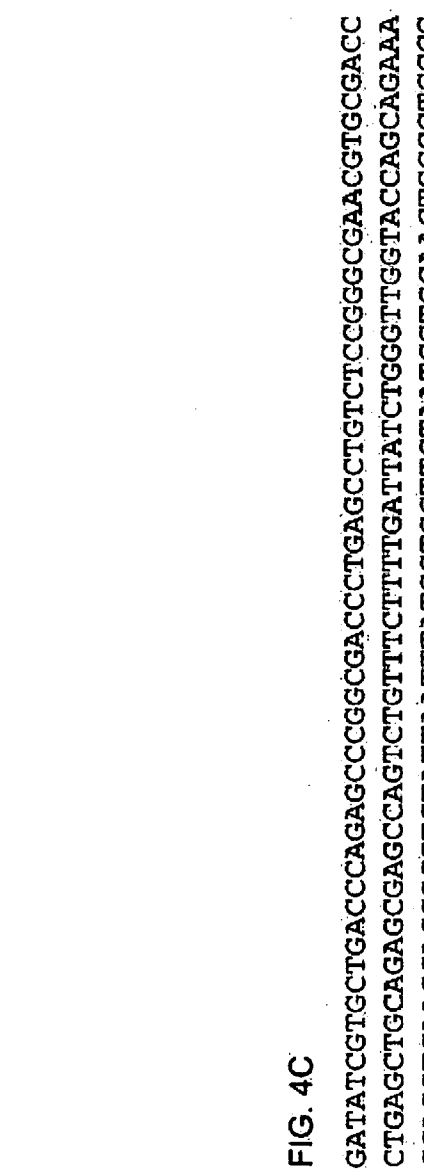
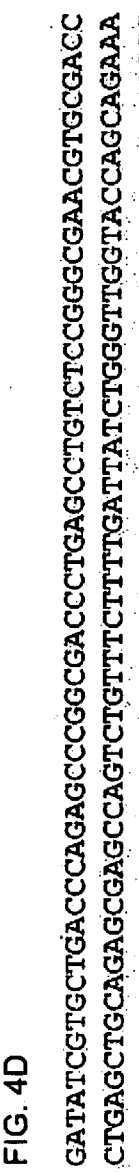


FIG. 4C
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACC
CTGAGCTGCAGAGCGAGCCAGTCTGTTTCTTTTTGATTATCTGGGTTGGTACCAGCAGAAA
CCAGGTCAAGCACCGCGTCTATTTAATTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCG
GCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAA
CCTGAAGACTTTGCGACCTATTATTGCTTTCAGTATCTTATTGTTCCTTTTACCTTTGGC
CAGGGTACGAAAGTTGAAATTAAACGTACG

[Fig. 4D]

FIG. 4D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GCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAA
CCTGAAGACTTTGCGACCTATTATTGCCAGCAGTATAATATTAATCCTTTTACCTTTGGC
CAGGGTACGAAAGTTGAAATTAAACGTACG

[Fig. 4E]

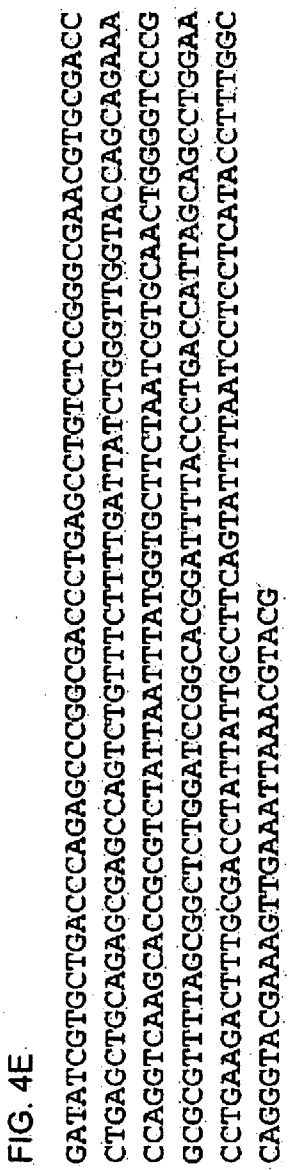
FIG. 4E
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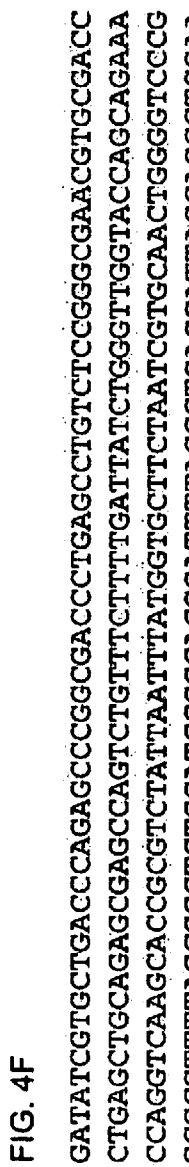
CTGAGCTGCAGAGCGAGCCAGTCTGTTTCTTTTGATTATCTGGGTTGGTACCAGCAGAAA
CCAGGTCAAGCACCGCGTCTATTAATTTATGGTGCTTCTAATCGTGCAACTGGGGTCCCG
GCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAA
CCTGAAGACTTTGCGACCTATTATTGCCTTCAGTATTTTAATCCTCCTCATACCTTTGGC
CAGGGTACGAAAGTTGAAATTAAACGTACG

[Fig. 4F]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GCGCGTTTTAGCGGCTCTGGATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAA
CCTGAAGACTTTGCGACCTATTATTGCTTTTCAGGCTCTTATTATGCCTTTTACCTTTGGC
CAGGGTACGAAAGTTGAAATTAAACGTACG

FIG. 4F

[Fig. 4G]

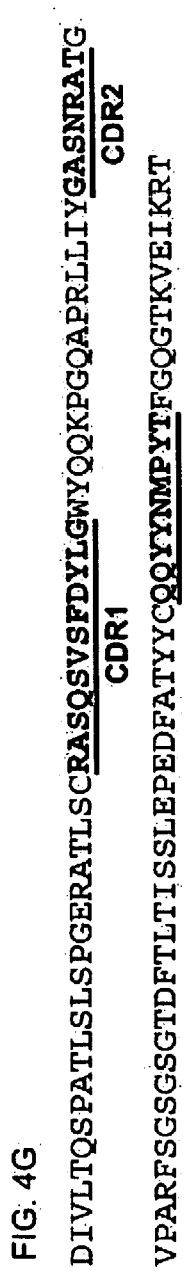


FIG. 4G
DIVLTQSPATLSLSPGERATLSCRASQSVSFDYLGWYQQKPGQAPRLLIYGASNRATG
CDR1
CDR2
VPARFSGSGSGTDFTLTISSLEPEDFATYYCQQYYNMPYTFGQGTKVEIKRT
CDR3

[Fig. 4H]

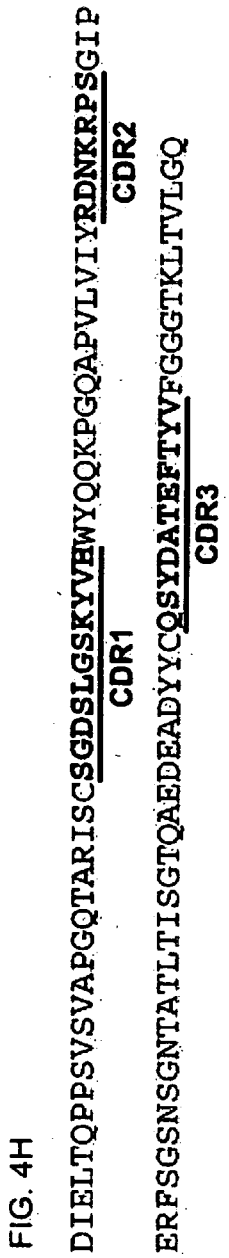


FIG. 4H
DIELTQPPSVSVAPGQTARISCSGDSLGSKYVHWYQQKPGQAPVLVIYRDNKRPSGIP
CDR1
CDR2
ERFSGSNSGNTATLTISGTQAEDEADYYCQSYDATEFTYVFGGGTKLTVLGQ
CDR3

[Fig. 4I]

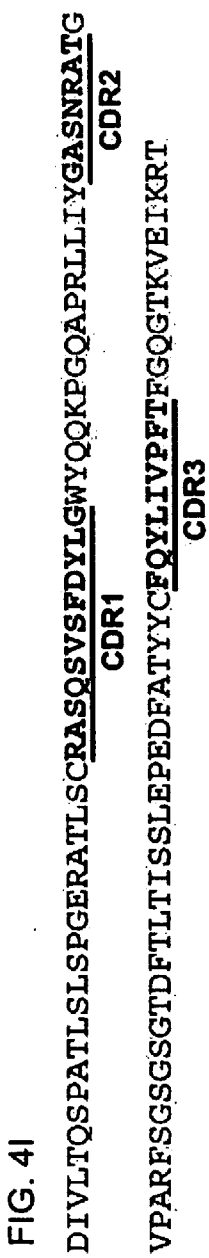


FIG. 4I
DIVLTQSPATLSLSPGERATLSCRASQSVSFDYLGWYQQKPGQAPRLLIYGASNRATG
CDR1
CDR2
VPARFSGSGSGTDFTLTISSLEPEDFATYYCFQYLIVPFTFGQGTKVEIKRT
CDR3

[Fig. 4J]

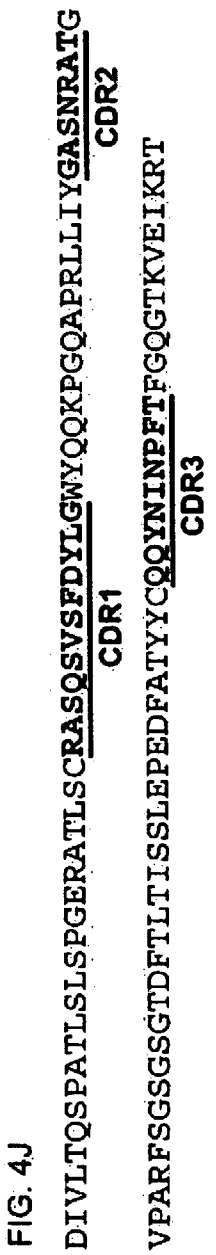
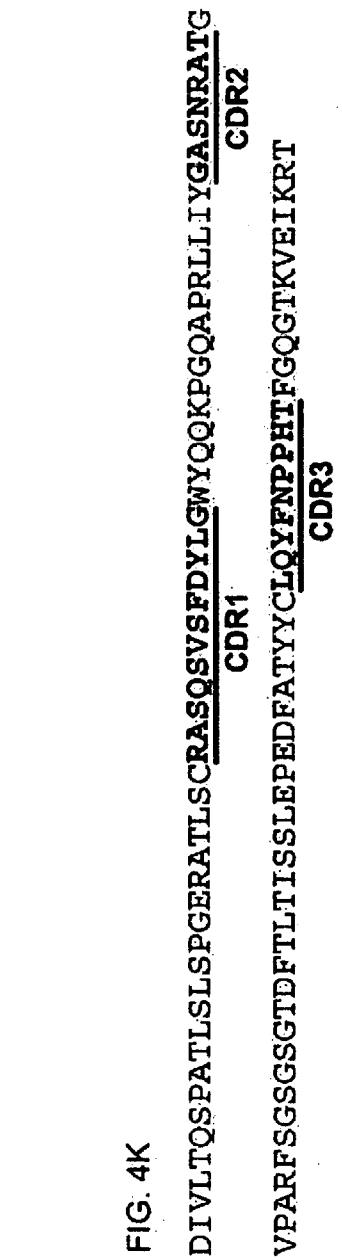


FIG. 4J
DIVLTQSPATLSLSPGERATLSCRASQSVSFDYLGWYQQKPGQAPRLLIYGASNRATG
CDR1
CDR2
VPARFSGSGSGTDFTLTISSLEPEDFATYYCQQYNINPFTFGQGTKVEIKRT
CDR3

[Fig. 4K]

FIG. 4K


DIVLTQSPATLSLSPGERATLSCRASQSVSFDYLGWYQQKPGQAPRLLIYGASNRATG
CDR1
CDR2
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CDR3

[Fig. 4L]

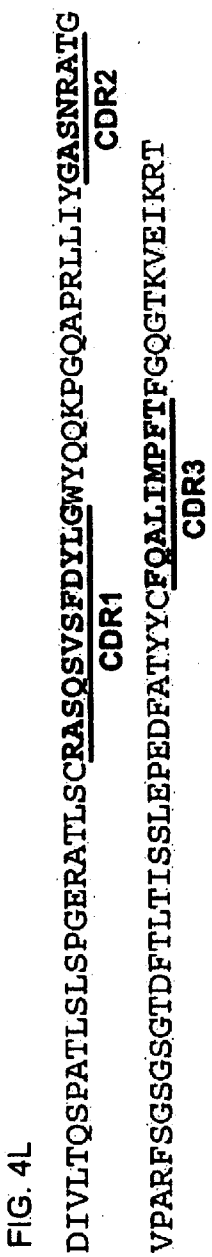
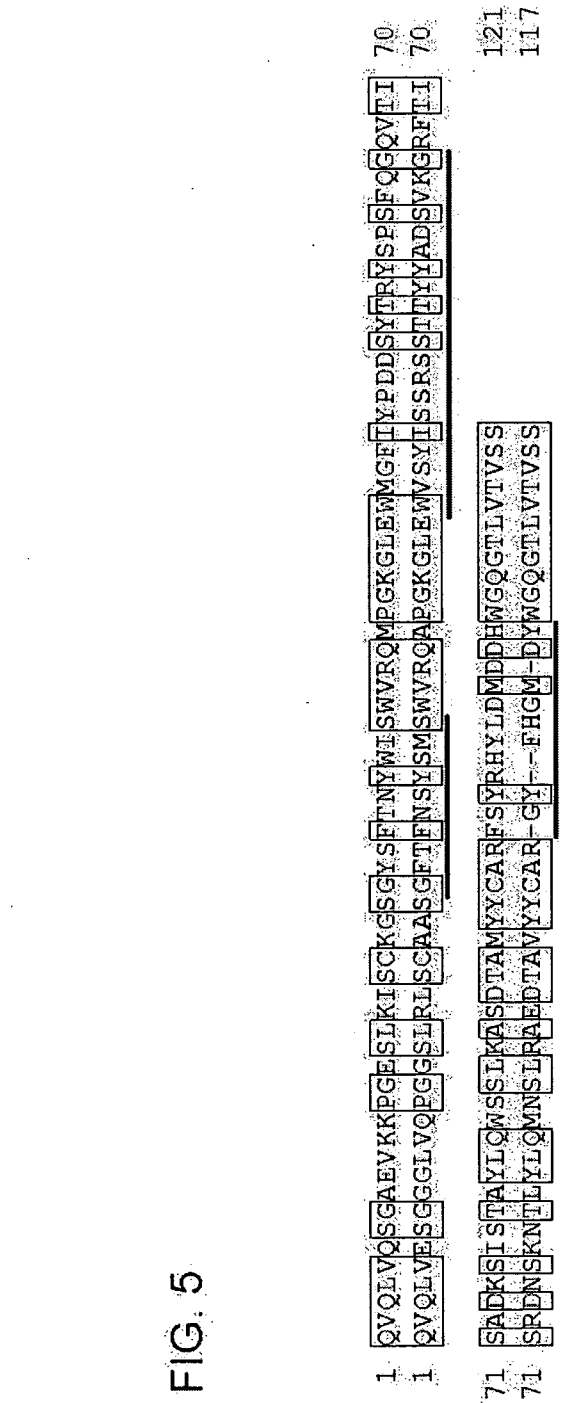


FIG. 4L
DIVLTQSPATLSLSPGERATLSCRASQSVSFDYLGWYQQKPGQAPRLLIYGASNRATG
CDR1
CDR2
VPARFSGSGSGTDFTLTISSLEPEDFATYYCFQALIMPFTFGQGTKVEIKRT
CDR3

[Fig. 5]

FIG. 5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1 QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYSMSWVRQAPGKGLEWVSYISSRSSTIYYADSVKGRFTI 70
71 SADKSISTAYLQWSSLKASDTAMYYCARFSYRHYLDMDDHWGQGTLVTVSS 121
71 SRDNSKNTLYLQMNSLRAEDTAVYYCAR-GY--FHGM-DYWGQGTLVTVSS 117

[Fig. 6]

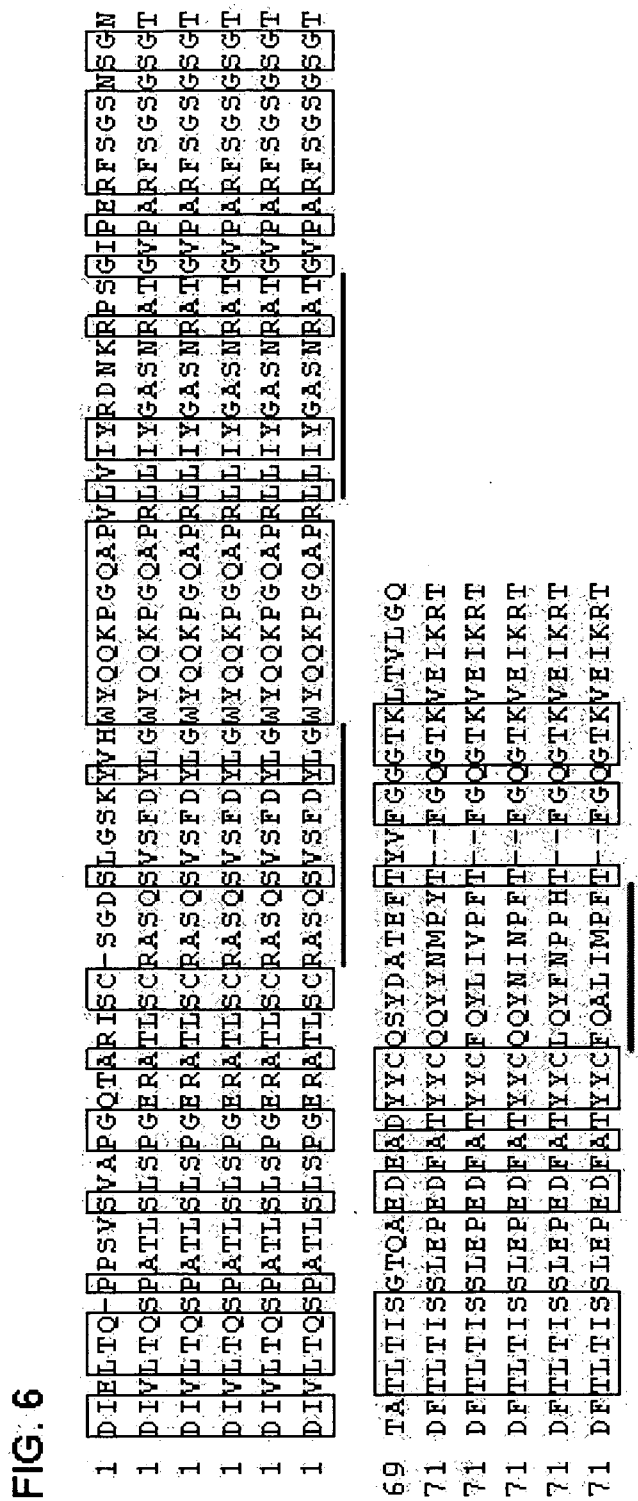
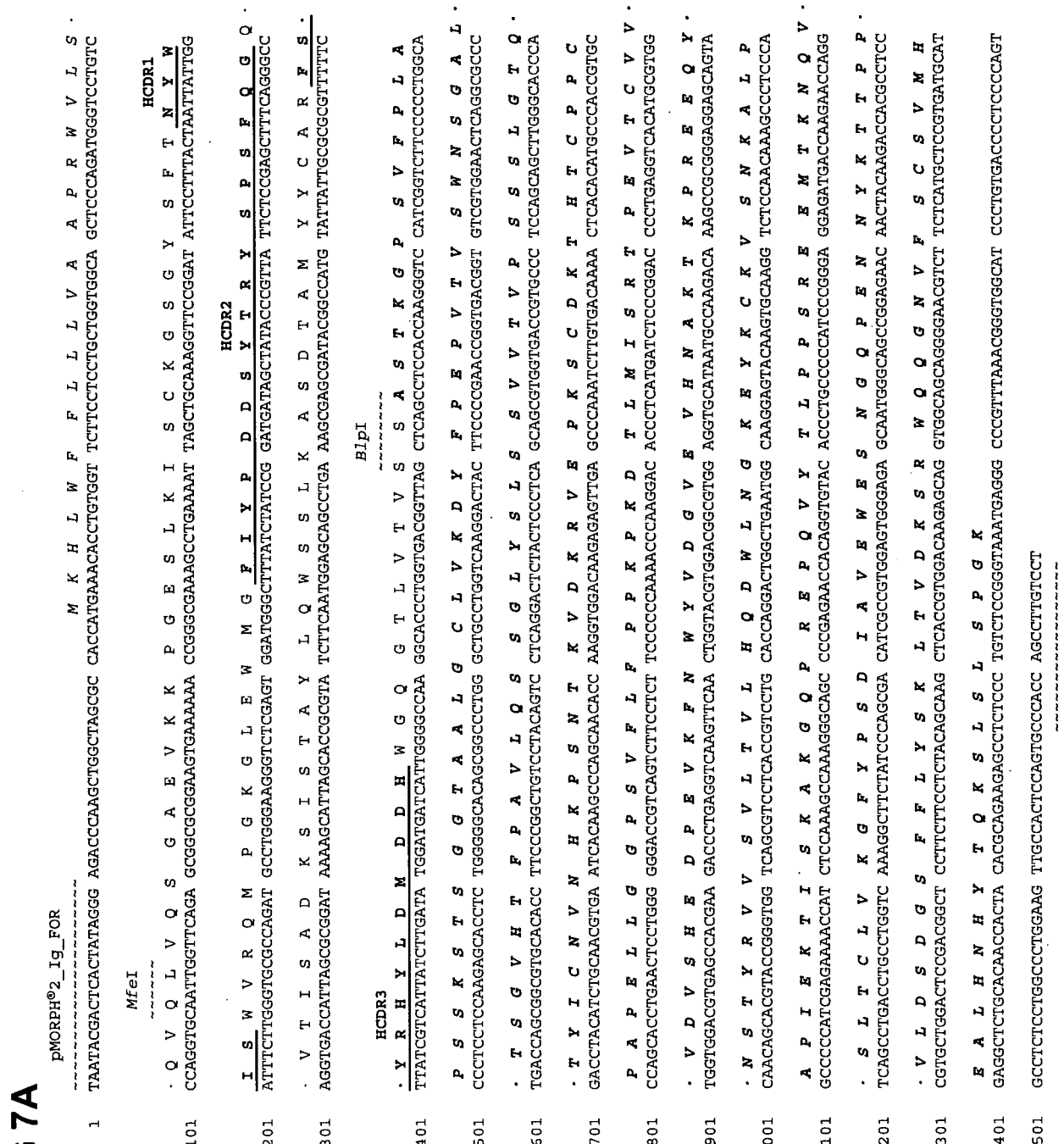


FIG. 6

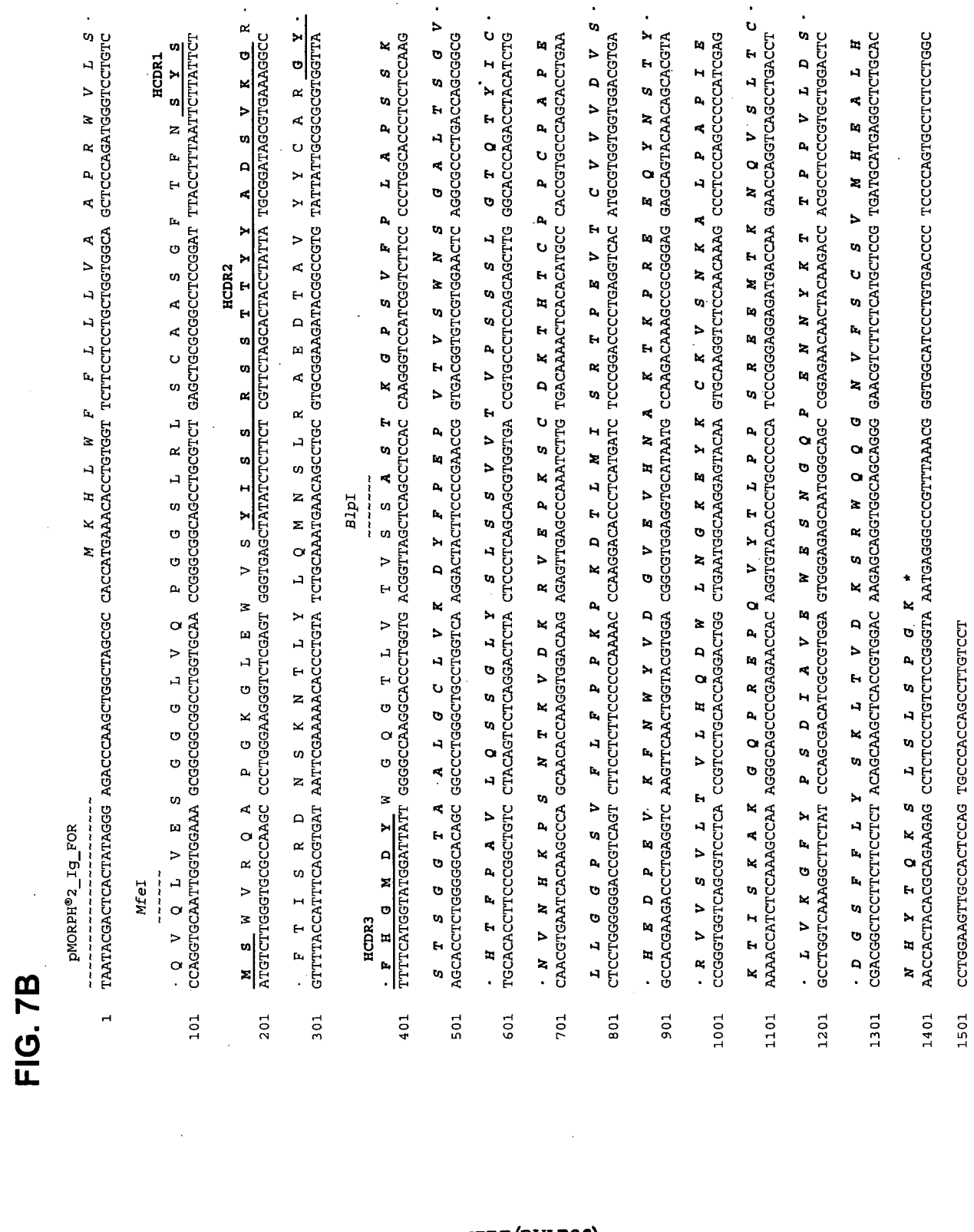
[Fig. 7A]

FIG 7A



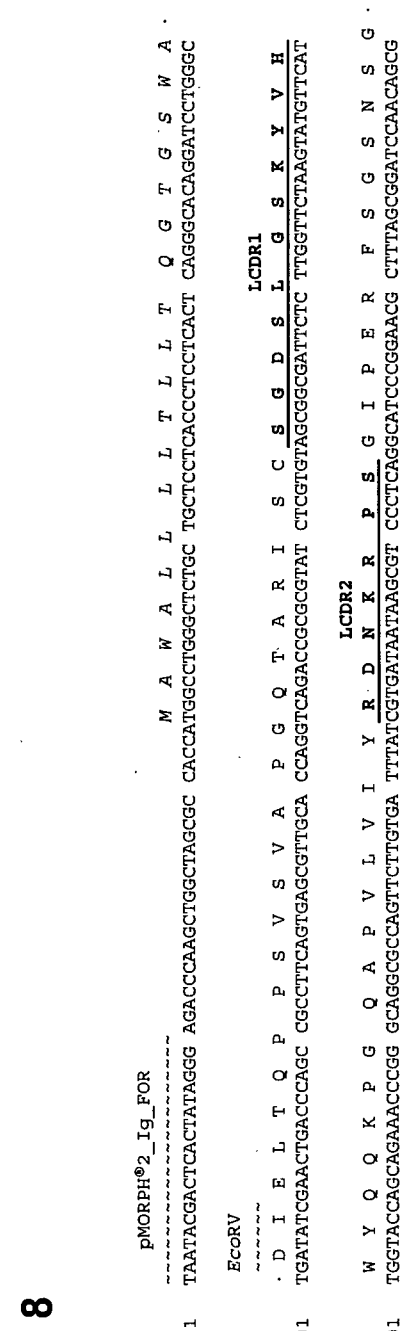
[Fig. 7B]

FIG. 7B



[Fig. 8]

FIG. 8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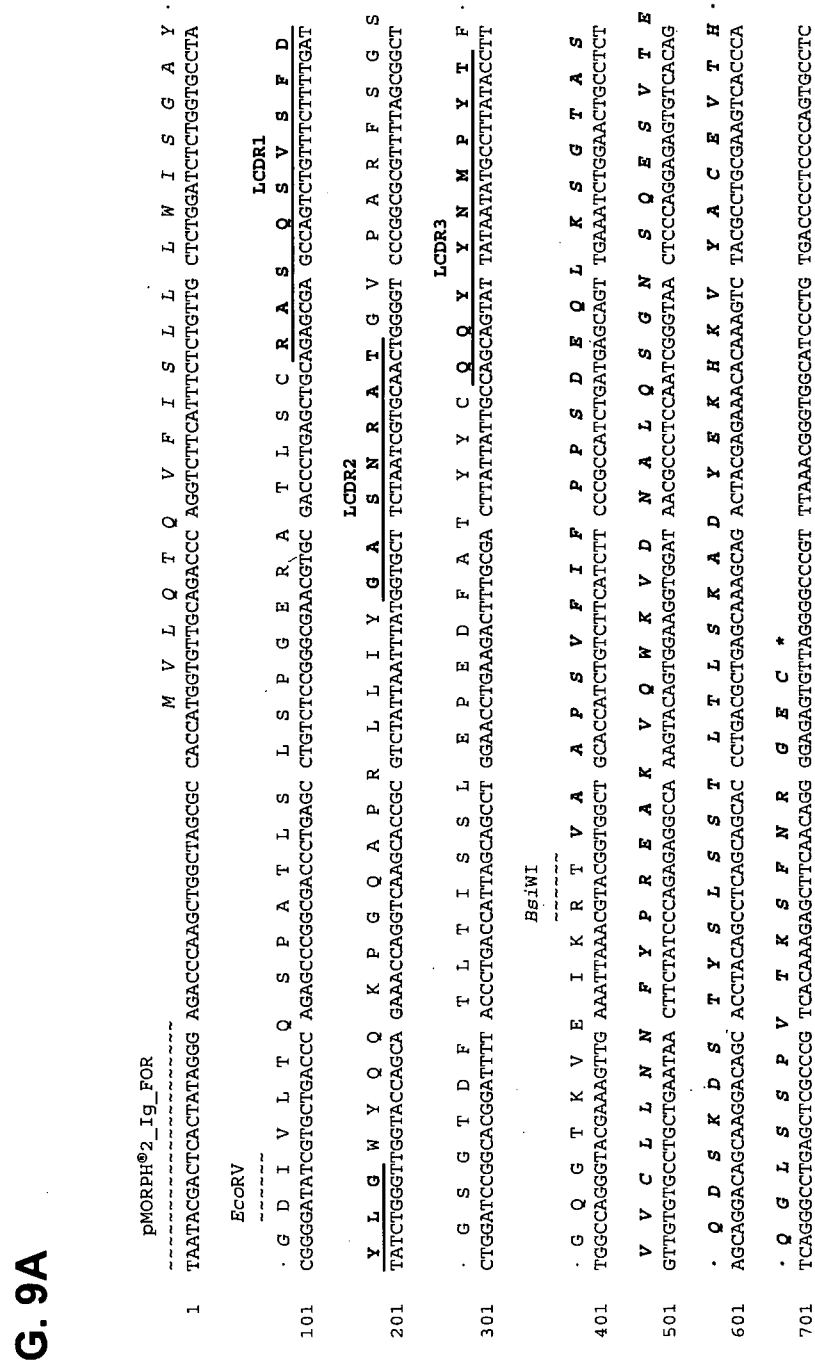
EcoRV
LCDR1
D I E L T Q P P S V S V A P G Q T A R I S C S G D S L G S K Y V H
101 TGATATCGAACTGACCCAGC CGCCTTCAGTGAGCGTTGCA CCAGGTCAGACCGCGCGTAT CTCGTGTAGCGGCGATTCTC TTGGTTCTAAGTATGTTCAT
LCDR2
W Y Q Q K P G Q A P V L V I Y R D N K R P S G I P E R F S G S N S G
201 TGGTACCAGCAGAAACCCGG GCAGGCGCCAGTTCTTGTGA TTTATCGTGATAATAAGCGT CCCTCAGGCATCCCGGAACG CTTTAGCGGATCCAACAGCG
LCDR3
N T A T L T I S G T Q A E D E A D Y Y C Q S Y D A T E F T Y V F G
301 GCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGA AGACGAAGCGGATTATTATT GCCAGTCTTATGATGCTACT GAGTTTACTTATGTGTTTGG
HpaI
G G T K L T V L G Q P K A A P S V T L F P P S S E E L Q A N K A T
401 CGGCGGCACGAAGTTAACCG TCCTAGGTCAGCCCAAGGCT GCCCCCTCGGTCACTCTGTT CCCGCCCTCCTCTGAGGAGC TTCAAGCCAACAAGGCCACA
L V C L I S D F Y P G A V T V A W K A D S S P V K A G V E T T T P S
501 CTGGTGTGTCTCATAAGTGA CTTCTACCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGAT AGCAGCCCCGTCAAGGCGGG AGTGGAGACCACACACCCT
K Q S N N K Y A A S S Y L S L T P E Q W K S H R S Y S C Q V T H E
601 CCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCT GAGCCTGACGCCTGAGCAGT GGAAGTCCCACAGAAGCTAC AGCTGCCAGGTCACGCATGA
G S T V E K T V A P T E C S *
701 AGGGAGCACCGTGGAGAAGA CAGTGGCCCCTACAGAATGT TCATAGGGGCCCGTTTAAAC GGGTGGCATCCCTGTGACCC CTCCCCAGTGCCTCTCCTGG
801 CCCTGGAAGTTGCCACTCCA GTGCCCACCAGCCTTGTCCT
pMORPH®2_Ig_REV 100.0%

[Fig. 9A]

FIG. 9A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LCDR2
Y L G W Y Q Q K P G Q A P R L L I Y G A S N R A T G V P A R F S G S
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G S G T D F T L T I S S L E P E D F A T Y Y C Q Q Y Y N M P Y T F
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BsiWI
G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S
TGGCCAGGGTACGAAAGTTG AAATTAAACGTACGGTGGCT GCACCATCTGTCTTCATCTT CCCGCCATCTGATGAGCAGT TGAAATCTGGAACTGCCTCT
V V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E
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Q D S K D S T Y S L S S T L T L S K A D Y E K H K V Y A C E V T H
AGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCAC CCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTC TACGCCTGCGAAGTCACCCA
Q G L S S P V T K S F N R G E C *
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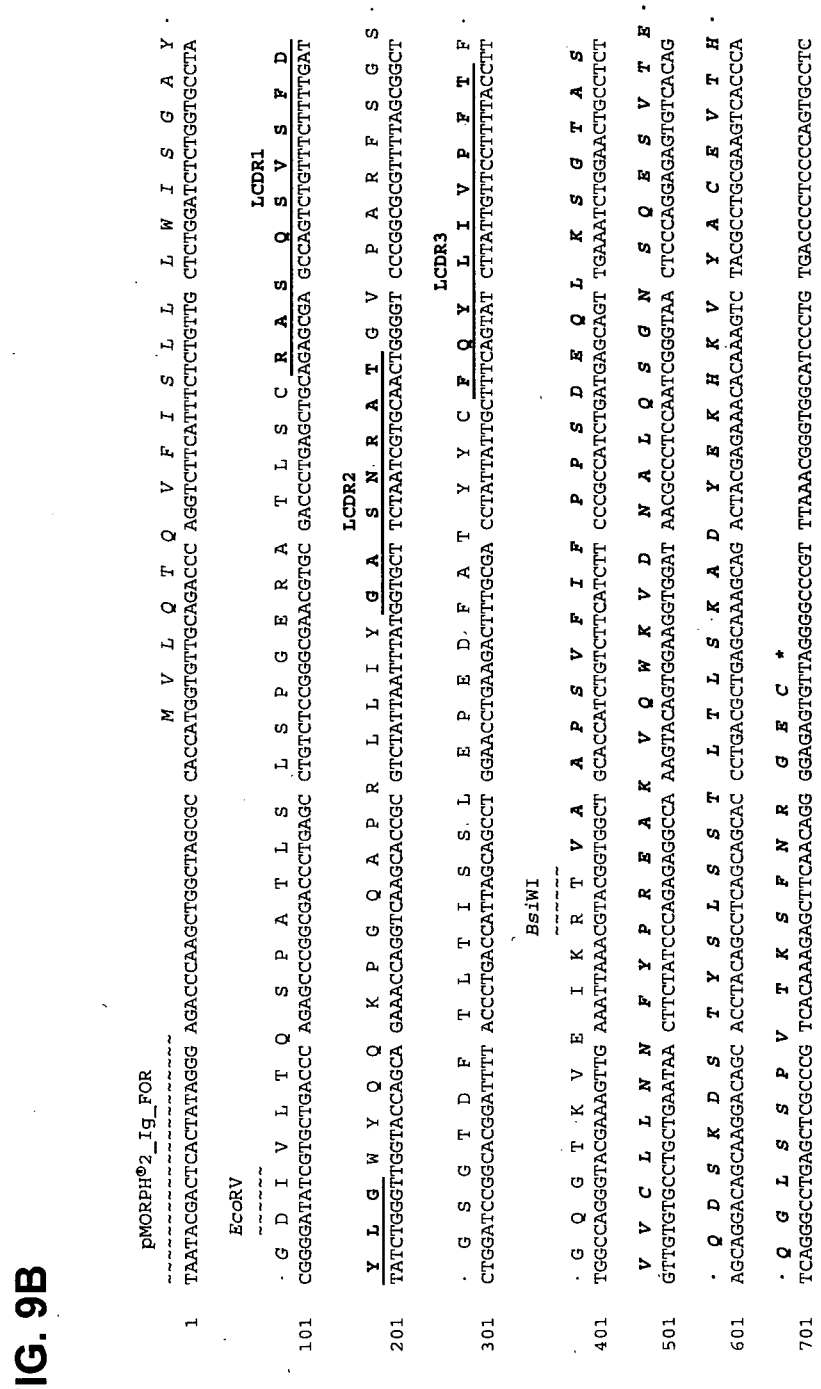
pMORPH®2_Ig_REV

[Fig. 9B]

FIG. 9B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EcoRV
LCDR1
G D I V L T Q S P A T L S L S P G E R A T L S C R A S Q S V S F D
101 CGGGGATATCGTGCTGACCC AGAGCCCGGCGACCCTGAGC CTGTCTCCGGGCGAACGTGC GACCCTGAGCTGCAGAGGCGA GCCAGTCTGTTTCTTTTGAT
LCDR2
Y L G W Y Q Q K P G Q A P R L L I Y G A S N R A T G V P A R F S G S
201 TATCTGGGTTGGTACCAGCA GAAACCAGGTCAAGCACCGC GTCTATTAATTTATGGTGCT TCTAATCGTGCAACTGGGGT CCCGGCGCGTTTTAGCGGCT
LCDR3
G S G T D F T L T I S S L E P E D F A T Y Y C F Q Y L I V P F T F
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BsiWI
G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S
401 TGGCCAGGGTACGAAAGTTG AAATTAAACGTACGGTGGCT GCACCATCTGTCTTCATCTT CCCGCCATCTGATGAGCAGT TGAAATCTGGAACTGCCTCT
V V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E
501 GTTGTGTGCCTGCTGAATAA CTTCTATCCCAGAGAGGCCA AAGTACAGTGGAAGGTGGAT AACGCCCTCCAATCGGGTAA CTCCCAGGAGAGTGTCACAG
Q D S K D S T Y S L S S T L T L S K A D Y E K H K V Y A C E V T H
601 AGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCAC CCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTC TACGCCTGCGAAGTCACCCA
Q G L S S P V T K S F N R G E C *
701 TCAGGGCCTGAGCTCGCCCG TCACAAAGAGCTTCAACAGG GGAGAGTGTTAGGGGCCCGT TTAAACGGGTGGCATCCCTG TGACCCCTCCCCAGTGCCTC
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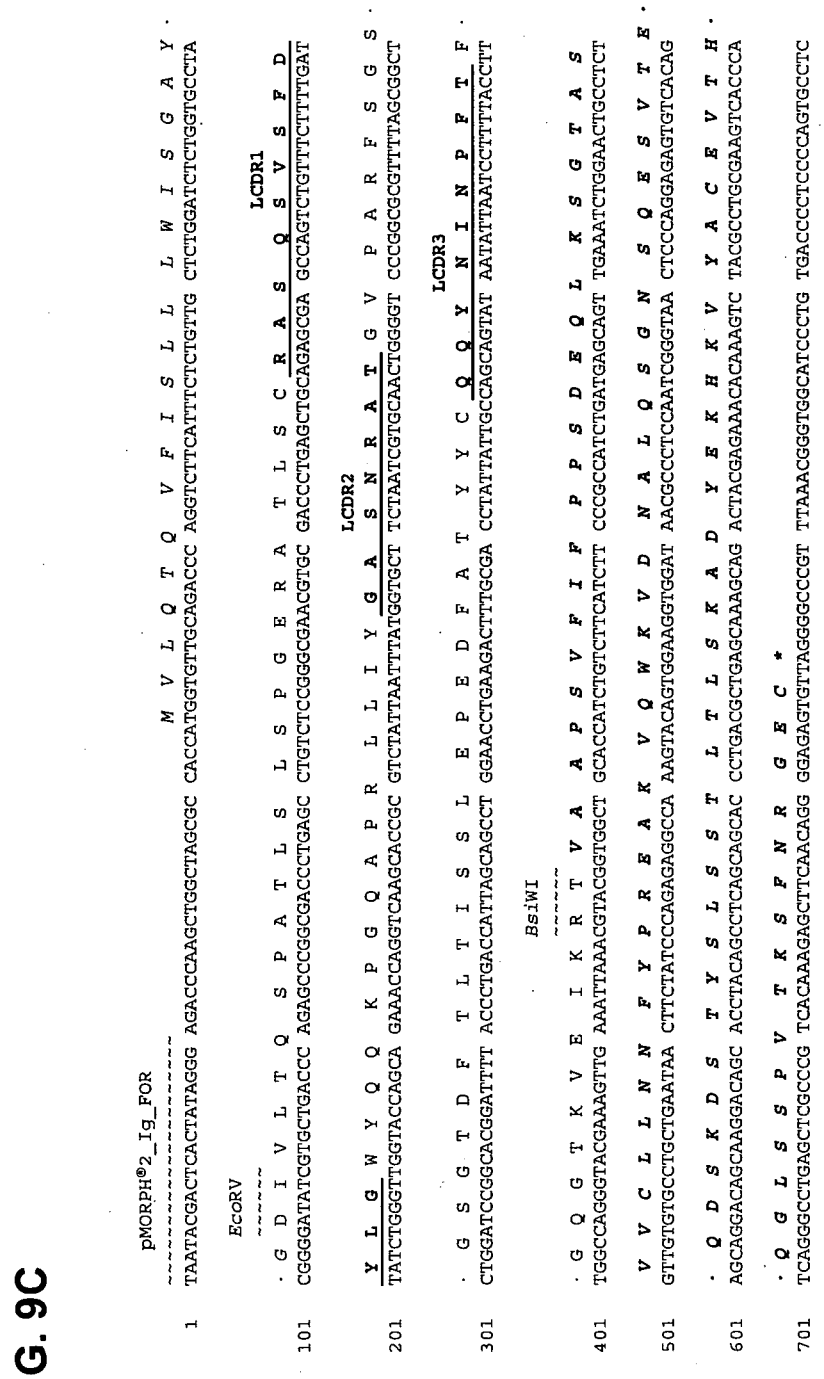
pMORPH®2_Ig_REV

[Fig. 9C]

FIG. 9C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EcoRV
G D I V L T Q S P A T L S L S P G E R A T L S C R A S Q S V S F D
101 CGGGGATATCGTGCTGACCC AGAGCCCGGCGACCCTGAGC CTGTCTCCGGGCGAACGTGC GACCCTGAGCTGCAGAGCGA GCCAGTCTGTTTCTTTTGAT
LCDR1
LCDR2
Y L G W Y Q Q K P G Q A P R L L I Y G A S N R A T G V P A R F S G S
201 TATCTGGGTTGGTACCAGCA GAAACCAGGTCAAGCACCGC GTCTATTAATTTATGGTGCT TCTAATCGTGCAACTGGGGT CCCGGCGCGTTTTAGCGGCT
LCDR3
G S G T D F T L T I S S L E P E D F A T Y Y C Q Q Y N I N P F T F
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BsiWI
G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S
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V V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E
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Q D S K D S T Y S L S S T L T L S K A D Y E K H K V Y A C E V T H
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Q G L S S P V T K S F N R G E C *
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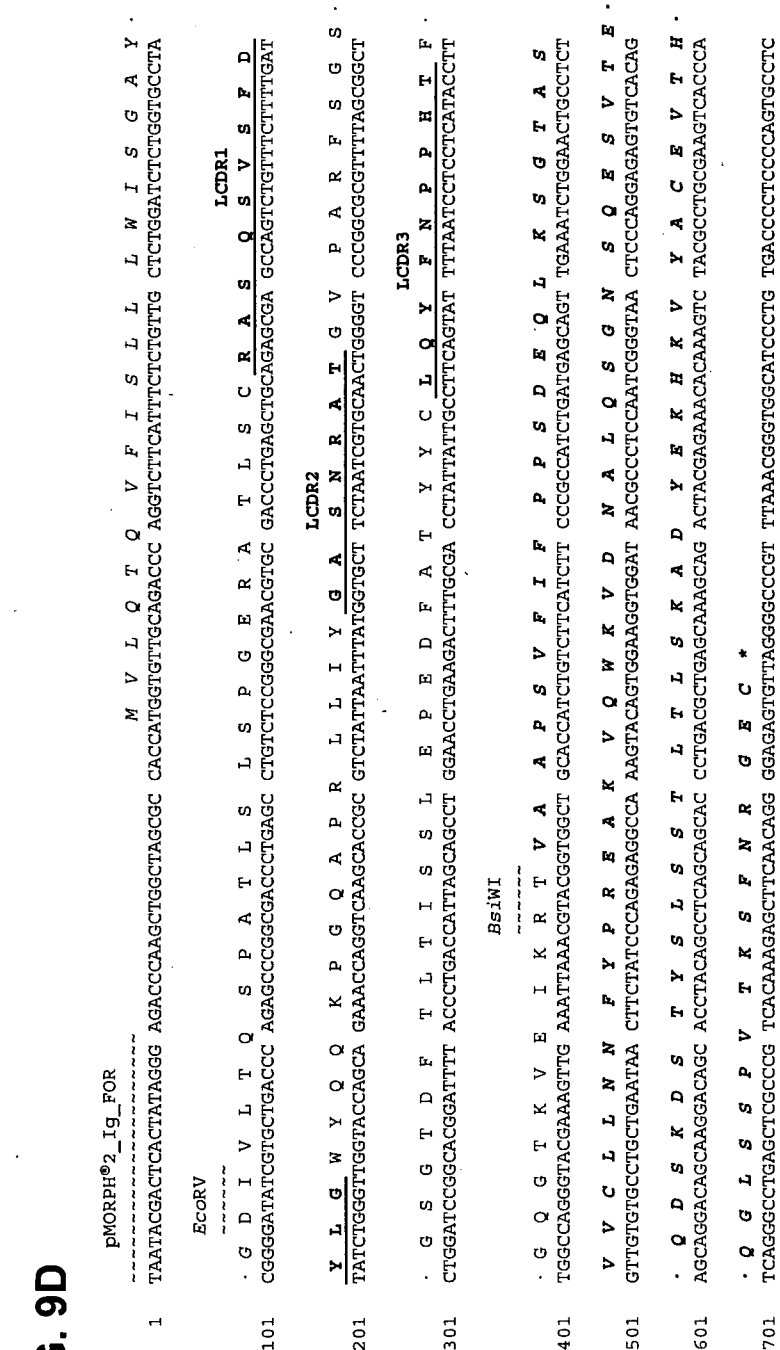
pMORPH®2_Ig_REV

[Fig. 9D]

FIG. 9D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EcoRV
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LCDR3
BsiWI
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Q G L S S P V T K S F N R G E C *
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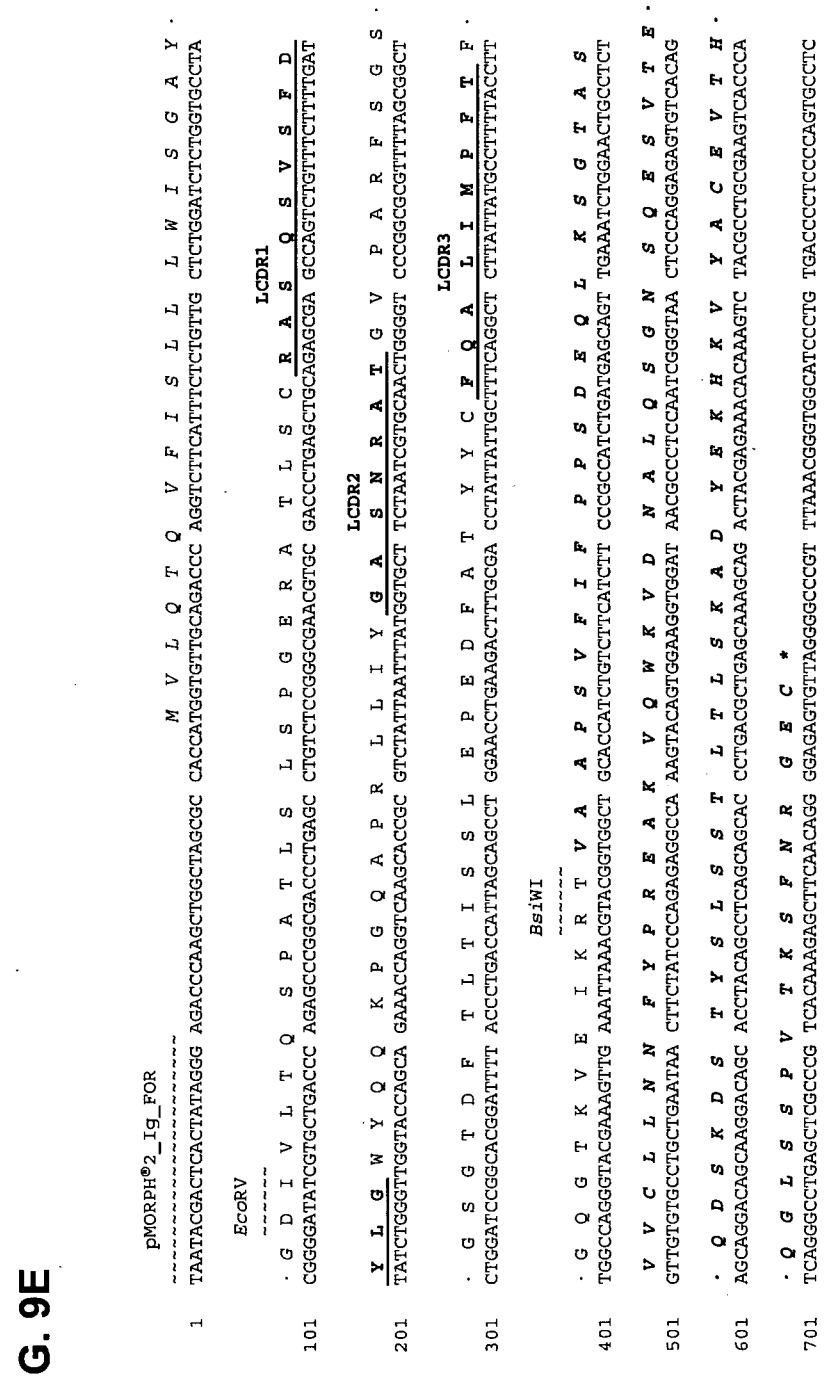
pMORPH®2_Ig_REV

[Fig. 9E]

FIG. 9E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Y L G W Y Q Q K P G Q A P R L L I Y GASNRAT G V P A R F S G S
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G S G T D F T L T I S S L E P E D F A T Y Y C FQALIMPFT F
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BsiWI
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Q G L S S P V T K S F N R G E C *
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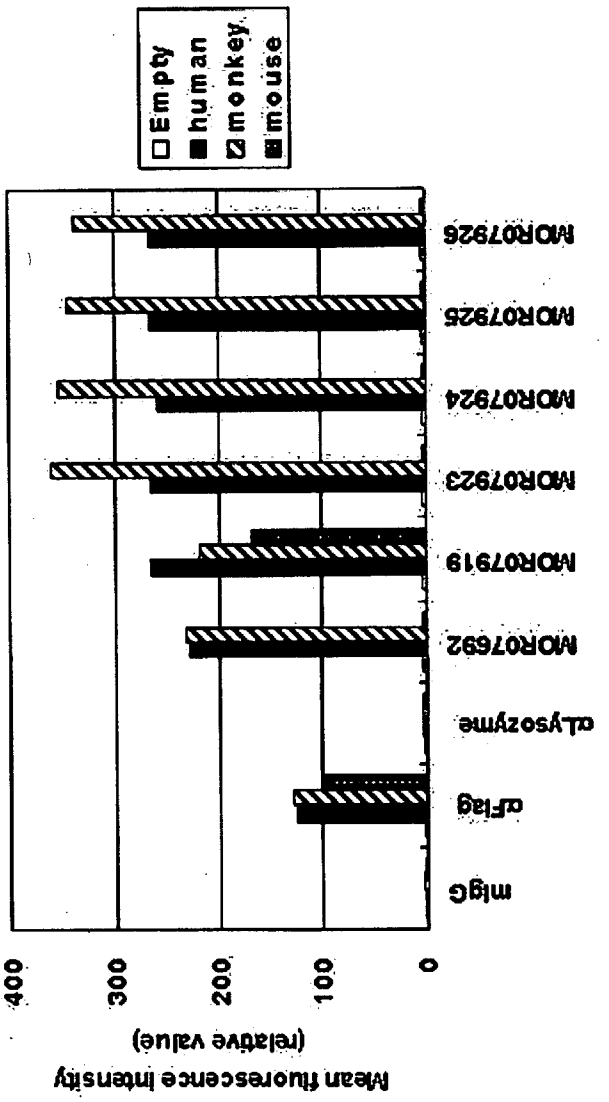
801 TCCTGGCCCTGGAAGTTGCC ACTCCAGTGCCCACCAGCCT TGTCCT
pMORPH®2_Ig_REV

[Fig. 10]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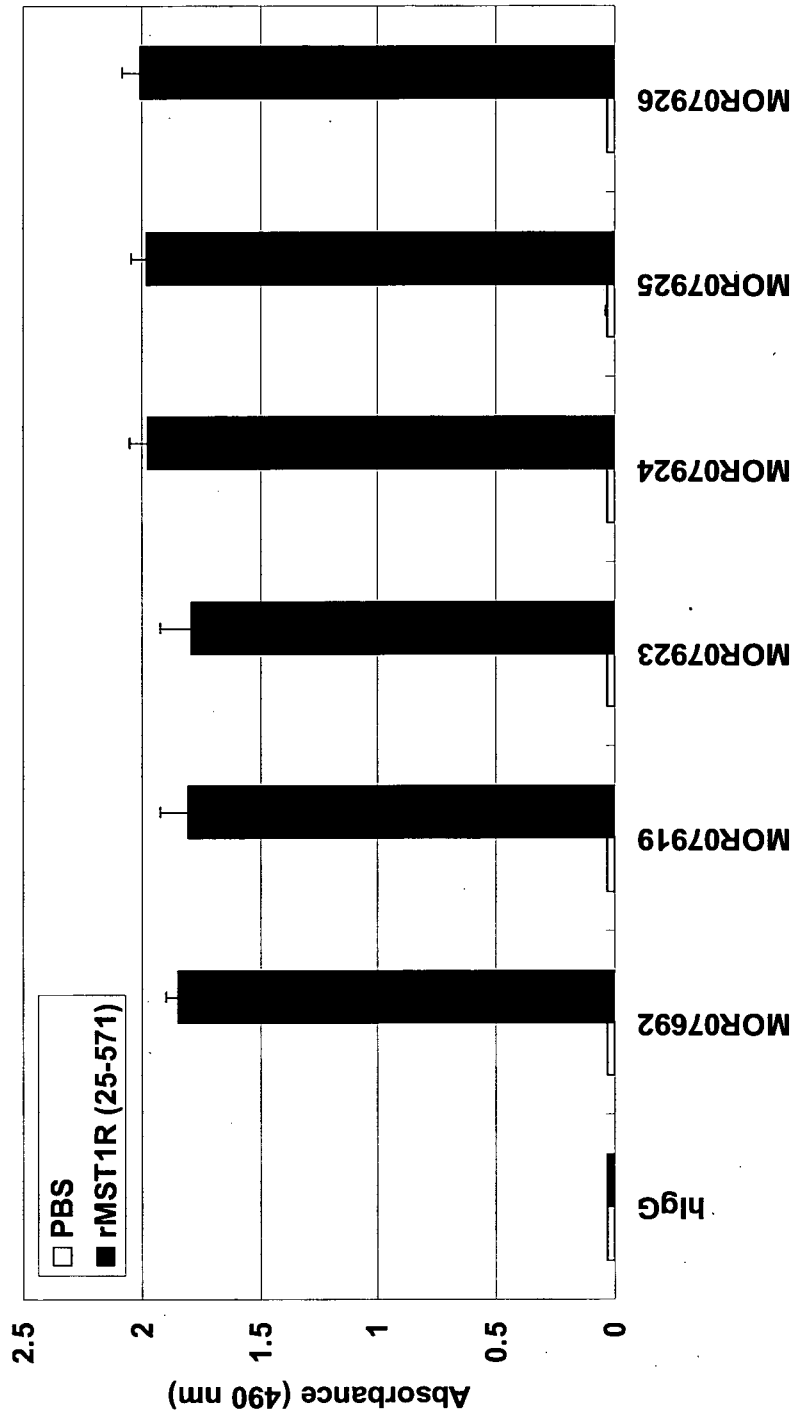
human
monkey
mouse
mIgG
αFlag
αLysozyme
MOR07692
MOR07919
MOR07923
MOR07924
MOR07925
MOR07926
0
100
200
300
400
Mean fluorescence intensity
(relative value)

FIG. 10

[Fig. 11]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MOR07919
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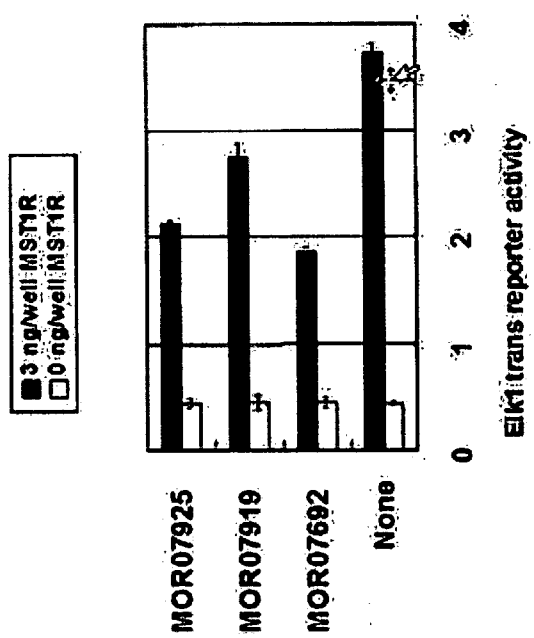
hIgG
□PBS
■rMST1R (25-571)
2.5
2
1.5
1
0.5
0
Absorbance (490 nm)

FIG. 11

[Fig. 12]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0 ng/well MSTNR
Elk1 trans-reporter activity
0
1
2
3
4
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MOR07692
None

FIG. 12

[Fig. 13]

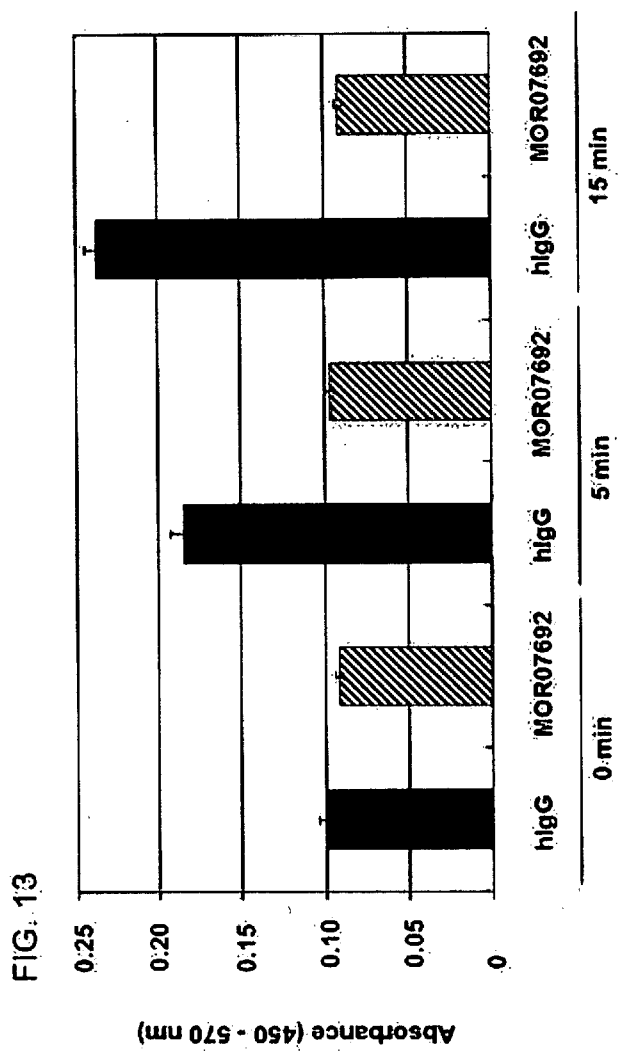
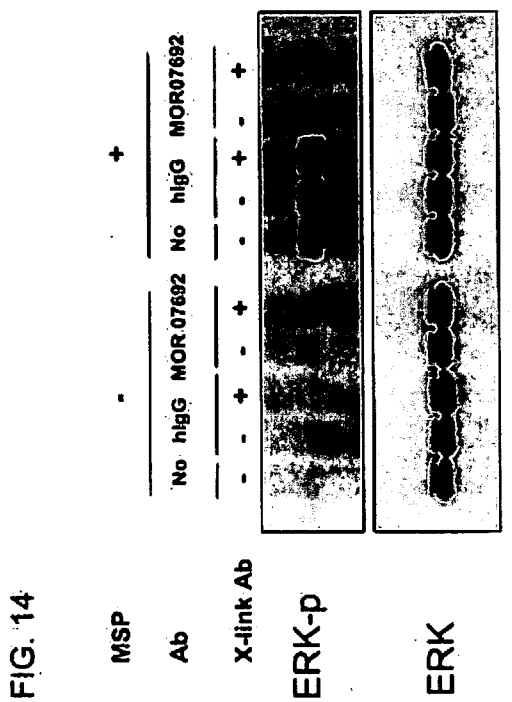

Absorbance (450 - 570 nm)
0.25
0.20
0.15
0.10
0.05
0
hIgG
MOR07692
hIgG
MOR07692
hIgG
MOR07692
0 min
5 min
15 min

FIG. 13

[Fig. 14]



[Fig. 15]

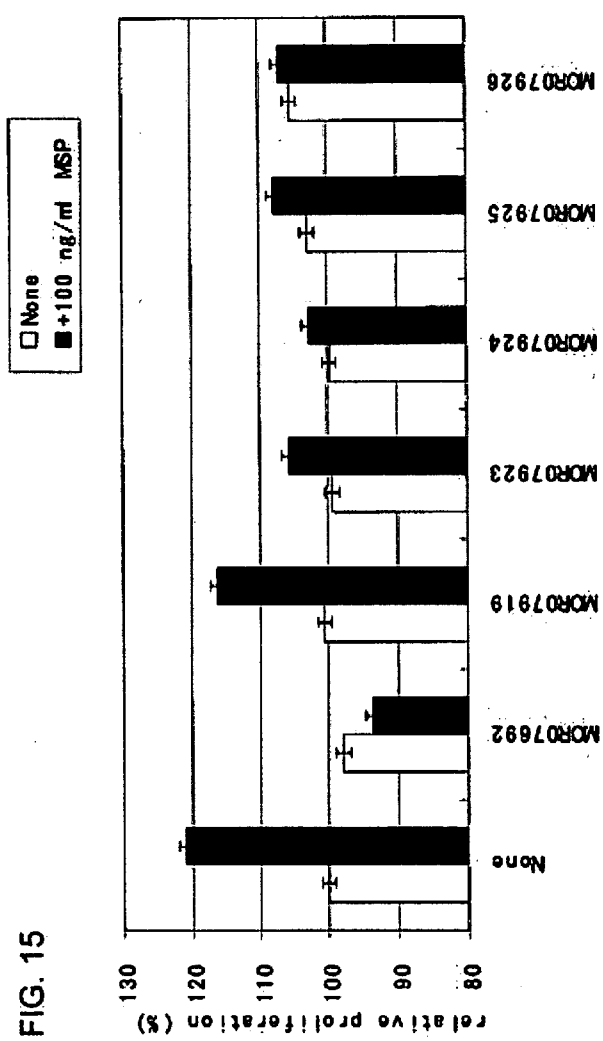

None
+100 ng/ml MSP
relative proliferation (%)
130
120
110
100
90
80
None
MOR07692
MOR07919
MOR07923
MOR07924
MOR07925
MOR07926

FIG. 15

[Fig. 16]

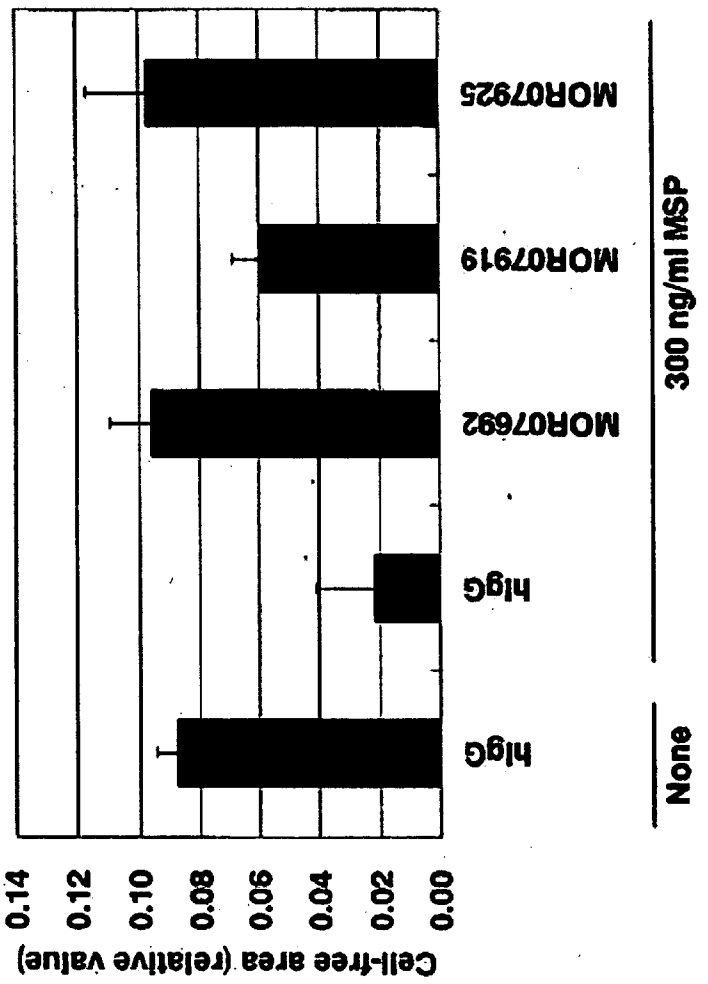

Cell-free area (relative value)
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
hIgG
hIgG
MOR07692
MOR07919
MOR07925
None
300 ng/ml MSP

FIG. 16

[Fig. 17]

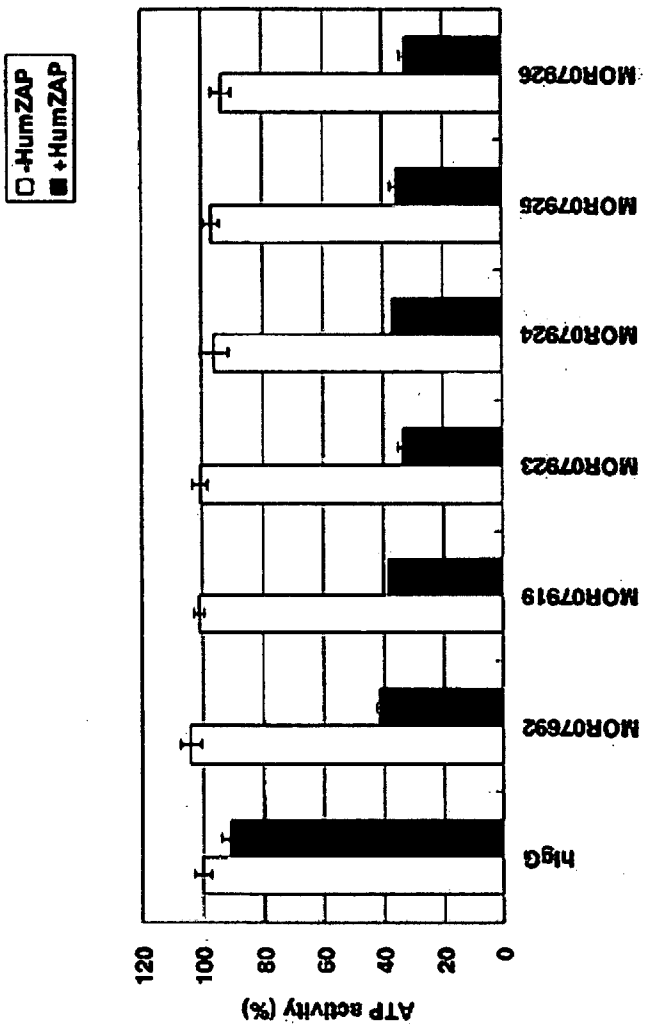

-HumZAP
+HumZAP
MOR07826
MOR07825
MOR07824
MOR07823
MOR07819
MOR07692
hIgG
120
100
80
60
40
20
0
ATP activity (%)

FIG. 17

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2010/052479

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 A61K39/00 C07K14/16 C12N15/86 G01N33/50
C12N5/10 C07K16/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K C12N G01N A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	O'TOOLE ET AL.: "Therapeutic Implications of a Human Neutralizing Antibody to the Macrophage-Stimulating Protein Receptor Tyrosine Kinase (RON), a c-MET Family Member" CANCER RESEARCH, vol. 66, no. 18, 15 September 2006 (2006-09-15), XP002589772 * abstract	1-63
A	WO 2006/020258 A2 (IMCLONE SYSTEMS INC [US]; ZHU ZHENPING [US]) 23 February 2006 (2006-02-23) claims 1,37,38	1-63

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2010	22/07/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rodrigo-Simón, Ana

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2010/052479

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SERENA GERMANO AND GIOVANNI GAUDINO: "Molecular targets in cancer therapy: the Ron approach" ONCOLOGY REVIEWS, vol. 1, no. 4, 2008, pages 215-224, XP002589773 page 221, column 1, paragraph 2	1-63
A	XU XIANG-MING ET AL: "RNA-mediated gene silencing of the RON receptor tyrosine kinase alters oncogenic phenotypes of human colorectal carcinoma cells" ONCOGENE, NATURE PUBLISHING GROUP, GB LNKD- DOI:10.1038/SJ.ONC.1207907, vol. 23, no. 52, 4 November 2004 (2004-11-04), pages 8464-8474, XP002411432 ISSN: 0950-9232 the whole document	1-63
X,P	WO 2009/094148 A2 (BIOGEN IDEC INC [US]; HUET HEATHER [US]; BAILLY VERONIQUE [US]; GARBER) 30 July 2009 (2009-07-30) the whole document	1-63

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2010/052479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006020258 A2	23-02-2006	EP 1786918 A2	23-05-2007
		JP 2008512352 T	24-04-2008
WO 2009094148 A2	30-07-2009	US 2009226442 A1	10-09-2009