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(54) Title: ANTL-IGF-IR ANTIBODIES AND USES THEREOF

(57) Abstract: The subject invention provides antibodies, or binding fragments thereof, that specifically bind to human IGF-IR. Also provided are nucleic acid molecules encoding the antibodies and binding fragments of the subject invention and vectors and host cells containing these nucleic acid molecules. The disclosure also provides methods of inhibiting cancer cell growth and metastasis in a mammal using the antibodies described herein, as well as compositions containing the antibodies, nucleic acid molecules encoding the antibodies, and host cells and vectors comprising the nucleic acid molecules. The disclosure also features the use of the polypeptides to detect the presence of IGF-IR in a mammal, and epitopes that can be used as cancer vaccine immunogens.



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DESCRIPTION

ANTI-IGF-IR ANTIBODIES AND USES THEREOF

5 CROSS-REFERENCE TO A RELATED APPLICATION

This application claims the benefit of U.S. provisional application Serial No. 61/266,681, filed December 4, 2009, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

10 This disclosure pertains generally to potent neutralizing monoclonal antibodies against IGF-IR, and methods of using the same for cancer therapy.

BACKGROUND OF THE INVENTION

15 The insulin-like growth factors (IGFs) signaling system has been shown to play important roles in neoplasia. Insulin-receptors (IR) belong to the IGF signaling network. IGF receptor type 1 (IGF-IR) and its ligands (IGFI and II) are over-expressed in many types of solid and hematopoietic malignancies, including prostate cancer, breast cancer, liver cancer, and colon cancer, etc. There is substantial experimental and clinical evidence that targeting IGF-IR is a promising therapeutic strategy against cancer.

20 Strategies for down-regulating the IGF signaling system include reducing ligand bioavailability and inhibiting receptor function. Inhibition of IGF receptor function can be achieved using receptor-specific antibodies or small molecule tyrosine kinase inhibitors. Desired IGF-IR-specific neutralizing antibodies can not only inhibit IGF-IR function, but also block the IGF-IR-mediated signaling pathway. There is a need to develop IGF-IR-specific antibodies that
25 can inhibit cell-surface IGF-IR and block the binding of IGF-IR ligands to IGF-IR, thereby inhibiting ligand-induced receptor phosphorylation and the downstream signaling. IGF-IR-specific antibodies without cross-reactivity with IR are particularly desired.

BRIEF SUMMARY OF THE INVENTION

The subject invention provides antibodies and binding fragments thereof that specifically bind to human insulin-like growth factor 1 receptor (also known as human IGF receptor type 1).

5 In one embodiment, the subject invention provides an antibody that binds to the extracellular domain of human IGF-IR, and thereby blocks the binding of both IGF-I and -II to IGF-IR and inhibits both IGF-I and IGF-II induced phosphorylation of IGF-IR and the downstream signaling, which lead to cancer cell proliferation and metastasis. These and other advantages of the invention, as well as additional inventive features, will be apparent from the description of the
10 invention provided herein.

In one embodiment, the subject invention provides an isolated antibody (H10), or a binding fragment thereof, comprising an amino acid sequence selected from H10 V_H (SEQ ID NO: 1), H10 V_L (SEQ ID NO: 2), H10 H3 (SEQ ID NO: 3), H10 L3 (SEQ ID NO: 4), or a combination thereof, wherein the antibody specifically binds to an epitope of IGF-IR.

15 The subject invention also includes pharmaceutical compositions comprising the antibody of the subject invention, epitopes that bind to the antibody, and methods of using the antibody to treat cancer in a mammal and to detect IGF-IR in a mammal.

Additionally, the subject invention provides an isolated nucleic acid molecule encoding the antibody of the subject invention, or a binding fragment thereof, comprising a nucleic acid
20 sequence selected from H10 V_H DNA (SEQ ID NO: 5), H10 V_L (SEQ ID NO: 6), H10 H3 (SEQ ID NO: 7), H10 L3 (SEQ ID NO: 8), or a combination thereof, wherein the nucleic acid molecule is optionally in a form of a vector, wherein the nucleic acid molecule or vector is optionally contained within a host cell, wherein the antibody or binding fragment thereof specifically binds to an epitope of IGF-IR. The disclosure also provides pharmaceutical
25 compositions containing the nucleic acid molecules or polypeptides, and methods of using the nucleic acid molecules or polypeptides, to inhibit cancer cell growth and cancer metastasis in a mammal.

To the accomplishment of the foregoing and related ends, the invention comprises the features hereinafter fully described and particularly pointed out in the claims. The following
30 description and the annexed drawings set forth in detail certain illustrative aspects and

implementations of the invention. These are indicative of, however, a few of the various ways in which the principles of the invention may be employed. Other objects, advantages, and novel features of the invention will become apparent from the following detailed description of the invention when considered in conjunction with the drawings.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates amino acid sequences of various regions of the H10 antibody and nucleic acid sequences encoding these amino acid sequences. The amino acid sequences are presented from N-terminus to C-terminus (from upper left to lower right of the Figure) in accordance with convention. Sequences of HCDR1-3 and LCDR1-3 are underlined.

10

Figure 2 is a graph that illustrates an exemplified procedure of humanizing mouse monoclonal antibody Fab m590. H: human; m: mouse.

Figure 3 illustrates the binding of H10 to cell-associated IGF-IR on breast cancer MCF-7 cells in flow cytometry.

15

BRIEF DESCRIPTION OF THE SEQUENCES

SEQ ID NO: 1 is an amino acid sequence of a V_H region of the H10 antibody of the subject invention.

SEQ ID NO: 2 is an amino acid sequence of a V_L region of the H10 antibody of the subject invention.

20

SEQ ID NO: 3 is an amino acid sequence of an H3 region (CDR3 of a V_H region) of the H10 antibody of the subject invention.

SEQ ID NO: 4 is an amino acid sequence of an L3 region (CDR3 of a V_L region) of the H10 antibody of the subject invention.

25

SEQ ID NO: 5 is a nucleic acid sequence of a V_H region of the H10 antibody of the subject invention.

SEQ ID NO: 6 is a nucleic acid sequence of a V_L region of the H10 antibody of the subject invention.

SEQ ID NO: 7 is a nucleic acid sequence of an H3 region (CDR3 of a V_H region) of the H10 antibody of the subject invention.

30

SEQ ID NO: 8 is a nucleic acid sequence of an L3 region (CDR3 of a V_L region) of the H10 antibody of the subject invention.

SEQ ID NO: 9 is an amino acid sequence of CDR1 of a V_H region of the H10 antibody of the subject invention.

5 **SEQ ID NO: 10** is an amino acid sequence of CDR2 of a V_H region of the H10 antibody of the subject invention.

SEQ ID NO: 11 is an amino acid sequence of CDR1 of a V_L region of the H10 antibody of the subject invention.

10 **SEQ ID NO: 12** is a nucleic acid sequence of CDR1 of a V_H region of the H10 antibody of the subject invention.

SEQ ID NO: 13 is a nucleic acid sequence of CDR2 of a V_H region of the H10 antibody of the subject invention.

SEQ ID NO: 14 is a nucleic acid sequence of CDR1 of a V_L region of the H10 antibody of the subject invention.

15

SEQ ID NO: 15 is an amino acid sequence of the human insulin-like growth factor 1 receptor (hIGF-IR) used according to the subject invention.

DETAILED DISCLOSURE OF THE INVENTION

20

The subject invention provides antibodies, or binding fragments thereof, that specifically bind to an epitope of the type 1 insulin-like growth factor receptor (IGF-IR). The disclosure more specifically provides antibodies, or binding fragments thereof, that bind to the extracellular domain of IGF-IR. Additionally, the disclosure provides epitopes that are recognized by the polypeptides (e.g., antibodies or binding fragments thereof) described herein, which epitopes can be used, in an embodiment in the development of cancer vaccine immunogens for the treatment of cancer.

25

The anti-IGF-IR antibodies can be used for cancer therapy, as well as to detect IGF-IR in an animal, including without limitation a human. The anti-IGF-IR antibodies of the subject invention can also be used to detect IGF-IR in a test sample. The test sample can be a tissue sample, a biopsy sample, and the like.

30

In one embodiment, the anti-IGF-IR antibody specifically binds to human insulin-like growth factor I receptor (also known as human insulin-like growth factor receptor type 1 (IGF-IR)). In a specific embodiment, the human IGF-IR has an amino acid sequence of SEQ ID NO: 19 (GenBank Accession No. P08069; GI: 124240). In an embodiment, the anti-IGF-IR antibody of the subject invention specifically binds to human IGF-IR expressed on cancer cells, such as for example, SKOV-3 and MCF-7 cells. In an embodiment, the anti-IGF-IR antibody of the subject invention specifically binds to human IGF-IR expressed on IGF-IR stably transfected Hela cells.

The term “binding specificity,” “specificity,” “specifically reacts,” or “specifically interacts,” as used herein, refers to the ability of an antibody or other agent to detectably bind an epitope presented on an antigen, such as an epitope of IGF-IR, while having relatively little detectable reactivity with other proteins or structures. Specificity can be relatively determined by binding or competitive assays, using e.g., Biacore instruments. Specificity can be exhibited by, e.g., an about 10:1, about 20:1, about 50:1, about 100:1, about 10,000:1 or greater ratio of affinity/avidity in binding to the specific antigen versus nonspecific binding to other irrelevant molecules.

In one embodiment, the disclosure provides an isolated polypeptide (e.g., antibody, or a binding fragment thereof), comprising the amino acid sequence selected from H10 V_H (SEQ ID NO: 1), H10 V_L (SEQ ID NO: 2), H10 H3 (CDR3 of a V_H region) (SEQ ID NO: 3), H10 L3 (CDR3 of a V_L region) (SEQ ID NO: 4), or a combination thereof, wherein the polypeptide binds to an epitope of IGF-IR ectodomain. The polypeptide can comprise sequences selected from (a) the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 2; (b) the amino acid sequences of SEQ ID NO: 3 and SEQ ID NO: 4; (c) the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 4; or (d) the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 3.

In an embodiment, CDR1 of a V_H region of the anti-IGF-IR antibody comprises SEQ ID NO: 9. In an embodiment, CDR2 of a V_H region of the anti-IGF-IR antibody comprises SEQ ID NO: 10. In an embodiment, CDR3 of a V_H region of the anti-IGF-IR antibody comprises SEQ ID NO: 3. In a specific embodiment, a V_H region of the anti-IGF-IR antibody comprises SEQ ID NO: 1. In an embodiment, CDR1 of a V_L region of the anti-IGF-IR antibody comprises SEQ ID NO: 11. In an embodiment, CDR2 of a V_L region of the anti-IGF-IR antibody comprises GTS.

In an embodiment, CDR3 of a V_L region of the anti-IGF-IR antibody comprises SEQ ID NO: 4. In a specific embodiment, a V_L region of the anti-IGF-IR antibody comprises SEQ ID NO: 2.

The disclosure also provides an isolated nucleic acid molecule encoding a polypeptide, or a binding fragment thereof, comprising H10 V_H DNA (SEQ ID NO: 5), H10 V_L DNA (SEQ ID NO: 6), H10 H3 DNA (SEQ ID NO: 7), H10 L3 DNA (SEQ ID NO: 8), or a combination thereof, wherein the nucleic acid molecule is optionally in the form of a vector, wherein the nucleic acid molecule or vector is optionally contained within a host cell. In certain embodiments, the nucleic acid molecule can encode a polypeptide comprising (a) the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 2; (b) the amino acid sequences of SEQ ID NO: 3 and SEQ ID NO: 4; (c) the amino acid sequences of SEQ ID NO: 1 and SEQ ID NO: 4; or (d) the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 3.

In an embodiment, CDR1 of a V_H region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 13. In an embodiment, CDR2 of a V_H region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 13. In an embodiment, CDR3 of a V_H region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 7. In a specific embodiment, a V_H region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 5. In an embodiment, CDR1 of a V_L region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 14. In an embodiment, CDR2 of a V_L region of the anti-IGF-IR antibody is encoded by a sequence comprising 5'ggcacgtcc 3'. In an embodiment, CDR3 of a V_L region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 8. In a specific embodiment, a V_L region of the anti-IGF-IR antibody is encoded by a sequence comprising SEQ ID NO: 6. The polypeptide can be any suitable polypeptide. For example, in one embodiment, the polypeptide is an antibody. Antibodies include both polyclonal and monoclonal antibodies. In addition to intact immunoglobulin molecules, also included are fragments or polymers of those immunoglobulin molecules, and human or humanized versions of immunoglobulin molecules or fragments thereof, as long as the molecules maintain the ability to bind with an epitope of the IGF-IR. The antibodies can be tested for their desired activity using the *in vitro* assays described herein, or by analogous methods, after which their *in vivo* therapeutic and/or diagnostic activities can be confirmed and quantified according to known clinical testing methods.

In another embodiment, the polypeptide is a monoclonal antibody or a binding fragment thereof. A monoclonal antibody refers to an antibody where individual antibodies within a population are identical.

The term "polypeptide" encompasses native or artificial proteins, protein fragments and polypeptide analogs of a protein sequence. A polypeptide may be monomeric or polymeric. The term "isolated polypeptide" is a polypeptide that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other proteins from the same species (3) is expressed by a cell of a species different from where the protein naturally originates, or (4) does not occur in nature. A polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates is also considered "isolated" from its naturally associated components. A polypeptide can also be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art.

The monoclonal antibodies can be made using any procedure known in the art. For example, monoclonal antibodies of the invention can be prepared using hybridoma methods, such as those described by Kohler *et al.*, Nature, 256, 495-497 (1975), which is hereby incorporated by reference. The monoclonal antibodies also can be made by recombinant DNA methods, such as those described in U.S. Patent 4,816,567, which is hereby incorporated by reference. DNA encoding the disclosed monoclonal antibodies can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). Libraries of antibodies or active antibody fragments can also be generated and screened using phage display techniques, e.g., as described in U.S. Patent 5,804,440 and U.S. Patent 6,096,441, both of which are hereby incorporated by reference.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can be performed using papain. Examples of papain digestion are described in International Patent Application WO 94/29348 and U.S. Patent 4,342,566, both of which are hereby incorporated by reference. Papain digestion of antibodies typically produces two identical antigen-binding fragments - Fab fragments and a

residual Fc fragment. Each Fab fragment has a single antigen binding site. Pepsin treatment yields a fragment that has two antigen combining sites and is still capable of cross-linking antigen.

5 The disclosure encompasses chimeric antibodies and hybrid antibodies, with dual or multiple antigen or epitope specificities, single chain antibodies and fragments, such as, Fab', F(ab')₂, Fab, scFv, and the like, including hybrid fragments. Such antibodies and fragments can be made by techniques known in the art and can be screened for specificity and activity according to general methods for producing antibodies and screening antibodies for specificity and activity (see, e.g., Harlow and Lane. *Antibodies, A Laboratory Manual*. Cold Spring Harbor
10 Publications, New York, (1988), which is hereby incorporated by reference).

The disclosure also encompasses human antibodies and/or humanized antibodies. Many non-human antibodies (e.g., those derived from mice, rats, or rabbits) are naturally antigenic in humans and, thus, can give rise to undesirable immune responses when administered to humans. Therefore, the use of human or humanized antibodies in the methods described herein serves to
15 lessen the chance that an antibody administered to a human will evoke an undesirable immune response.

The human antibodies and humanized antibodies described herein can be prepared by any known technique. Examples of techniques for human monoclonal antibody production include those described by Boerner *et al.*, *J. Immunol.*, 147(1), 86-95 (1991), which is hereby
20 incorporated by reference. Human antibodies described herein (and fragments thereof) can also be produced using phage display libraries (see, e.g., Marks *et al.*, *J. Mol. Biol.*, 222, 581-597 (1991)), which is hereby incorporated by reference. The human antibodies described herein can also be obtained from transgenic animals. For example, transgenic mutant mice that are capable of producing a full repertoire of human antibodies in response to immunization have been
25 described (see, e.g., Jakobovits *et al.*, *PNAS*, 90, 2551-255 (1993); and Jakobovits *et al.*, *Nature*, 362, 255-258 (1993)), all of which are hereby incorporated by reference.

Methods for humanizing non-human antibodies are known in the art. For example, humanized antibodies can be generated by substituting rodent complementarity-determining regions (CDRs) or CDR sequences for the corresponding sequences of a human antibody.
30 Detailed procedures are disclosed in Jones *et al.*, *Nature*, 321, 522-525 (1986); Riechmann *et al.*,

Nature, 332, 323-327 (1988); Verhoeyen *et al.*, Science, 239, 1534-1536 (1988), all of which are hereby incorporated by reference.

Methods that can be used to produce humanized antibodies are also described in U.S. Patent 4,816,567; U.S. Patent 5,565,332; U.S. Patent 5,721,367; U.S. Patent 5,837,243; U.S. Patent 5, 939,598; U.S. Patent 6,130,364; and U.S. Patent 6,180,377; all of which are hereby incorporated by reference.

The polypeptides, according to the subject invention also encompass bivalent antibodies, as well as fusion molecules and conjugates with other molecules that can enhance the inhibitory effect of the polypeptide. The generation of fusion molecules (e.g., proteins) and conjugates (e.g., through physical or chemical conjugation) is within the ordinary skill in the art and can involve the use of restriction enzyme or recombinant cloning techniques (see, e.g., U. S. Patent 5,314,995, which is hereby incorporated by reference).

The fusion molecule (e.g., proteins and nucleic acid molecules) or conjugate can comprise one or more of SEQ ID NOs: 1-8 in combination with any suitable second molecule. For example, the fusion molecule or conjugate can comprise one or more of SEQ ID NOs: 1-8 in combination with a neutralizing scFv antibody fragment or a Fab fragment (e.g., that binds to an epitope of IGF-IR).

Toxins are poisonous substances that usually are produced by plants, animals, or microorganisms that, in sufficient doses, are lethal. Preferred toxin for use in the fusion molecules or conjugates described herein include Pseudomonas toxin, Diphtheria toxin tetanus toxoid, ricin, cholera toxin, Shiga-like toxin (SL T-I, SL T- II, SL T-10 IIV), L T toxin, C3 toxin, Shiga toxin, pertussis toxin, tetanus toxin, Pseudomonas exotoxin, alorin, saporin, modeccin, and gelatin. The polypeptide (e.g., antibody, or a binding fragment thereof), and the toxin can be linked in several ways. If the hybrid molecule is produced by expression of a fused gene, a peptide bond serves as the link between the toxin and the polypeptide.

Alternatively, the toxin and the polypeptide can be produced separately and later coupled (e.g., by means of a non-peptide covalent bond). For example, the covalent linkage may take the form of a disulfide bond. In this case, the nucleic acid molecule encoding the polypeptide can optionally contain an extra cysteine codon. The cysteine condon can be positioned so as to not interfere with the binding activity of the molecule. The toxin molecule can be derivatized with a

sulfhydryl group reactive with the cysteine of the modified polypeptide. In the case of a peptide toxin, this optionally can be accomplished by inserting DNA encoding a cysteine codon into the nucleic acid molecule encoding the toxin. In another alternative, a sulfhydryl group, either by itself or as part of a cysteine residue, can be introduced into the polypeptide of the subject invention using solid phase polypeptide techniques.

Moreover, the polypeptides described herein can be combined with other well-known therapies already in use. The combination of the polypeptide described herein and one or more other therapeutic agents can provide a greater therapeutic effect than either agent alone, and preferably generate an additive or a synergistic effect with current treatments. For example, the polypeptide of the invention can be combined with other therapies targeting the IGF-IR, Her2 or other components in the IGF signaling network, including IGF-I, IGF-II, IGF binding proteins, such as anti-Her 2 monoclonal antibody herceptin, anti-IGF-IR monoclonal antibodies CP751,871 (Pfizer), MK-0646 (Pierre-Fabre/Merck), AmG479 (Amgen), IMC-A12 (ImClone), R1507 (Hoffmann LaRoche), robatumumab (Schering-Plough), and cytokine immune enhancement therapy (interleukin (IL)-2, IL-12, CD40L + IL-12, IL-7, and interferons (IFNs)). Such therapies can be administered in the manner already in use for the known treatment providing a therapeutic effect. The polypeptide of the invention can be a neutralizing antibody against IGF-IR useful for cancer therapy. In an embodiment, the antibody (or binding fragment thereof) of the subject invention inhibits IGF-IR function and inhibits IGF-IR-mediated signaling. The antibody (or binding fragment thereof) of the subject invention has a high affinity for IGF-IR and is specific for IGF-IR.

In an embodiment, the antibody, or binding fragment thereof physically associates with other molecules (e.g., anti-IGF-IR antibodies, anti-Her2 antibodies) to inhibit IGF-IR- and Her2-mediated signaling. In other words, the polypeptide specifically binds, specifically reacts with, or specifically interacts with other target molecules (e.g. IGF-I, -II, IGF binding proteins). In an alternative embodiment, the polypeptide does not substantially physically associate with other molecules.

The epitopes recognized by the polypeptides described herein can be used as cancer vaccine immunogens, as active portions of cancer vaccine immunogens, and as targets for inhibitors of IGF signaling network. For example, the epitopes described herein (or polypeptides

comprising the epitopes) can be used as targets to isolate antibodies that, other than those described herein, bind to the epitopes described herein. These antibodies can be used in the treatment and diagnosis of cancer.

5 While it is possible to administer (for example, as a vaccine) an epitope (or polypeptide comprising the epitope) that is recognized by the antibodies of the subject invention in a pure or substantially pure form, the epitope can be formulated into a pharmaceutical composition, formulation, or preparation. Accordingly, the disclosure encompasses a composition containing an epitope (or polypeptide comprising the epitope) recognized by the antibody described herein. The composition can further contain one or more pharmaceutically acceptable carriers (as
10 described herein) and, optionally, other therapeutic ingredients. The composition comprising such epitope can be used therapeutically or to otherwise generate an immune response.

For example, a vaccine is provided to enhance the patient's own immune response to the antigens present due to tumorigenesis. Such vaccine, which acts as an immunogen, optionally can be a partially or substantially purified recombinant polypeptide containing the epitope or an
15 analog thereof. The polypeptide comprising the epitope can be conjugated with one or more lipoproteins, administered in liposomal form, or with an adjuvant. Also encompassed by the disclosure are methods of developing vaccines or immunogenic compositions using the epitopes described herein.

The disclosure is also directed to methods of downregulating IGF-IR and inhibiting IGF-
20 IR-mediated signaling in a mammal. The methods involve administering an effective amount of the polypeptide (e.g. the antibody or a binding fragment thereof that specifically binds to human IGF-IR), nucleic acid molecule that encodes the polypeptide, a vector comprising the nucleic acid molecule, a cell comprising the nucleic acid molecule and/or vector, or compositions comprising the foregoing, to the mammal, wherein cancer cell growth and cancer metastasis are reduced or
25 inhibited. In one embodiment, the mammal is a human.

In one embodiment, the subject invention provides administering to a mammal a polypeptide (e.g. the antibody or a binding fragment thereof that specifically binds to human IGF-IR), a nucleic acid molecule, a vector containing the nucleic acid encoding the polypeptide, or a cell (e.g., a host cell) containing any of the above.

In one embodiment, the subject invention provides a method for treating tumor or cancer, comprising administering to a subject in need of such treatment an effective amount of an isolated antibody, or a binding fragment thereof, to a subject. In another embodiment, the subject invention embodies the administration of nucleic acid molecules, vectors, and host cells of the subject invention for tumor or cancer therapy. In a specific embodiment, the subject invention can be used to treat or ameliorate prostate cancer, breast cancer, liver cancer, and colon cancer.

The term "treatment" or any grammatical variation thereof (*e.g.*, treat, treating, and treatment *etc.*), as used herein, includes but is not limited to, ameliorating or alleviating a symptom of a disease or condition, reducing, suppressing, inhibiting, lessening, or affecting the progression, severity, and/or scope of a condition.

The term "subject," as used herein, describes an organism, including mammals such as primates, to which treatment with the compositions according to the subject invention can be provided. Mammalian species that can benefit from the disclosed methods of treatment include, but are not limited to, apes, chimpanzees, orangutans, humans, monkeys; and domesticated animals such as dogs, cats, horses, cattle, pigs, sheep, goats, chickens, mice, rats, guinea pigs, and hamsters.

Vectors include, for example, nucleic acid vectors, such as naked DNA and plasmids, and viral vectors, such as retroviral vectors, parvovirus-based vectors (*e.g.*, adenoviral-based vectors and adeno-associated virus (AAV)-based vectors), lentiviral vectors (*e.g.*, Herpes simplex (HSV)-based vectors), and hybrid or chimeric viral vectors, such as an adenoviral backbone with lentiviral components (see, *e.g.*, Zheng *et al.*, *Nat. Biotech.*, 18(2), 176-80 (2000); International Patent Application WO 98/22143; International Patent Application WO 98/46778; and International Patent Application WO 00/17376) and an adenoviral backbone with AAV components (see, *e.g.*, Fisher *et al.*, *Hum. Gene Ther.*, 7, 2079-2087 (1996)), all of which are hereby incorporated by reference). Vectors and vector construction are known in the art (see, *e.g.*, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2d edition, Cold Spring Harbor Laboratory, NY (1989); and Ausubel *et al.*, *Current Protocols in Molecular Biology*, Green Publishing Associates and John Wiley & Sons, New York, N.Y. (1994), both of which are hereby incorporated by reference).

The vector can contain any suitable promoter and other regulatory sequences (e.g., transcription and translation initiation and termination codons, which are specific to the type of host) to control the expression of the nucleic acid sequence encoding the polypeptide. The promoter can be a native or nonnative promoter operably linked to the nucleic acid molecule described above. The selection of promoters, including various constitutive and regulatable promoters, is within the skill of an ordinary artisan.

Examples of regulatable promoters include inducible, repressible, and tissue-specific promoters. Specific examples include viral promoters, such as adenoviral promoters and AAV promoters. Additionally, combining the nucleic acid described above with a promoter is within the skill in the art.

Cells (e.g., isolated host cells) containing the above-described polypeptide or nucleic acid molecule encoding the polypeptide, optionally in the form of a vector, are also provided by the disclosure. Any suitable cell can be used. Examples include host cells, such as *E. coli* (e.g., *E. coli* Tb-1, TG-2, DH5a, XL-Blue MRF¹ (Stratagene), SA2821, and Y1090), *Bacillus subtilis*, *Salmonella typhimurium*, *Serratia marcescens*, *Pseudomonas* (e.g., *P. aeruginosa*), *N. grassa*, insect cells (e.g., Sf9, Ea4), yeast (*S. cerevisiae*) cells, and cells derived from a mammal, including human cell lines. Specific examples of suitable eukaryotic host cells include VERO, HeLa, 3T3, Chinese hamster ovary (CHO) cells, W138 BHK, COS-7, and MDCK cells. Alternatively, cells from a mammal, such as a human, to be treated in accordance with the methods described herein can be used as host cells.

Methods of introducing vectors into isolated host cells and the culture and selection of transformed host cells *in vitro* are known in the art and include the use of calcium chloride-mediated transformation, transduction, conjugation, triparental mating, DEAE, dextran-mediated transfection, infection, membrane fusion with liposomes, high velocity bombardment with DNA-coated microprojectiles, direct microinjection into single cells, and electroporation (see, e.g., Sambrook *et al.*, *Molecular Biology: A Laboratory Manual*, Cold Spring Harbor Laboratory, NY (1989); Davis *et al.*, *Basic Methods in Molecular Biology* (1986); and Neumann *et al.*, *EMBO J.* 1, 841 (1982), all of which are hereby incorporated by reference). In one embodiment, the cell containing the vector or nucleic acid molecule is transcribed and translated efficiently by the cell.

The nucleic acid molecules, vectors, cells, and polypeptides can be administered to a mammal alone, or in combination with a pharmaceutically acceptable carrier. By pharmaceutically acceptable is meant a material that is not biologically or otherwise undesirable (e.g., the material can be administered to a mammal, along with the nucleic acid, vector, cell, or polypeptide, without causing undesirable biological effects or interacting in a deleterious manner with other components of the pharmaceutical composition in which it is contained). The carrier is selected to minimize the degradation of the agent and to minimize adverse side effects in the mammal. The selection of carrier is well-known to one of ordinary skill in the art.

Suitable carriers and their formulations are described in Remington: The Science and Practice of Pharmacy (19th ed.) ed. A.R. Gennaro, Mack Publishing Company, Easton, PA (1995). Examples of pharmaceutical carriers include sterile water, saline, Ringer's solution, dextrose solution, and buffered solutions at physiological pH.

Typically, an appropriate amount of a pharmaceutically acceptable salt is used in the formulation to render the formulation isotonic. In one embodiment, the pH of the solution is from about 5 to about 8 (e.g., about 5.5, about 6, about 6.5, about 7, about 7.5, and ranges including any of these amounts therebetween), although pHs outside this range can be employed. In another embodiment, the pH is about 7 to about 7.5.

The pharmaceutical composition of the subject invention can also include sustained-release preparations, such as semipermeable matrices of solid hydrophobic polymers containing the polypeptide, which matrices are in the form of shaped articles (e.g., films, liposomes, or microparticles). It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and the concentration of composition being administered.

Examples of compositions (e.g., pharmaceutical compositions) containing the nucleic acid molecule, vector, cell, or polypeptide can include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like. The compositions can also include one or more active ingredients, such as anti-IGF-I, -II antibodies, chemotherapy drugs, and the like. The compositions described herein can be approved for use by the U.S. FDA or the equivalent in other countries. The composition (e.g., pharmaceutical composition) containing the nucleic acid

molecule, vector, cell, or polypeptide can be administered in any suitable manner depending on whether local or systemic treatment is desired, and on the area to be treated.

If the composition is to be administered parenterally, the administration is generally by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for being prepared as a solution or suspension prior to injection, or as emulsions. Additionally, parental administration can involve the preparation of a slow-release or sustained-release system, such that a constant dosage is maintained (see, e.g., U.S. Patent 3,610,795, which is hereby incorporated by reference). Preparations for parenteral administration include sterile aqueous or nonaqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives also can be present such as, for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like.

The compositions can be in a form of acid- or base- addition salts, obtainable by reaction with inorganic acids, such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base, such as sodium hydroxide, ammonium hydroxide, potassium hydroxide, and organic bases, such as mono-, di-, trialkyl, and aryl amines and substituted ethanolamines.

The nucleic acid molecules, vectors, or polypeptides can be administered with a pharmaceutically acceptable carrier and can be delivered to the mammal's cells *in vivo* and/or *ex vivo* by a variety of mechanisms well-known in the art (e.g., uptake of naked DNA, liposome fusion, intramuscular injection of DNA via a gene gun, endocytosis, and the like).

The exact amount of the compositions required to treat cancer may vary, depending on the species, age, gender, weight, and general conditions of the mammal, the particular

polypeptide, nucleic acid, vector, or cell used, the route of administration, and whether other drugs are included in the regimen. Thus, it is not possible to specify an exact amount for every composition. However, an appropriate, suitable amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein. The dosage ranges for the administration of the compositions are those large enough to produce the desired effect; however, the dosage should not be so large as to cause adverse side effects, such as unwanted cross-reactions, anaphylactic reactions, and the like. Dosage can vary, and can be administered in one or more (*e.g.*, two or more, three or more, four or more, or five or more) doses daily, for one or more days (or any suitable period of time to advance treatment). The composition can be administered immediately upon determination of cancer and continuously or intermittently administered.

The term "effective amount," as used herein, refers to an amount that is capable of treating or ameliorating a disease or condition or otherwise capable of producing an intended therapeutic effect. In an embodiment, an effective amount is an amount that is useful for treating or ameliorating tumor or cancer. In an embodiment, an effective amount enables an inhibition or reduction of cancer cell growth or metastasis in a subject. Effective dosages and schedules for administering the therapeutic agents and compositions described herein can be determined empirically, and making such determinations is routine to one of ordinary skill in the art.

The skilled artisan will understand that the dosage of the polypeptides varies, depending upon, for example, the route of administration, the particular polypeptide to be used, other drugs being administered, and the age, condition, gender and seriousness of the disease in the subject as described above. An effective dose of the polypeptide described herein generally ranges between about 1 $\mu\text{g}/\text{kg}$ of body weight and 100 mg/kg of body weight. Examples of such dosage ranges are, *e.g.*, about 1 μg - 100 $\mu\text{g}/\text{kg}$, about 100 μg - 1 mg/kg , about 1 mg/kg - 10 mg/kg , or about 10 mg - 100 mg/kg , once a month, a week, bi-weekly, daily, or two to four times daily.

Guidance in selecting appropriate doses for anti-IGF-IR antibodies, such as the polypeptides described herein, is found in the literature on therapeutic uses of antibodies (see, *e.g.*, Handbook of Monoclonal Antibodies, Ferrone et al., eds., Noyes Publications, Park Ridge, N.J., (1985); and Smith et al., Antibodies in Human Diagnosis and Therapy, Haber et al., eds., Raven Press, New York (1977), all of which are hereby incorporated by reference. A typical

daily dosage of the polypeptide used might range from about 1 µg/kg to up to about 100 mg/kg of body weight or more per day, depending on the factors mentioned above. For example, the range can be from about 100 mg to about 1 g per dose. Nucleic acids, vectors, and host cells should be administered so as to result in comparable levels of production of polypeptides.

5 The disclosure also includes kits comprising the polypeptides, nucleic acid molecules, vectors, cells, epitopes, or compositions of the foregoing. The kits can include a separate container containing a suitable carrier, diluent, or excipient. The kits also can include an adjuvant, cytokine, antiviral agent, immunoassay reagents, PCR reagents, radiolabels, and the like. Additionally, the kits can include instructions for mixing or combining ingredients and/or
10 administration.

 The disclosure also provides a method of detecting IGF-IR in a mammal comprising contacting a sample obtained from the mammal with the polypeptide described herein. If an antigen is present in the mammal, to which the polypeptide can bind, a complex forms between the polypeptide and the antigen. Detection of the complex indicates the presence of elevated
15 IGF-IR in the mammal.

 The sample from the mammal can be of any suitable sample to detect the presence of IGF-IR. The complex can be detected by any suitable manner. The polypeptides described herein are utilizable as labeled molecules employed in radioimmunoassay (RIA) or enzyme immunoassay (EIA), particularly enzyme linked immunosorbent assay (ELISA), by introducing
20 thereto radioactive substances such as 1125, 1131, H3 (tritium), C14, and the like; various enzyme reagents such as peroxidase (POX), chymotrypsinogen, procarboxypeptidase, glyceraldehyde-3-phosphate dehydrogenase, amylase, phosphorylase, D-Nase, P-Nase, i3-galactosidase, glucose-6-phosphate dehydrogenase, ornithine decarboxylase, and the like. The radioactive substance can be introduced in a conventional manner. For example, the introduction
25 of radioactive iodine, 1125, can be carried out by the oxidative ionization method using chloramine T (see, e.g., Hunter *et al.*, Nature, 194, 495-496 (1962)) or by using the Boltzen-Hunter reagent (1125-iodinated p-hydroxyphenyl propionic acid N-hydroxy-succinimide ester), which is hereby incorporated by reference.

 The label for use in the method can be any suitable label known in the art, such as
30 biotinylated proteins or peptides.

EXAMPLE

Binding of H10 to cell-associated IGF-IR on breast cancer MCF-7 cells in flow cytometry

MCF-7 cells expressing IGF-IR were incubated with PBS buffer containing 1% FBS (filled curve) or with 10 µg/ml of recombinant H10 (empty curve) at 4°C for 1h. The bound antibodies were detected using phycoerythrin conjugated to goat anti-human IgG, F(ab')₂ (1:500) (ImmunoJackson). A FACSAarray plate reader (BD biosciences) was used for fluorescence-activated cell sorting (FACS) and FlowJo software for data interpretation. The result is shown in figure 3.

Other than in the operating examples, or where otherwise indicated, all numbers, values and/or expressions referring to quantities of ingredients, reaction conditions, etc., used in the specification and claims are to be understood as modified in all instances by the term "about."

While the invention has been explained in relation to certain embodiments, it is to be understood that various modifications thereof will become apparent to those skilled in the art upon reading the specification. Therefore, it is to be understood that the invention disclosed herein is intended to cover such modifications as fall within the scope of the appended claims.

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

CLAIMS

What is claimed is:

- 5 1. An isolated antibody or a binding fragment thereof that specifically binds to human insulin-like growth factor I receptor (IGF-IR), wherein CDR1 of a V_H region of which comprises SEQ ID NO: 9, CDR2 of a V_H region of which comprises SEQ ID NO: 10, and CDR3 of a V_H region of which comprises SEQ ID NO: 3.
- 10 2. The isolated antibody or a binding fragment thereof according to claim 1, wherein a V_H region of which comprises SEQ ID NO: 1.
3. The isolated antibody or a binding fragment thereof according to claim 1, wherein CDR1 of a V_L region of which comprises SEQ ID NO: 11, CDR2 of a V_L region of which comprises
15 GTS, and CDR3 of a V_L region of which comprises SEQ ID NO: 4.
4. The isolated antibody or a binding fragment thereof according to claim 3, a V_L region of which comprises SEQ ID NO: 2.
- 20 5. The isolated antibody or a binding fragment thereof according to claim 1, which specifically binds to human IGF-IR expressed on cancer cells.
6. The isolated antibody or a binding fragment thereof according to claim 1, which
25 specifically binds to extracellular domain of human IGF-IR.
7. The isolated antibody or a binding fragment thereof according to claim 1, which is a monoclonal antibody.

8. The isolated antibody or a binding fragment thereof according to claim 1, which comprises an Fab, Fab', F(ab')₂, or scFv.

5 9. The isolated antibody or a binding fragment thereof according to claim 1, which is a humanized antibody.

10. A pharmaceutical composition comprising an isolated antibody or a binding fragment thereof of claim 1 and a pharmaceutically acceptable carrier.

10 11. A nucleic acid molecule encoding an isolated antibody or a binding fragment thereof of claim 1.

12. The nucleic acid molecule according to claim 11, which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, and 5'ggcagctcc 3'.

15

13. A pharmaceutical composition comprising a nucleic acid molecule of claim 11 and a pharmaceutically acceptable carrier.

20

14. A method for treating a tumor or cancer, comprising administering to a subject in need of such treatment an effective amount of an isolated antibody or a binding fragment thereof of claim 1.

25 15. The method according to claim 14, wherein a V_H region of said antibody comprises SEQ ID NO: 1.

16. The method according to claim 14, wherein CDR1 of a V_L region of said antibody comprises SEQ ID NO: 11, CDR2 of a V_L region of said antibody comprises GTS, and CDR3 of a V_L region of said antibody comprises SEQ ID NO: 4.

30

17. The method according to claim 14, wherein the subject is a human.

18. The method according to claim 14, used to treat prostate cancer, breast cancer, liver cancer, or colon cancer.

5

19. A method for treating a tumor or cancer, comprising administering to a subject in need of such treatment an effective amount of an isolated nucleic acid molecule of claim 12.

10

20. The method according to claim 19, used to treat prostate cancer, breast cancer, liver cancer, or colon cancer.

21. Use of an isolated antibody or a binding fragment thereof of claim 1 in the manufacture of a medicament for treating a tumor or cancer.

15

22. The use according to claim 21, wherein a V_H region of said antibody comprises SEQ ID NO: 1.

20

23. The use according to claim 21, wherein CDR1 of a V_L region of said antibody comprises SEQ ID NO: 11, CDR2 of a V_L region of said antibody comprises GTS, and CDR3 of a V_L region of said antibody comprises SEQ ID NO: 4.

24. The use according to claim 21, wherein the subject is a human.

25

25. The use according to claim 21, said cancer comprises prostate cancer, breast cancer, liver cancer, and colon cancer.

26. Use of an isolated nucleic acid molecule of claim 12 in the manufacture of a medicament for treating a tumor or cancer.

27. The use according to claim 26, said cancer comprises prostate cancer, breast cancer, liver cancer, and colon cancer.

Figure 1

H10 VH (SEQ ID No: 1):

EVQLLESGAEVKRPGSSVRVSCQVSGYSFTAYYVSWVRQTPGHGLEWMGGINPDNG
5 GNNYAQKFHGRVTFIADESTRTVHMELRSLRSEDTAVYFCAKSTSYDYDGYWYFDVW
GQGTAVTVFSS

H10 VL (SEQ ID NO: 2):

ELQMTQSPSSVSASVGDRVTITCRASSSVSYLAWYQQKPGKAPKLLINGTSSLQSGVP
SRFSGSGSGTDFTLTISLQPEDFATYYCQQRSSYPFTFGGGTKVEIKR

H10 H3 (SEQ ID No: 3): AKSTSYDYDGYWYFDV

10 **H10 L3 (SEQ ID NO: 4): QQRSSYPFT**

H10 VH DNA (SEQ ID NO: 5):

gaggtgcagctgctcagctctggggctgaggtgaagaggcctgggtcctcggtgagagtctcctgccaagttctggttact
cattcactgcctactacgtcagttgggtgacagaccctggacacgggcttgagtgatgggagggattaatcctgaca
atggtggttaacaactacgcacagaagttcacggccgagtgacattatcgccgacgagtcacgaggacagtccacat
15 ggaactgcgagcctgagatctgaggacacggcctatctttgtgcaaagtcaacctcctatgattacgacggttactggt
acttcgatgtctggggccaagggaccgcggtcaccgtcttctcctca

H10 VL DNA (SEQ ID NO: 6):

gagctccagatgaccagtcctccatcttccgtgtctgcatctgctggagacagagtcaccatcactgtogggcgagttcaa
gtgtaagttacttagcctggtatcagcagaaaccagggaaagcccctaagctcctgatcaatggcacgtccagttgcaaa
20 gtgggtcccatcaaggtcagcggcagtgatctgggacagattcactctaccatcagcagcctgcagcctgaagatt
ttcgactactattgtcagcaaaggagtagttaccattcaggtcggcggaggaccgaaggtggagatcaaacga

H10 H3 DNA (SEQ ID NO: 7): gcaaagtcaacctcctatgattacgacggttactggtacttcgatgtc**H10 L3 DNA (SEQ ID NO: 8): cagcaaaggagtagttaccattcagc**

Figure 2

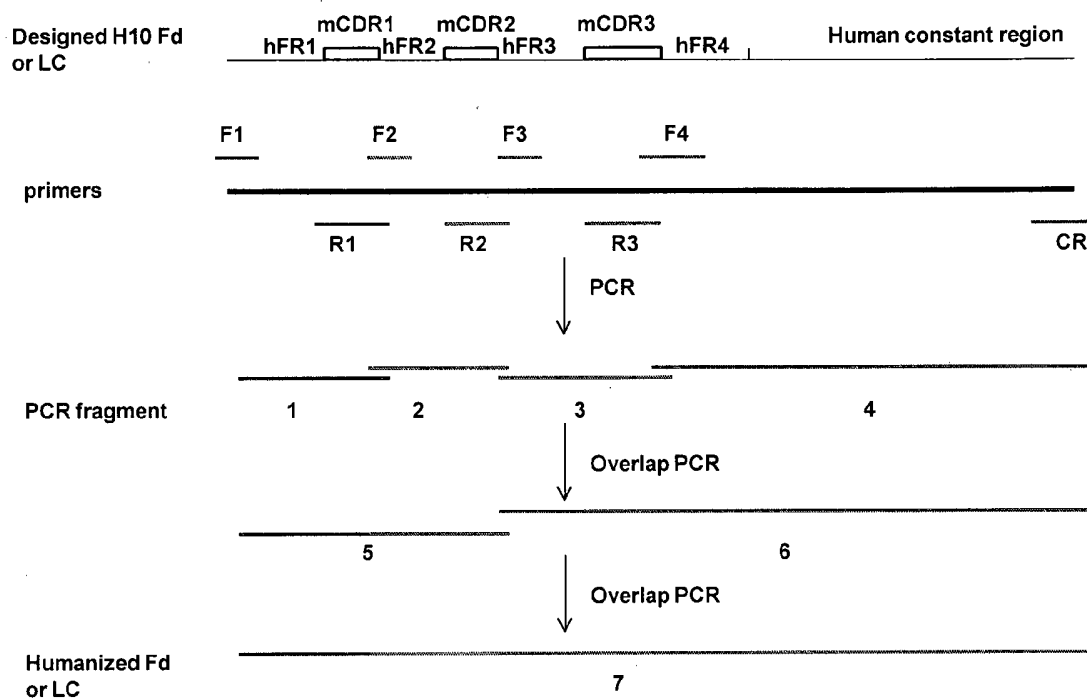
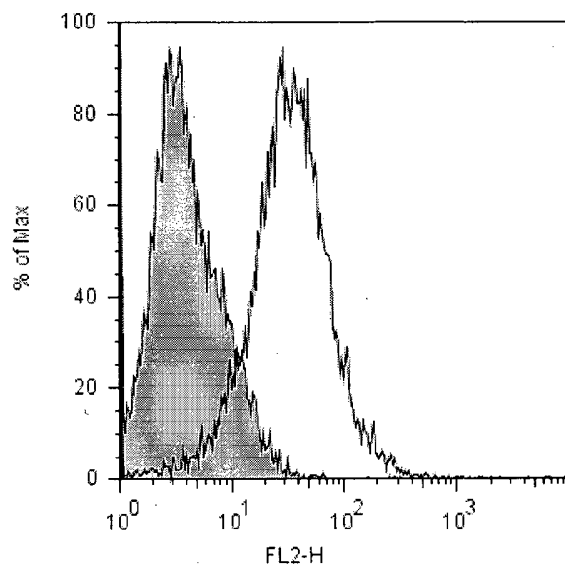


Figure 3



Filled curve: 2nd antibody control
Empty curve: 10 µg/ml of recombinant H10

5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001963

A. CLASSIFICATION OF SUBJECT MATTER		
See extra sheet		
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)		
IPC:C07K 16/-; C12N 5/-; C12N 15/-; A61K 39/-		
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 practicable, search terms used)		
EPODOC, WPI, ISI, CNPAT, GenBank, MEDLINE, CNKI, CDR1, CDR2, CDR3, Antibody, binding, inhibiting, specifically, human, insulin-like growth factor I, receptor, IGF-IR, monoclonal antibodies, murine, chimeric, humanized, amino acid and nucleic acid, sequences		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN101014625A (FABRE MEDICAMENT SA PIERRE) 08 Aug.2007 (08.08.2007), claims 1-27, description: page 12, lines 1-8, page 1, lines 1-15, page 10, lines 3-5, 13-17, 23-31, page 13, lines 1-3, 15-18, 23-26, page 18, lines 9-12, example 2, page 16, lines 28-30, page 22, lines 26-29, pages 23, lines 1-3	1-27
X	WO 2007012614 A2 (FABRE MEDICAMENT SA PIERRE) 01 Feb.2007(01.02.2007), claims 1-70, examples 1-8	1-27
A	FENG, Lingfei et al.Expression and clinic significance of IGF-IR in Breast Cancer tissue. Journal of Medical Forum. Mar.2008, Vol. 29, no. 5, pages 8-10	1-27
A	SUN, Liyan et al, Advancement in research on insulin-like growth factor in cancer metastasis. International Journal of Internal Medicine. Jun.2008, Vol. 35, no. 6, pages 329-336	1-27
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents:	"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	
"A" document defining the general state of the art which is not considered to be of particular relevance		
"E" earlier application or patent 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		
Date of the actual completion of the international search	Date of mailing of the international search report	
17 Feb. 2011 (17.02.2011)	10 Mar. 2011 (10.03.2011)	
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer DING, Hai Telephone No. +86-10-82245245	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001963

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item item 1.c of the first sheet)

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

a. a sequence listing filed or furnished

on paper

in electronic form

b. time of filing or furnishing

contained in the applicant as filed

filed together with the application in electronic form

furnished subsequently to this Authority for the purposes of search

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

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001963

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 14-20
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 14-20 are directed to methods for treating a tumor or cancer, which pertain to methods of disease treatment. But the search has been carried out and based on the use for preparing a medicament or a pharmaceutical composition with the alleged effect.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001963

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 101014625 A	08.08.2007	WO 2006013472 A2	09.02.2006
		EP 1771481 A2	11.04.2007
		AU 2005268505 A1	09.02.2006
		INDELNP200700743E	27.04.2007
		KR 20070057814 A	07.06.2007
		JP 2008515773T	15.05.2008
		BRPI0513890 A	20.05.2008
		MXPA07001109 A	01.05.2007
		ZA 200700593 A	28.05.2008
		NO 20071093 A	27.02.2007
		TW 200628490 A	16.08.2006
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		EP 1907426 A2	09.04.2008
		NO 20080892 A	16.04.2008
		AU 2006274086 A1	01.02.2007
		INDELNP200800436E	04.04.2008
		KR 20080032117 A	14.04.2008
		JP 2009502129T	29.01.2009
		CA 2616099 A1	01.02.2007
		MXPA08000964 A	01.03.2008
		US 2009265797 A1	22.10.2009

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001963

Continuation of :classification of subject matter:

C07K 16/28 (2006.01) i

C12N 5/18 (2006.01) i

C12N 15/13 (2006.01) i

A61K 39/00 (2006.01) i

A61K 39/395 (2006.01) i