The present invention relates to a therapeutic method comprising administering anti-IGF-IR antibodies, particularly human anti-IGF-IR antibodies to a subject for the treatment of certain disorders preferably in conjunction with administration of another therapeutic agent. The invention further relates to pharmaceutical compositions comprising these antibodies and methods of using the antibodies and compositions thereof for treatment.
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USES OF ANTI-INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR ANTIBODIES

Vehicle

31.25 μm

125 μm

500 μm

KLH, 500 μm

(57) Abstract: The present invention relates to a therapeutic method comprising administering antiIGF-IR antibodies, particularly human anti-IGF-IR antibodies to a subject for the treatment of certain disorders preferably in conjunction with administration of another therapeutic agent. The invention further relates to pharmaceutical compositions comprising these antibodies and methods of using the antibodies and compositions thereof for treatment.
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USES OF ANTI-INSULIN-LIKE GROWTH FACTOR I RECEPTOR ANTIBODIES

Background of the Invention

The present invention relates to uses of, and compositions containing, anti-insulin-like growth factor I receptor (IGF-IR) antibodies.

Insulin-like growth factor (IGF-I) is a 7.5-kD polypeptide that circulates in plasma in high concentrations and is detectable in most tissues. IGF-I stimulates cell differentiation and cell proliferation, and is required by most mammalian cell types for sustained proliferation. These cell types include, among others, human diploid fibroblasts, epithelial cells, smooth muscle cells, T lymphocytes, neural cells, myeloid cells, chondrocytes, osteoblasts and bone marrow stem cells.

The first step in the transduction pathway leading to IGF-I-stimulated cellular proliferation or differentiation is binding of IGF-I or IGF-II (or insulin at supraphysiological concentrations) to the IGF-I receptor. The IGF-I receptor (IGF-IR) is composed of two types of subunits: an alpha subunit (a 130-135 kD protein that is entirely extracellular and functions in ligand binding) and a beta subunit (a 95-kD transmembrane protein, with transmembrane and cytoplasmic domains). The IGF-IR is initially synthesized as a single chain proreceptor polypeptide that is processed by glycosylation, proteolytic cleavage, and covalent bonding to assemble into a mature 460-kD heterotetramer comprising two alpha-subunits and two beta-subunits. The beta subunit(s) possesses ligand-activated tyrosine kinase activity. This activity is implicated in the signaling pathways mediating ligand action which involve autophosphorylation of the beta-subunit and phosphorylation of IGF-IR substrates.

Calorie restriction is the most effective and reproducible intervention for increasing the life span in a variety of animal species, including mammals. It is also the most potent, broadly acting cancer-prevention regimen in experimental carcinogenesis models. A key biological mechanism underlying many of its beneficial effects is the insulin-like growth factor-1 pathway (Hursting et al., Annu. Rev. Med. 54:131-52, 2003).

In view of the roles that IGF-I and IGF-IR have in such disorders as cancer and other proliferative disorders when IGF-I and/or IGF-IR are overexpressed, antibodies to IGF-IR have been produced that block binding of IGF-I or IGF-II to IGF-IR. Such antibodies are described, for example, in WO 02/05359, published July 11, 2002. The text of these publications, including all sequences described, is hereby incorporated by reference. It is desirable to use such high-affinity human anti-IGF-IR antibodies to treat relevant diseases in humans.

Summary of the Invention

The present invention relates to a method for the treatment or prevention of a disorder wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated auto-immune disease, endocrinological disorder, ischemia, and neurodegenerative disorder in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody that is effective in treating said disorder. In one embodiment, the method also comprises administering to said mammal said antibody in combination with an agent selected from the group consisting of a corticosteroid, anti-emetic, cancer vaccine, analgesic, anti-vascular agent, and anti-proliferative agent.

The liquid tumor is preferably acute lymphocytic leukemia (ALL) or chronic myelogenic leukemia (CML). The liver cancer is preferably hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, or hepatoblastoma. The thymus disorder is preferably thymoma or thyroiditis. The T-cell mediated autoimmune disease is preferably Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave’s Disease, Hashimoto’s Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, or Bechet’s Disease. The endocrinological disorder is preferably Diabetes II, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and hypoadrenocorticism. The ischemia is preferably post-cardiac ischemia. The neurodegenerative disorder is preferably Alzheimer’s Disease.

Where the antibody is administered in combination with an anti-proliferative agent, the agent is preferably selected from the group consisting of farnesyl protein transferase inhibitors, αvβ3 inhibitors, αvβ5 inhibitors, p53 inhibitors, and PDGFR inhibitors.

Where the antibody is administered in combination with an anti-vascular agent, the agent is preferably selected from the group consisting of bevacizumab or rhuMAb-VEGF.
Where the antibody is administered in combination with an anti-emetic agent, the agent is preferably selected from the group consisting of ondansetron hydrochloride, granisetron hydrochloride, metoclopramide, domperidone, haloperidol, cyclazine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, or tropisetron.

Where the antibody is administered in combination with a vaccine, the vaccine is preferably selected from GM-CSF DNA and cell-based vaccines, dendritic cell vaccines, recombinant viral vaccines, heat shock protein (HSP) vaccines, allogeneic or autologous tumor vaccines. In one embodiment, the vaccine is peptide, DNA, or cell based.

Where the antibody is administered in combination with an analgesic agent, the agent is preferably selected from the group consisting of ibuprofen, naproxen, choline magnesium trisalicylate, or oxycodone hydrochloride.

In a preferred embodiment, the mammal is a human.

In one embodiment, the antibody that binds to IGF-IR has the following properties:

- a binding affinity for human IGF-IR of K_d of 8 x 10^{-9} or less;
- inhibition of binding between human IGF-IR and IGF-I with an IC_{50} of less than 100 nM; and
- comprises a heavy chain amino acid sequence comprising human FR1, FR2, and FR3 amino acid sequences that correspond to those of the VH DP-35, VIV-4/4.35, VH DP-47, or VH DP-71 gene, or conservative substitutions or somatic mutations therein, wherein the FR sequences are linked with CDR1, CDR2, and CDR3 sequences, and wherein the antibody also comprises CDR regions in its light chain from the A27, A30, or O12 gene.

Alternatively, the antibody competes for binding with an antibody having heavy and light chain amino acid sequences of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3, and 6.1.1. For example, the antibody can bind to the epitope to which an antibody binds that has heavy and light chain amino acid sequences of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3, and 6.1.1.

In another embodiment, the invention is practiced using an antibody that comprises a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, and a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3, and 6.1.1, or sequences having changes from said CDR sequences selected from the group consisting of conservative changes, wherein said conservative changes are selected from the group consisting of replacement of nonpolar residues by other nonpolar residues, replacement of polar charged residues by other polar uncharged residues, replacement of polar charged residues by other polar charged residues, and substitution of structurally similar residues; and non-conservative substitutions, wherein said non-conservative substitutions are selected from
the group consisting of substitution of polar charged residue for polar uncharged residues and substitution of nonpolar residues for polar residues, additions and deletions.

In a preferred embodiment, the antibody comprises a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, and a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3, or 6.1.1. In another embodiment, the antibody comprises a heavy chain amino acid sequence derived from human gene DP-47 and a light chain amino acid derived from human gene A30.

The invention also relates to a pharmaceutical composition for treatment of a disorder in a mammal comprising an amount of a human anti-IGF-IR antibody that is effective in treating said disorder and a pharmaceutically acceptable carrier, wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated autoimmune disease, endocrinological disorder, ischemia, and neurodegenerative disorder. In one embodiment, the invention relates to a combination pharmaceutical composition that also comprises an amount of a corticosteroid, anti-emetic, cancer vaccine, analgesic, anti-vascular agent, or an anti-proliferative agent that, in combination with said antibody, is effective in treating said disorder.

The invention also relates to use of an amount of a human anti-IGF-IR antibody in the preparation of a composition for the treatment of a disorder in a mammal that is effective in treating said disorder, wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated autoimmune disease, endocrinological disorder, ischemia, and neurodegenerative disorder.

**Brief Description of the Drawings**

Figs. 1A-1C show alignments of the nucleotide sequences of the light chain variable regions from six human anti-IGF-IR antibodies to each other and to germline sequences. Fig. 1A shows the alignment of the nucleotide sequences of the variable region of the light chain (VL) of antibodies 2.12.1 (SEQ ID NO: 1) 2.13.2 (SEQ ID NO: 5), 2.14.3 (SEQ ID NO: 9) and 4.9.2 (SEQ ID NO: 13) to each other and to the germline Vk A30 sequence (SEQ ID NO: 39). Fig. 1B shows the alignment of the nucleotide sequence of VL of antibody 4.17.3 (SEQ ID NO: 17) to the germline Vk O12 sequence (SEQ ID NO: 41). Fig. 1C shows the alignment of the nucleotide sequence of VL of antibody 6.1.1 (SEQ ID NO: 21) to the germline Vk A27 sequence (SEQ ID NO: 37). The alignments also show the CDR regions of the VL from each antibody. The consensus sequences for Figs. 1A-1C are shown in SEQ ID NOS: 53-55, respectively.

Figs. 2A-2D show alignments of the nucleotide sequences of the heavy chain variable regions from six human anti-IGF-IR antibodies to each other and to germline sequences. Fig. 2A shows the alignment of the nucleotide sequence of the VH of antibody 2.12.1 (SEQ ID
NO: 3) to the germline VH DP-35 sequence (SEQ ID NO: 29). Fig. 2B shows the alignment of the nucleotide sequence of the VH of antibody 2.14.3 (SEQ ID NO: 11) to the germline VIV-4/4.35 sequence (SEQ ID NO: 43). Figs. 2C-1 and 2C-2 show the alignments of the nucleotide sequences of the VH of antibodies 2.13.2 (SEQ ID NO: 7), 4.9.2 (SEQ ID NO: 15) and 6.1.1 (SEQ ID NO: 23) to each other and to the germline VH DP-47 sequence (SEQ ID NO: 31). Fig. 2D shows the alignment of the nucleotide sequence of the VH of antibody 4.17.3 (SEQ ID NO: 19) to the germline VH DP-71 sequence (SEQ ID NO: 35). The alignment also shows the CDR regions of the antibodies. The consensus sequences for Figs. 2A-2D are shown in SEQ ID NOS: 56-59, respectively.

Fig. 3A shows the number of mutations in different regions of the heavy and light chains of 2.13.2 and 2.12.1 compared to the germline sequences. Figs. 3A-D show alignments of the amino acid sequences from the heavy and light chains of antibodies 2.13.2 and 2.12.1 with the germline sequences from which they are derived. Fig. 3B shows an alignment of the amino acid sequence of the heavy chain of antibody 2.13.2 (SEQ ID NO: 45) with that of germline sequence DP-47(3-23)/D6-19/JH6 (SEQ ID NO: 46). Fig. 3C shows an alignment of the amino acid sequence of the light chain of antibody 2.13.2 (SEQ ID NO: 47) with that of germline sequence A30/Jk2 (SEQ ID NO: 48). Fig. 3D shows an alignment of the amino acid sequence of the heavy chain of antibody 2.12.1 (SEQ ID NO: 49) with that of germline sequence DP-35(3-11)/D3-3/JH6 (SEQ ID NO: 50). Fig. 3E shows an alignment of the amino acid sequence of the light chain of antibody 2.12.1 (SEQ ID NO: 51) with that of germline sequence A30/Jk1 (SEQ ID NO: 52). For Figures 3B-E, the signal sequences are in italic, the CDRs are underlined, the constant domains are bold, the framework (FR) mutations are highlighted with a plus sign (+) above the amino acid residue and CDR mutations are highlighted with an asterisk above the amino acid residue.

Fig. 4 shows that anti-IGF-IR antibodies 2.13.2 and 4.9.2 reduce IGF-IR phosphotyrosine signal in 3T3-IGF-IR tumors.

Fig. 5 shows that anti-IGF-IR antibody 2.13.2 inhibits 3T3-IGF-IR tumor growth in vivo.

Detailed Description of the Invention

All patents, patent applications, and other references cited herein are hereby incorporated by reference in their entirety.

The antibody can also be used with other agents useful in treating abnormal IGF-IR activity, including, but not limited to different anti-IGF-IR antibodies such as those described in WO 02/053596, and other agents also capable of blocking IGF-IR.

Conjoint (combination) treatment described herein may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.
The antibody can be administered to treat or prevent initial disease, or to treat or prevent recurrence. It can be employed to treat early or advanced disease.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

An "antibody" refers to an intact immunoglobulin or to an antigen-binding portion thereof that competes with the intact antibody for specific binding. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, inter alia, Fab, Fab', F(ab')2, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

Immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J. Mol. Biol. 196:901-917 (1987); Chothia et al. Nature 342:878-883 (1989).

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. Examples of isolated antibodies include an anti-IGF-IR antibody that has been affinity purified using IGF-IR is an isolated
antibody, an anti-IGF-IR antibody that has been synthesized by a hybridoma or other cell line in vitro, and a human anti-IGF-IR antibody derived from a transgenic mouse.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In a preferred embodiment, one or more of the CDRs are derived from a human anti-IGF-IR antibody. In a more preferred embodiment, all of the CDRs are derived from a human anti-IGF-IR antibody. In another preferred embodiment, the CDRs from more than one human anti-IGF-IR antibodies are mixed and matched in a chimeric antibody. Further, the framework regions may be derived from one of the same anti-IGF-IR antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar sides chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is \( \leq 1 \mu M \), preferably \( \leq 100 \) nM and most preferably \( \leq 10 \) nM.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 75% or 80% sequence identity, preferably at least 90% or 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson, Methods Mol. Biol. 24: 307-31 (1994), herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; and 6) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine.
Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie et al. Science 253:164 (1991). Thus, the foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various mutations of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence).

The term patient includes human and veterinary subjects.

Human antibodies avoid certain of the problems associated with antibodies that possess mouse or rat variable and/or constant regions. Therefore, in one embodiment, the invention provides humanized anti-IGF-IR antibodies. More preferred are fully human anti-human IGF-IR antibodies. Fully human anti-IGF-IR antibodies are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized monoclonal antibodies (Mabs) and thus to increase the efficacy and safety of the administered antibodies. The use of fully human antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as inflammation and cancer, which may require repeated antibody administrations. In another embodiment, the invention provides an anti-IGF-IR antibody that does not bind complement.

In another aspect of the invention, the anti-IGF-IR antibodies bind to IGF-IR with high affinity. In one embodiment, the anti-IGF-IR antibody binds to IGF-IR with a $K_d$ of $1 \times 10^{-8}$ M or less. In a more preferred embodiment, the antibody binds to IGF-IR with a $K_d$ of $1 \times 10^{-9}$ M or less. In an even more preferred embodiment, the antibody binds to IGF-IR with a $K_d$ of $5 \times$
10^{-10} \text{ M} \text{ or less. In another preferred embodiment, the antibody binds to IGF-IR with a } K_d \text{ or 1} x 10^{-10} \text{ M or less. In another preferred embodiment, the antibody binds to IGF-IR with substantially the same } K_d \text{ as an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the antibody binds to IGF-IR with substantially the same } K_d \text{ as an antibody that comprises one or more CDRs from an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.}

The invention also employs an anti-IGF-IR antibody that binds the same antigen or epitope as a human anti-IGF-IR antibody. Further, the invention can employ an anti-IGF-IR antibody that cross-competes with a human anti-IGF-IR antibody. In a preferred embodiment, the human anti-IGF-IR antibody is 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the human anti-IGF-IR comprises one or more CDRs from an antibody selected from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

The invention can also be practiced using an anti-IGF-IR antibody that comprises variable sequences encoded by a human κ gene. In a preferred embodiment, the variable sequences are encoded by either the Vκ A27, A30 or O12 gene family. In a preferred embodiment, the variable sequences are encoded by a human Vκ A30 gene family. In a more preferred embodiment, the light chain comprises no more than ten amino acid substitutions from the germline Vκ A27, A30 or O12, preferably no more than six amino acid substitutions, and more preferably no more than three amino acid substitutions. In a preferred embodiment, the amino acid substitutions are conservative substitutions.

In a preferred embodiment, the VL of the anti-IGF-IR antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VL of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

In another preferred embodiment, the light chain comprises an amino acid sequence that is the same as the amino acid sequence of the VL of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another highly preferred embodiment, the light chain comprises amino acid sequences that are the same as the CDR regions of the light chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the light chain comprises an amino acid sequence from at least one CDR region of the light chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

The present invention can also be carried out using an anti-IGF-IR antibody or portion thereof comprising a human heavy chain or a sequence derived from a human heavy chain. In one embodiment, the heavy chain amino acid sequence is derived from a human V\textsubscript{H} DP-35, DP-47, DP-70, DP-71 or VIV-4/4.35 gene family. In a preferred embodiment, the heavy chain amino acid sequence is derived from a human V\textsubscript{H} DP-47 gene family. In a more preferred embodiment, the heavy chain comprises no more than eight amino acid changes.
from germline V\textsubscript{H} DP-35, DP-47, DP-70, DP-71 or VIV-4/4.35, more preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

In a preferred embodiment, the VH of the anti-IGF-IR antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VH of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another embodiment, the amino acid substitutions are made in the same position as those found in any one or more of the VH of antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.17.3, 4.9.2 or 6.1.1, but conservative amino acid substitutions are made rather than using the same amino acid.

In another preferred embodiment, the heavy chain comprises an amino acid sequence that is the same as the amino acid sequence of the VH of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another highly preferred embodiment, the heavy chain comprises amino acid sequences that are the same as the CDR regions of the heavy chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the heavy chain comprises an amino acid sequence from at least one CDR region of the heavy chain of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1. In another preferred embodiment, the heavy chain comprises amino acid sequences from CDRs from different heavy chains. In a more preferred embodiment, the CDRs from different heavy chains are obtained from 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 or 6.1.1.

In another embodiment, the invention employs an anti-IGF-IR antibody that inhibits the binding of IGF-I to IGF-IR or the binding of IGF-II to IGF-IR. In a preferred embodiment, the IGF-IR is human. In another preferred embodiment, the anti-IGF-IR antibody is a human antibody. In another embodiment, the antibody or portion thereof inhibits binding between IGF-IR and IGF-I with an IC\textsubscript{50} of no more than 100 nM. In a preferred embodiment, the IC\textsubscript{50} is no more than 10 nM. In a more preferred embodiment, the IC\textsubscript{50} is no more than 5 nM. The IC\textsubscript{50} can be measured by any method known in the art. Typically, an IC\textsubscript{50} can be measured by ELISA or RIA. In a preferred embodiment, the IC\textsubscript{50} is measured by RIA.

In another embodiment, the invention employs an anti-IGF-IR antibody that prevents activation of the IGF-IR in the presence of IGF-I. In another aspect of the invention, the antibody causes the downregulation of IGF-IR from a cell treated with the antibody. In a preferred embodiment, the antibody is selected 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, or 6.1.1, or comprises a heavy chain, light chain or antigen-binding region thereof.

Human antibodies can be produced by immunizing a non-human animal comprising of some or all of the human immunoglobulin locus with an IGF-IR antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE™, which is an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. See, e.g., Green et al. Nature Genetics 7:13-21 (1994) and United States Patents 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001,

The IGF-IR antigen can be administered with a adjuvant to stimulate the immune response. Such adjuvants include complete or incomplete Freund's adjuvant, RIBI (muramyl dipeptides) or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. Preferably, if a polypeptide is being administered, the immunization schedule will involve two or more administrations of the polypeptide, spread out over several weeks.

The nucleic acid molecule encoding the variable region of the light chain may be derived from the A30, A27 or O12 Vκ gene. In a preferred embodiment, the light chain is derived from the A30 Vκ gene. In an even more preferred embodiment, the nucleic acid molecule encoding the light chain contains no more than ten amino acid changes from the germline A30 Vκ gene, preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

In one embodiment, the antibody contains no greater than ten amino acid changes in either the VH or VL regions of the mutated anti-IGF-IR antibody compared to the anti-IGF-IR antibody prior to mutation. In a more preferred embodiment, there are no more than five amino acid changes in either the VH or VL regions of the mutated anti-IGF-IR antibody, more preferably no more than three amino acid changes. In another embodiment, there are no more than fifteen amino acid changes in the constant domains, more preferably, no more than ten amino acid changes, even more preferably, no more than five amino acid changes.

SEQ ID NOS: 2, 6, 10, 14, 18 and 22 provide the amino acid sequences of the variable regions of six anti-IGF-IR κ' light chains. SEQ ID NOS: 4, 8, 12, 16, 20 and 24 provide the amino acid sequences of the variable regions of six anti-IGF-IR heavy chains. SEQ ID NO: 26 depicts the amino acid sequence and SEQ ID NO: 25 depicts the nucleic acid
sequence encoding the constant region of the light chain of the anti-IGF-IR antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 and 6.1.1. SEQ ID NO: 28 depicts the amino acid sequence and SEQ ID NO: 27 depicts the nucleic acid sequence encoding the constant region of the heavy chain of the anti-IGF-IR antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 and 6.1.1. SEQ ID NOS: 30, 32, 34, 36 and 44 provide the amino acid sequences of the germline heavy chains DP-35, DP-47, DP-70, DP-71 and VIV-4, respectively. SEQ ID NO: 33 provides the nucleotide sequence of the germline heavy chain DP-70. SEQ ID NOS: 38, 40 and 42 provide the amino acid sequences of the three germline κ light chains from which the six anti-IGF-IR κ light chains are derived.

In another preferred embodiment, the invention relates to the use of anti-IGF-IR in the prevention of aging.

In another embodiment, the invention relates to pharmaceutical compositions for the treatment of a mammal that requires activation of IGF-IR, wherein the pharmaceutical composition comprises a therapeutically effective amount of an activating antibody of the invention and a pharmaceutically acceptable carrier. Pharmaceutical compositions comprising activating antibodies may be used to treat animals that lack sufficient IGF-I or IGF-II.

The anti-IGF-IR antibodies can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

The pharmaceutical compositions may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the
antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the anti-IGF-IR antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

The antibodies can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intraperitoneal, subcutaneous, intramuscular, intravenous or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In one embodiment, the antibodies can be administered as a single dose or may be administered as multiple doses.

In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polynorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, the antibody may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets,
buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an anti-IGF-IR antibody is coformulated with and/or coadministered with one or more additional therapeutic agents, such as anti-emetics, cancer vaccines, analgesics, anti-vascular agents, and anti-proliferative agents.

The pharmaceutical composition may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Pharmaceutical composition comprising the antibody or comprising a combination therapy comprising the antibody and one or more additional therapeutic agents may be formulated for single or multiple doses. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in
individuals. A particularly useful formulation is 5 mg/ml anti-IGF-IR antibody in a buffer of 20mM sodium citrate, pH 5.5, 140mM NaCl, and 0.2mg/ml polysorbate 80.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1-100 mg/kg, more preferably 0.5-50 mg/kg, more preferably 1-20 mg/kg, and even more preferably 1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. In one embodiment, the therapeutically or prophylactically effective amount of an antibody or antigen-binding portion thereof is administered along with one or more additional therapeutic agents.

The antibody employed in the method of the invention can be labeled. This can be done by incorporation of a detectable marker, e.g., incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., $^3$H, $^{14}$C, $^{15}$N, $^{35}$S, $^{90}$Y, $^{99}$Tc, $^{111}$In, $^{125}$I, $^{131}$I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, $\beta$-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

The antibodies employed in the present invention are preferably derived from cells that express human immunoglobulin genes. Use of transgenic mice is known in the art to produce such "human" antibodies. One such method is described in Mendez et al. Nature Genetics 15:146-156 (1997), Green and Jakobovits J. Exp. Med. 188:483-495 (1998), and U.S. Patent Application Serial 08/759,620 (filed December 3, 1996). The use of such mice to obtain human antibodies is also described in U.S. Patent Applications 07/466,008 (filed January 12, 1990), 07/610,515 (filed November 8, 1990), 07/919,297 (filed July 24, 1992), 07/922,649 (filed July 30, 1992), filed 08/031,801 (filed March 15,1993), 08/112,848 (filed August 27, 1993), 08/234,145 (filed April 28, 1994), 08/376,279 (filed January 20, 1995), 08/430,938 (filed April 27, 1995), 08/464,584 (filed June 5, 1995), 08/464,582 (filed June 5,

As noted above, the invention encompasses use of antibody fragments (included herein in the definition of "antibody"). Antibody fragments, such as Fv, F(ab')2, and Fab may be prepared by cleavage of the intact protein, e.g. by protease or chemical cleavage. Alternatively, a truncated gene is designed. For example, a chimeric gene encoding a portion of the F(ab')2 fragment would include DNA sequences encoding the CH1 domain and hinge region of the H chain, followed by a translational stop codon to yield the truncated molecule.

In one approach, consensus sequences encoding the heavy and light chain J regions may be used to design oligonucleotides for use as primers to introduce useful restriction sites into the J region for subsequent linkage of V region segments to human C region segments. C region cDNA can be modified by site directed mutagenesis to place a restriction site at the analogous position in the human sequence.

Expression vectors for use in obtaining the antibodies employed in the invention include plasmids, retroviruses, cosmids, YACs, EBV derived episomes, and the like. A convenient vector is normally one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The resulting chimeric antibody may be joined to any strong promoter, including retroviralLTRs, e.g. SV-40 early promoter, (Okayama et al. Mol. Cell. Bio. 3:280 (1983)), Rous sarcoma virus LTR (Gorman et al. P.N.A.S. 79:6777 (1982)), and moloney murine leukemia virus LTR (Grosschedl et al. Cell 41:885 (1985)); native Ig promoters, etc.

Antibodies that are generated for use in the invention need not initially possess a particular desired isotype. Rather, the antibody as generated can possess any isotype and can be isotype switched thereafter using conventional techniques. These include direct recombinant techniques (see e.g., U.S. Patent 4,816,397), and cell-cell fusion techniques (see e.g., U.S. Patent Application 08/730,639 (filed October 11, 1996).
As noted above, the effector function of the antibodies of the invention may be changed by isotype switching to an IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM for various therapeutic uses. Furthermore, dependence on complement for cell killing can be avoided through the use of bispecifics, immunotoxins, or radiolabels, for example.

Bispecific antibodies can be generated that comprise (i) two antibodies: one with a specificity for IGF-IR and the other for a second molecule (ii) a single antibody that has one chain specific for IGF-IR and a second chain specific for a second molecule, or (iii) a single chain antibody that has specificity for IGF-IR and the other molecule. Such bispecific antibodies can be generated using well known techniques, e.g., Fanger et al. Immunol Methods 4:72-81 (1994), Wright and Harris, supra, and Traunecker et al. Int. J. Cancer (Suppl.) 7:51-52 (1992).


The antibodies employed can be modified to act as immunotoxins by conventional techniques. See e.g., Vitetta Immunol Today 14:252 (1993). See also U.S. Patent 5,194,594. Radiolabeled antibodies can also be prepared using well-known techniques. See e.g., Junghans et al. in Cancer Chemotherapy and Biotherapy 655-686 (2d edition, Chafner and Longo, eds., Lippincott Raven (1996)). See also U.S. Patents 4,681,581, 4,735,210, 5,101,827, 5,102,990 (RE 35,500), 5,648,471, and 5,697,902.

Particular antibodies useful in practice of the invention include those described in WO 02/053596, which further describes antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, and 4.17.3. As disclosed in that published application, hybridomas producing these antibodies were deposited in the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on December 12, 2000 with the following deposit numbers:

<table>
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<th>Hybridome</th>
<th>Deposit No.</th>
</tr>
</thead>
<tbody>
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<td>3.1.1</td>
<td>PTA-2791</td>
</tr>
<tr>
<td>4.9.2</td>
<td>PTA-2789</td>
</tr>
</tbody>
</table>
These antibodies are either fully human IgG2 or IgG4 heavy chains with human kappa light chains. In particular the invention concerns use of antibodies having amino acid sequences of these antibodies.

Antibodies employed in the invention preferably possess very high affinities, typically possessing Kds of from about $10^{-8}$ through about $10^{-11}$ M, when measured by either solid phase or solution phase.

Antibodies used in the present invention can be expressed in cell lines other than hybridoma cell lines. Sequences encoding the cDNAs or genomic clones for the particular antibodies can be used for transformation of suitable mammalian or nonmammalian host cells. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patents 4,399,216, 4,912,040, 4,740,461, and 4,959,455. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, particle bombardment, encapsulation of the polynucleotide(s) in liposomes, peptide conjugates, dendrimers, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, NS0, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), and human hepatocellular carcinoma cells (e.g., Hep G2). Non-mammalian cells can also be employed, including bacterial, yeast, insect, and plant cells. Site directed mutagenesis of the antibody CH2 domain to eliminate glycosylation may be preferred in order to prevent changes in either the immunogenicity, pharmacokinetic, and/or effector functions resulting from non-human glycosylation. The glutamine synthase system of expression is discussed in whole or part in connection with European Patents 216 846, 256 055, and 323 997 and European Patent Application 89303964.4.

Antibodies for use in the invention can also be produced transgenically through the generation of a mammal or plant that is transgenic for the immunoglobulin heavy and light chain sequences of interest and production of the antibody in a recoverable form therefrom. Transgenic antibodies can be produced in, and recovered from, the milk of goats, cows, or other mammals. See, e.g., U.S. Patents 5,827,690, 5,756,687, 5,750,172, and 5,741,957.
The antibody, with or without an additional agent, may be administered once, but more preferably is administered multiple times. The antibody may be administered from three times daily to once every six months. The administering may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months. The antibody may be administered by an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor or topical route.

In certain embodiments, the antibody may be administered in an aerosol or inhaleable form. Dry aerosol in the form of finely divided solid particles that are not dissolved or suspended in a liquid are also useful in the practice of the present invention. The pharmaceutical formulations of the present invention may be administered in the form of an aerosol spray using for example, a nebulizer such as those described in U.S. Pat. Nos. 4,624,251 issued Nov. 25, 1986; 3,703,173 issued Nov. 21, 1972; 3,561,444 issued Feb. 9, 1971 and 4,635,627 issued Jan. 13, 1971.

Hubbard, R. C. et al. (Proc. Natl. Acad. Sci. (USA) 86: 680-684, 1989) disclose the administration of a relatively large protein alpha.sub.1 -antitrypsin (AAT) via the pulmonary epithelial surface for the treatment of alpha anti-trypsin deficiency. AAT, a 45,000 dalton molecular weight single-chain polypeptide that functions as an inhibitor of neutrophil elastase was administered to sheep in an aerosol form. Aerosolized AAT remained fully functional and intact in the tissues of the mammal and diffused across the alveolar epithelium, as evidenced by the presence of AAT in the lung, lymph and blood tissue.

The antibody may be administered at a site distant from the site of the tumor. The antibody may also be administered continuously via a minipump. The antibody may be administered once, at least twice or for at least the period of time until the condition is treated, palliated or cured. The antibody generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in weight or volume. The antibody will generally be administered as part of a pharmaceutical composition as described supra. The dosage of antibody will generally be in the range of 0.1-100 mg/kg, more preferably 0.5-50 mg/kg, more preferably 1-20 mg/kg, and even more preferably 1-10 mg/kg. The serum concentration of the antibody may be measured by any method known in the art. The antibody may also be administered prophylactically in order to prevent a cancer or tumor from occurring. This may be especially useful in patients that have a "high normal" level of IGF-I because these patients have been shown to have a higher risk of developing common cancers. See Rosen et al., supra.

Co-administration of the antibody with an additional therapeutic agent (combination therapy) encompasses administering a pharmaceutical composition comprising the anti-IGF-
IR antibody and the additional therapeutic agent and administering two or more separate pharmaceutical compositions, one comprising the anti-IGF-IR antibody and the other(s) comprising the additional therapeutic agent(s). Further, although co-administration or combination therapy generally means that the antibody and additional therapeutic agents are administered at the same time as one another, it also encompasses instances in which the antibody and additional therapeutic agents are administered at different times. For instance, the antibody may be administered once every three days, while the additional therapeutic agent is administered once daily. Alternatively, the antibody may be administered prior to or subsequent to treatment of the disorder with the additional therapeutic agent. Similarly, administration of the anti-IGF-IR antibody may be administered prior to or subsequent to other therapy, such as radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

**EXAMPLE I: Effects of the Antibodies of the Invention on IGF-IR in vivo**

We induced tumors in athymic mice according to published methods (V.A. Pollack et al., "Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: Dynamics of receptor inhibition in situ and antitumor effects in athymic mice," J. Pharmacol. Exp. Ther. 291:739-748 (1999). Briefly, we injected IGF-IR-transfected NIH-3T3 cells (5x10^3) subcutaneously into 3-4 week-old athymic (nu/nu) mice with 0.2 ml of Matrigel preparation. We then injected mice with an antibody of the invention intraperitoneally after established (i.e. approximately 400 mm^3) tumors formed.

After 24 hours, we extracted the tumors, homogenized them and determined the level of IGF-IR. To determine IGF-IR levels, we diluted the SC-713 antibody in Blocking buffer to a final concentration of 4 μg/ml and added 100 μl to each well of a Reacti-Bind Goat anti-rabbit (GAR) coated plate (Pierce). We incubated the plates at room temperature for 1 hour with shaking and then washed the plates five times with wash buffer. We then weighed tumor samples that had been prepared as described above and homogenized them in lysis buffer (1 ml/100 mg). We diluted 12.5 μl of tumor extract with lysis buffer to a final volume of 100 μl and added this to each well of a 96-well plate. We incubated the plates at room temperature with shaking for 1-2 hours and then washed the plates five times with Wash buffer. We then added 100μl of biotinylated anti-IGF-IR antibody in Blocking buffer to each well and incubated
at room temperature with shaking for 30 minutes. We then washed the plates five times with wash buffer. We developed the plates probed with anti-IGF-IR antibody by adding 100 μl of streptavidin-HRP diluted in Blocking buffer to each well, incubating at room temperature with shaking for 30 minutes. We developed the plates by adding 100 μl of the TMB microwell substrate per well and stopped color development with the addition 100 μl 0.9 M H₂SO₄. We then quantitated the signal by measuring the OD₄₅₀nm. The signal was normalized to total protein.

We observed that intraperitoneal injection of an antibody of this invention, particularly 2.13.2 and 4.9.2, resulted in inhibition of IGF-IR activity as measured by a decrease of both IGF-IR phosphotyrosine (phosphorylated IGF-IR) and total IGF-IR protein (Figure 4). Furthermore, this inhibition was responsive to the dose of antibody injected (Figure 4). These data demonstrate that the antibodies of the invention are able to target the IGF-IR in vivo in a manner analogous to what we observed in vitro.

EXAMPLE II: Growth Inhibition (TGI) of 3T3/IGF-IR Cell Tumors

We tested whether anti-IGF-IR antibodies of the invention would function to inhibit tumor growth. We induced tumors as described above (Example I) and when established, palpable tumors formed (i.e. 250 mm³, within 6-9 days), we treated the mice with a single, 0.20 ml dose of antibody by intraperitoneal injection. We measured tumor size by Vernier calipers across two diameters every third day and calculated the volume using the formula (length x [width]²)/2 using methods established by Geran, et al., "Protocols for screening chemical agents and natural products against animal tumors and other biological systems," Cancer Chemother. Rep. 3:1-104.

When we performed this analysis with an antibody of the invention, we found that a single treatment with antibody 2.13.2 alone inhibited the growth of IGF-IR-transfected NIH-3T3 cell-induced tumors (Figure 5).

**Detailed Description Of The Drawings**

Figs. 1A-1C show alignments of the nucleotide sequences of the light chain variable regions from six human anti-IGF-IR antibodies to each other and to germline sequences. Fig. 1A shows the alignment of the nucleotide sequences of the variable region of the light chain (VL) of antibodies 2.12.1 (SEQ ID NO: 1), 2.13.2 (SEQ ID NO: 5), 2.14.3 (SEQ ID NO: 9) and 4.9.2 (SEQ ID NO: 13) to each other and to the germline Vκ A30 sequence (SEQ ID NO: 39). Fig. 1B shows the alignment of the nucleotide sequence of VL of antibody 4.17.3 (SEQ ID NO: 17) to the germline Vκ O12 sequence (SEQ ID NO: 41). Fig. 1C shows the alignment of the nucleotide sequence of VL of antibody 6.1.1 (SEQ ID NO: 21) to the germline Vκ A27 sequence (SEQ ID NO: 37). The alignments also show the CDR regions of the VL from each antibody. The consensus sequences for Figs. 1A-1C are shown in SEQ ID NOS: 53-55, respectively.
Figs. 2A-2D show alignments of the nucleotide sequences of the heavy chain variable regions from six human anti-IGF-IR antibodies to each other and to germline sequences. Fig. 2A shows the alignment of the nucleotide sequence of the VH of antibody 2.12.1 (SEQ ID NO: 3) to the germline VH DP-35 sequence (SEQ ID NO: 29). Fig. 2B shows the alignment of the nucleotide sequence of the VH of antibody 2.14.3 (SEQ ID NO: 11) to the germline VIV-4/4.35 sequence (SEQ ID NO: 43). Figs. 2C-1 and 2C-2 show the alignments of the nucleotide sequences of the VH of antibodies 2.13.2 (SEQ ID NO: 7), 4.9.2 (SEQ ID NO: 15) and 6.1.1 (SEQ ID NO: 23) to each other and to the germline VH DP-47 sequence (SEQ ID NO: 31). Fig. 2D shows the alignment of the nucleotide sequence of the VH of antibody 4.17.3 (SEQ ID NO: 19) to the germline VH DP-71 sequence (SEQ ID NO: 35). The alignment also shows the CDR regions of the antibodies. The consensus sequences for Figs. 2A-2D are shown in SEQ ID NOS: 56-59, respectively.

Fig. 3A shows the number of mutations in different regions of the heavy and light chains of 2.13.2 and 2.12.1 compared to the germline sequences. Figs. 3A-D show alignments of the amino acid sequences from the heavy and light chains of antibodies 2.13.2 and 2.12.1 with the germline sequences from which they are derived. Fig. 3B shows an alignment of the amino acid sequence of the heavy chain of antibody 2.13.2 (SEQ ID NO: 45) with that of germline sequence DP-47(3-23)/D6-19/JH6 (SEQ ID NO: 46). Fig. 3C shows an alignment of the amino acid sequence of the light chain of antibody 2.13.2 (SEQ ID NO: 47) with that of germline sequence A30/Jk2 (SEQ ID NO: 48). Fig. 3D shows an alignment of the amino acid sequence of the heavy chain of antibody 2.12.1 (SEQ ID NO: 49) with that of germline sequence DP-35(3-11)/D3-3/JH6 (SEQ ID NO: 50). Fig. 3E shows an alignment of the amino acid sequence of the light chain of antibody 2.12.1 (SEQ ID NO: 51) with that of germline sequence A30/Jk1 (SEQ ID NO: 52). For Figures 3B-E, the signal sequences are in italic, the CDRs are underlined, the constant domains are bold, the framework (FR) mutations are highlighted with a plus sign (+) above the amino acid residue and CDR mutations are highlighted with an asterisk above the amino acid residue.

Figure 4 shows that anti-IGF-IR antibodies 2.13.2 and 4.9.2 reduce IGF-IR phosphotyrosine signal in 3T3-IGF-IR tumors.

Figure 5 shows that anti-IGF-IR antibody 2.13.2 inhibits 3T3-IGF-IR tumor growth in vivo.
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acacctctca gggacaagcc caagaactca ctgtatctgc aatatgaacag cctgagagcc 240
gagacaccgg cctgatattat cttgtccaga gatggagtgaa aactacttttt tactactactc 300
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| Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser | 35 | 40 | 45 |
| Thr Arg Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg | 50 | 55 | 60 |
| Asp Asn Ala Lys Asn Ser Leu Tyr Leu Glu Ltn Met Asn Ser Leu Arg Ala | 65 | 70 | 75 | 80 |
| Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg Asp Gly Val Glu Thr Thr | 85 | 90 | 95 |
| Phe Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr | 100 | 105 | 110 |
| Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu | 115 | 120 | 125 |
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<213> Homo sapiens

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Tyr Ala Ala Ser Arg Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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     25          30
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     40          45
Ala  Ile  Ser  Gly  Ser  Gly  Gly  Thr  Thr  Phe  Tyr  Ala  Asp  Ser  Val  Lys  50
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Gly  Arg  Phe  Thr  Ile  Ser  Arg  Asp  Ser  Arg  Thr  Thr  Leu  Tyr  Leu  65
     70          75          80
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35  40  45
Tyr Ala Ala Ser Lys Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
50  55  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Arg Leu Gln Pro
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35     40     45
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50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65     70     75     80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ile His Val Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
35  40  45

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
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Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Ala Pro
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35  40  45

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   65  70  75  80
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
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35 40 45
 SER Gly Ile Thr Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
25 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys
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Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
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Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Tyr Glu Lys
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30  35  40  45

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40  50  55  60

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       Obrocea, Mihail
       Gomez-Navarro, Jesus
       Cusmano, John D.
       Wang, Huifen F.
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Tyr Ala Ala Ser Arg Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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20 25 30

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35 40 45

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Tyr Ala Ala Ser Lys Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
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50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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| 50 | 55 | 60 |

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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   35      40      45
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   50      55      60
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Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
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Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190
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195 200 205
Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg,Glut
210 215 220
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
  245        250        255
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
  260        265        270
Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
  275        280        285
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
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Ser Leu Ser Pro Gly Lys
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<213> Homo sapiens

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<210> 30
<211> 98
<212> PRT
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Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
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Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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<213> Homo sapiens

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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35  40  45
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50  55  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65  70  75  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85  90  95
Ala Lys

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39 acctgcgcttg tctctgggtg gttctacagc gtagtaact ggtggagtgtg ggtccgccag 120
cccccagggaa aggggctgga gtggattggg gaaatctctc atagtgggag caccacaactac 180
80 aacccgctccct ctaagagttg cgtcaccata tcagtagaca agtccaagaa ccagttttcgc 240
cctgaaggtga ggtcctgtgac cgcgcgggac acgccccgtgt atacagtgtgc gagaga 296

34 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
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20 25 30
35 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
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65 Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
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cagggaggg gactggaggtg gatggtgtat acctcaccg caagaggagc 180
cctttctctca agatgtcgagc caccatatct gtagacaagct ccaagaacctggtcct 240
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Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys 50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu 65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala 85 90 95
Arg

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cctgagggcagc ctccaggctc cttcatctat ggtgccttcga gcaggcctca tggcaagcaa 180
gacagttca gtgcagttgg gtcctgggaca gacttcacttc tccacatcag cagactggag 240
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<210> 38
<211> 96
<212> PRT
<213> Homo sapiens

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35  40  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50  55  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
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<212> DNA
<213> Homo sapiens

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gggaaagccc ctaacgcct gatctatgct gcatccagtt tgcaaatggtg ggtcccatca 180
aggttcagcc gcagttggtc tgggacagaa ttcacctcca caatcagcag cctgcagcct 240
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<210> 40
<211> 96
<212> PRT

19
Homo sapiens

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

DNA

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gggaaagccc ctaagctctt gatctatgct gcctcagtt tgacaaagtgg ggtcccatca 180
aggttcaagtg gcagtgtgcc tgggacagt ttcactctctta ccacgcagcag tctgcaacct 240
gagatctttg caacttacta ctgtcacaag agttacagta cccctccch 288

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
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gccgggaagg gactggaagt gattggaact atctatatca gttggagcag caactacaac 180
cccctccctca agagtcgagt caccatgtca gtagacagct ccaagaacca gtctctctctg 240
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<210> 44
<211> 97
<212> PRT
<213> Homo sapiens

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

Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50  55  60

21
Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
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Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
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95
Arg

<210> 45
<211> 470
<212> PRT
<213> Homo sapiens

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25
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Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
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Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
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Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala
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Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr
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Tyr Tyr Cys Ala Lys Asp Leu Gly Trp Ser Asp Ser Tyr Tyr Tyr Tyr
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Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
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Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
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Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
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Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
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Ser Thr Phe Arg Val Ser Val Leu Thr Val Val His Gln Asp Trp
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<213> Homo sapiens

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20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95
Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Ala Lys Gly Tyr Ser Ser Gly Trp Tyr Tyr Tyr Tyr
115 120 125
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
130 135 140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145 150 155 160
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    165  170  175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
    180  185  190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    195  200  205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
    210  215  220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
    225  230  235  240
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
    245  250  255
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    260  265  270
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    275  280  285
Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
    290  295  300
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
    305  310  315  320
Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
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Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
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Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    355  360  365
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    370  375  380
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    385  390  395  400
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    405  410  415
Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
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Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
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Ser Leu Ser Pro Gly Lys
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30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
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Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
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Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu His Arg Gly Val
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75
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Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
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90
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Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100
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His Asn Ser Tyr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
115
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Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
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Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
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Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
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180 185 190
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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35 40 45
Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
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Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
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Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110
Tyr Tyr Cys Val Arg Asp Gly Val Glu Thr Thr Phe Tyr Tyr Tyr Tyr
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Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
   145     150     155      160
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
   165     170      175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
   180     185      190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
   195     200      205
Leu Ser Ser Val Thr Val Thr Pro Ser Ser Asn Phe Gly Thr Gln Thr
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Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
   225     230     235      240
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
   245     250      255
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Asp
   260     265      270
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
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Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
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Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
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Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
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CLAIMS

1. A method for the treatment or prevention of a disorder wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated autoimmune disease, endocrinological disorder, ischemia, and neurodegenerative disorder in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody that is effective in treating said disorder.

2. The method of claim 1 wherein said liquid tumor is selected from the group consisting of acute lymphocytic leukemia (ALL) and chronic myelogenic leukemia (CML); wherein said liver cancer is selected from the group consisting of hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, hepatoblastoma; wherein said thymus disorder is selected from the group consisting of thymoma and thyroiditis, wherein said T-cell mediated autoimmune disease is selected from the group consisting of Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave's Disease, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's Disease, wherein said endocrinological disorder is selected from the group consisting of Type II Diabetes, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and hypoadrenocorticism; wherein said ischemia is post cardiac ischemia, and wherein said neurodegenerative disorder is Alzheimer's Disease.

3. The method of claim 1 comprising administering to said mammal said antibody in combination with an agent selected from the group consisting of a corticosteroid, anti-emetic, cancer vaccine, analgesic, anti-vascular agent, and anti-proliferative agent.

4. The method of claim 1 comprising administering said antibody in combination with a vaccine, wherein said vaccine is selected from GM-CSF DNA and cell-based vaccines, dendritic cell vaccines, recombinant viral vaccines, heat shock protein (HSP) vaccines, allogeneic or autologous tumor vaccines.

5. The method of claim 1 comprising administering said antibody in combination with an analgesic agent, wherein said agent is selected from the group consisting of ibuprofen, naproxen, choline magnesium trisalicylate, or oxycodone hydrochloride.

6. The method of claim 1 comprising administering said antibody in combination with an anti-vascular agent, wherein said agent is selected from the group consisting of bevacizumab, or rhuMAb-VEGF.

7. The method of claim 1 comprising administering said antibody in combination with an anti-proliferative agent, wherein said agent is selected from the group consisting of farnesyl protein transferase inhibitors, avg3 inhibitors, avg5 inhibitors, p53 inhibitors, and PDGFR inhibitors.

8. The method of claim 1 wherein the antibody that binds to IGF-IR has the following properties:
a binding affinity for human IGF-IR of $K_d$ of $8 \times 10^{-9}$ or less;

inhibition of binding between human IGF-IR and IGF-1 with an IC$_{50}$ of less than 100 nM; and

comprises a heavy chain amino acid sequence comprising human FR1, FR2, and FR3 amino acid sequences that correspond to those of the VH DP-35, VIV-4/4.35, VH DP-47, or VH DP-71 gene, or conservative substitutions or somatic mutations therein, wherein the FR sequences are linked with CDR1, CDR2, and CDR3 sequences, and wherein the antibody also comprises CDR regions in its light chain from the A27, A30, or O12 gene.

9. The method of claim 1 wherein said antibody competes for binding with IGF-IR with an antibody having heavy and light chain amino acid sequences of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1.

10. The method of claim 1 wherein said antibody comprises a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, and a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1, or sequences having changes from said CDR sequences selected from the group consisting of conservative changes, wherein said conservative changes are selected from the group consisting of replacement of nonpolar residues by other nonpolar residues, replacement of polar charged residues by other polar uncharged residues, replacement of polar charged residues by other polar uncharged residues, substitution of structurally similar residues; and non-conservative substitutions, wherein said non-conservative substitutions are selected from the group consisting of substitution of polar charged residue for polar uncharged residues and substitution of nonpolar residues for polar residues, additions and deletions.

11. The method of claim 11 wherein said antibody comprises a heavy chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, and a light chain comprising the amino acid sequences of CDR-1, CDR-2, and CDR-3, of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 4.9.2, 4.17.3, and 6.1.1.

12. The method of claim 1 wherein said antibody is selected from the group consisting of an antibody comprising a heavy chain amino acid sequence derived from human gene DP-47 and a light chain amino acid sequence derived from human gene A30.

13. A pharmaceutical composition for the treatment or prevention of a disorder in a mammal comprising an amount of a human anti-IGF-IR antibody that is effective in treating said disorder and a pharmaceutically acceptable carrier, wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated autoimmune disease, endocrinological disorder, ischemia, and neurodegenerative disorder.
14. Use of an amount of a human anti-IGF-IR antibody in the preparation of a composition for the treatment or prevention of a disorder in a mammal that is effective in treating said disorder, wherein said disorder is selected from the group consisting of multiple myeloma, liquid tumor, liver cancer, thymus disorder, T-cell mediated autoimmune disease, endocrinological disorder, ischemia, and neurodegenerative disorder.

15. A method for the treatment or prevention of aging in a mammal comprising administering to said mammal an amount of an anti-IGF-IR antibody that is effective in said treatment or prevention.
FIG. 1A

2.13.2K  GACATCCAGA TGACCAGTT TCCATCTCC CCTGCTGGCAT CTGTAGAGGA 50
A30    GACATCCAGA TGACCAGTC TCCATCTCC CCTGCTGGCAT CTGTAGAGGA 50
2.14.3k  ------------  ------------  ----TCTCC  CCTGCTGGCAT CTGTAGAGGA 26
2.12.1k  ------------  ------------  -----TGGCAT  CTGTAGAGGA 15
4.9.2k    GACATCCAGA TGACCAGTC TCCATCTCC CCTGCTGGCAT CTGTAGAGGA 50
Consensus  GACATCCAGA TGACCAGTY TCCATCTCC CCTGCTGGCAT CTGTAGAGGA 50

CDR1

2.13.2K  CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA AATGATTTAG 100
A30    CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA AATGATTTAG 100
2.14.3k  CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA CGTGAATTTAG 76
2.12.1k  CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA CGTGAATTTAG 65
4.9.2k    CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA AATGATTTAG 100
Consensus  CAGAGTCACC ATCACTGGCC GGGCAAGTCG GCACATTAGA AATGATTTAG 100

CDR2

2.13.2K  GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 200
A30    GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 200
2.14.3k  GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 176
2.12.1k  GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 165
4.9.2k    GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 200
Consensus  GCATCCCGTT TCCACACAGG GTGCCCCTCA AAGTCAGGCG GCAGTGGRTC 200

CDR3

2.13.2K  TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 250
A30    TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 250
2.14.3k  TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 226
2.12.1k  TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 215
4.9.2k    TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 250
Consensus  TGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 250

Consensus  GGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 250

2.13.2K  CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 300
A30    CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 300
2.14.3k  CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 276
2.12.1k  CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 265
4.9.2k    CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 300
Consensus  CAACCTTATT ACGTGTTACAA CATAAATCTTT AGCCCTGAC GTTTGGCCAG 300

A30    ------------  ------------  ------------  ------------  322
2.14.3k  GGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 302
2.12.1k  GGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 291
4.9.2k    GGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 322
Consensus  GGGGACAGAA TTTACTTTCA GATTCAGAG GCTGAGGCTT GAGATTGTTG 326
FIG. 1C

6.1.1K
A27
Consensus
GAAATTGTGTTGACGCAGTCCTCAGGCACCCTGTCTTGTGTCCAAGGGAG

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---------------
---------------
---------------
50
50

6.1.1K
A27
Consensus
AGAGCCACCCTCTCCTGTA GGCCACGTA GAGTTTGAGC GACAGCTACT

---------------
---------------
---------------
---------------
49
100
100

6.1.1K
A27
Consensus
TAGGCTGGTACACGCAGAAA CCGGCAAGGCTCCCAAGGCTCTCATCTAT

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---------------
---------------
---------------
99
150
150

6.1.1K
A27
Consensus
GGTGCATCCA GCAGGGCCACC GACAGGTCCA GTGCCAGTGG

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---------------
---------------
---------------
149
200
200

6.1.1K
A27
Consensus
GCTCTGGGACA GACTTCATCC TCCCATCAGCAGACTGGAGGACTGAGATT

---------------
---------------
---------------
---------------
199
250
250

6.1.1K
A27
Consensus
TGCTGGGACA GACTTCATCC TCCCATCAGCAGACTGGAGGACTGAGATT

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---------------
---------------
---------------
249
288
300

6.1.1K
A27
Consensus
CAAGGGACCA AGGTGGAAAT GAAAC

---------------
---------------
---------------
---------------
274
290
325
### FIG. 3A

<table>
<thead>
<tr>
<th>Clone</th>
<th>C domain mutations</th>
<th>FR mutation</th>
<th>CDR mutation</th>
<th>Change in Cys</th>
<th>Change in glycosylation</th>
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<tbody>
<tr>
<td>2.13.2 Heavy</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>0</td>
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<td>2.13.2 Light</td>
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<td>1</td>
<td>4</td>
<td>1 (CDR3)</td>
<td>0</td>
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<tr>
<td>2.12.2 Heavy</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.12.2 Light</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>0</td>
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</table>

### FIG. 3B

PF2 2.13.2 Heavy chain (DP-47 (3-23)/D6-19/JH6)

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<tr>
<th>PEPTIDE</th>
<th>AA1</th>
<th>AA2</th>
</tr>
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<tbody>
<tr>
<td>MEPGLSWLFL</td>
<td>VAILKGVQCE</td>
<td>VQNLZZGGGL VQPGSSRLS</td>
</tr>
<tr>
<td>MEPGLSWLFL</td>
<td>VAILKGVQCE</td>
<td>VQNLZZGGGL VQPGSSRLS</td>
</tr>
<tr>
<td>QMNISRRAEDT</td>
<td>AVYYCAK</td>
<td>--D LGSNDSYLY YGMDVWQGT</td>
</tr>
<tr>
<td>QMNISRRAEDT</td>
<td>AVYYCAKGS --SGN--YYY YGMDVWQGT</td>
<td></td>
</tr>
<tr>
<td>AVLQSSGLYS</td>
<td>LSSWTVFSS</td>
<td>NGFTQTYTGN VDHKPSNTKV</td>
</tr>
<tr>
<td>AVLQSSGLYS</td>
<td>LSSWTVFSS</td>
<td>NGFTQTYTGN VDHKPSNTKV</td>
</tr>
<tr>
<td>NWWYDGVESVH</td>
<td>NAKTKPREEQ</td>
<td>FNSTFRVVSV LTVVHQDNLN</td>
</tr>
<tr>
<td>NWWYDGVESVH</td>
<td>NAKTKPREEQ</td>
<td>FNSTFRVVSV LTVVHQDNLN</td>
</tr>
<tr>
<td>DIAVEWESNG</td>
<td>QPENNYKTTT</td>
<td>PMLDSDGSSF LYSKLTVDKS RWWQGNVFSC SVMHEALHNH YTQKSLSLSP GK</td>
</tr>
<tr>
<td>DIAVEWESNG</td>
<td>QPENNYKTTT</td>
<td>PMLDSDGSSF LYSKLTVDKS RWWQGNVFSC SVMHEALHNH YTQKSLSLSP GK</td>
</tr>
</tbody>
</table>
FIG. 3C

PF2 2.13.2 LC (A30/JK2)

**

QPEDFATYYC LHNSYPFCSF GQGTKLIEKR TVAAPSVFIF PPSDEQLKSG TASVVCILNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYLSST

LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC

FIG. 3D

PF2 2.12.1 Heavy chain (DP-35-(3-11)/D3-3/JH6)

**

QMNLSRAEDT AVYYCARVHR GVEFTFYXY YGMDWGGQQ TTVTSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEEFTVSWNS GALTSGVHFT

PAVLQSSGLY SLSVSTIVPS SNFGTQTYTC NVHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLLP PPKPDTLMIS RTPEVTCVVV DVSHEDEPVO

PAVLQSSGLY SLSVSTIVPS SNFGTQTYTC NVHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLLP PPKPDTLMIS RTPEVTCVVV DVSHEDEPVO

PNWYVDGVEV HNAKTKPREE QFNSTERVVS VLTIVHDQWDL NGKEYCKKS NGKLPAFIEK TISRTKQOPRE PQVTLLPPS REEMTKNQVS LTLVKGFPY

SDIAVEWSEN GQFENNYKKT PFMIDSGSF FLYSKLTVDK SRWQQGNVFS C5SVHEAHLN HYTQKSLSLSP GK

SDIAVEWSEN GQFENNYKKT PFMIDSGSF FLYSKLTVDK SRWQQGNVFS C5SVHEAHLN HYTQKSLSLSP GK
FIG. 4

IGF1R Receptor, % of Control

Dose (µg)

FIG. 5

Tumor Size, mm³

Time, days

- Vehicle
- 31.25 µm
- 125 µm
- 500 µm
- KLH, 500 µm