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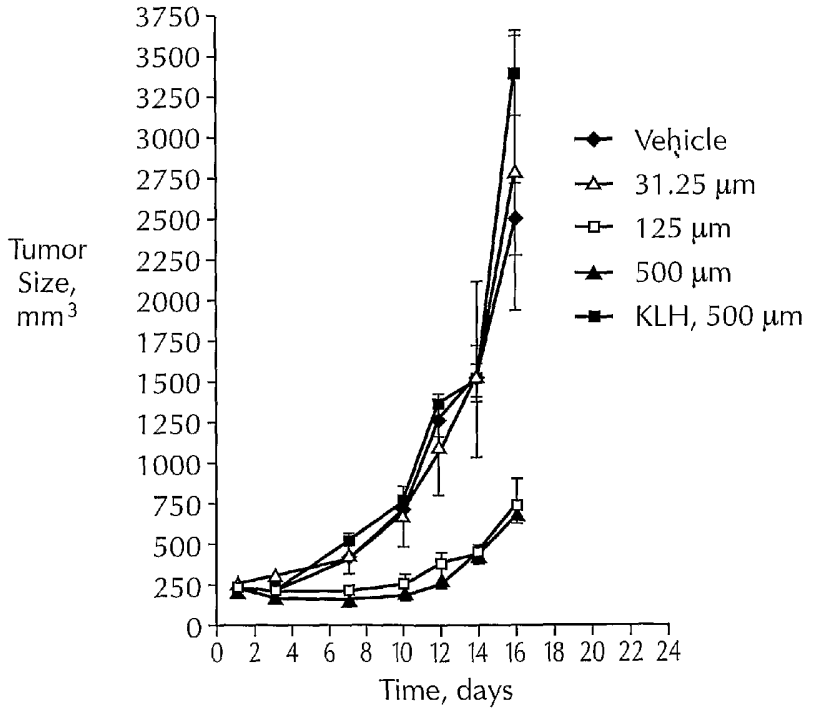

(57) Abstract: The present invention relates to a therapeutic method comprising administering antiIGF-IR antibodies, particularly human anti-IGF-IR antibodies to a subject for the treatment of certain disorders preferably in conjunction with administration of another therapeutic agent. The invention 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.

There is considerable evidence for a role for IGF-I and/or IGF-IR in the maintenance of tumor cells *in vitro* and *in vivo*. IGF-IR levels are elevated in tumors of lung (Kaiser et al., J. Cancer Res. Clin. Oncol. 119: 665-668, 1993; Moody et al., Life Sciences 52: 1161-1173, 1993; Macauley et al., Cancer Res., 50: 2511-2517, 1990), breast (Pollak et al., Cancer Lett. 38: 223-230, 1987; Foekens et al., Cancer Res. 49: 7002-7009, 1989; Cullen et al., Cancer Res. 49: 7002-7009, 1990; Arteaga et al., J. Clin. Invest. 84: 1418-1423, 1989), prostate and colon (Remaole-Bennet et al., J. Clin. Endocrinol. Metab. 75: 609-616, 1992; Guo et al., Gastroenterol. 102: 1101-1108, 1992). In addition, IGF-I appears to be an autocrine stimulator of human gliomas (Sandberg-Nordqvist et al., Cancer Res. 53: 2475-2478, 1993), while IGF-I stimulated the growth of fibrosarcomas that overexpressed IGF-IR (Butler et al., Cancer Res. 58: 3021-27, 1998). Further, individuals with "high normal" levels of IGF-I have an increased risk of common cancers compared to individuals with IGF-I levels in the "low normal" range (Rosen et al., Trends Endocrinol. Metab. 10: 136-41, 1999). For a review of the role IGF-I/IGF-I receptor interaction plays in the growth of a variety of human tumors, see Macaulay, Br. J. Cancer, 65: 311-320, 1992.

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, endocronological 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 milogenic 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 endocronological 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, αvß3 inhibitors, αvß5 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, metroclopramide, domperidone, haloperidol, cyclizine, 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 8×10^{-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, endocronological 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, endocronological 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 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.

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 entireties.

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 ≤ 1 μM, preferably ≤ 100 nM and most preferably ≤ 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 x 10^{-8} M or less. In a more preferred embodiment, the antibody binds to IGF-IR with a K_d or 1 x 10^{-9} M or less. In an even more preferred embodiment, the antibody binds to IGF-IR with a K_d or 5 x

10^{-10} M or less. In another preferred embodiment, the antibody binds to IGF-IR with a K_d or 1 x 10^{-10} M or less. In another preferred embodiment, the antibody binds to IGF-IR with substantially the same K_d 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 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_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_H DP-47 gene family. In a more preferred embodiment, the heavy chain comprises no more than eight amino acid changes

from germline V_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_{50} of no more than 100 nM. In a preferred embodiment, the IC_{50} is no more than 10 nM. In a more preferred embodiment, the IC_{50} is no more than 5 nM. The IC_{50} can be measured by any method known in the art. Typically, an IC_{50} can be measured by ELISA or RIA. In a preferred embodiment, the IC_{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,

6,114,598 and 6,130,364. See also WO 91/10741, published July 25, 1991, WO 94/02602, published February 3, 1994, WO 96/34096 and WO 96/33735, both published October 31, 1996, WO 98/16654, published April 23, 1998, WO 98/24893, published June 11, 1998, WO 98/50433, published November 12, 1998, WO 99/45031, published September 10, 1999, WO 99/53049, published October 21, 1999, WO 00 09560, published February 24, 2000 and WO 00/037504, published June 29, 2000. The XENOMOUSE ™ produces an adult-like human repertoire of fully human antibodies, and generates antigen-specific human Mabs. A second generation XENOMOUSE ™ contains approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and κ light chain loci. See Mendez et al. *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998), the disclosures of which are hereby incorporated by reference.

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-1R 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, polyorthoesters, 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, β-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,

1995), 08/463,191 (filed June 5, 1995), 08/462,837 (filed June 5, 1995), 08/486,853 (filed June 5, 1995), 08/486,857 (filed June 5, 1995), 08/486,859 (filed June 5, 1995), 08/462,513 (filed June 5, 1995), 08/724,752 (filed October 2, 1996), and 08/759,620 (filed December 3, 1996). *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). *See also* European Patent EP 0 463 151 (grant published June 12, 1996), International Patent Application WO 94/02602 (published February 3, 1994), International Patent Application WO 96/34096 (published October 31, 1996), and WO 98/24893 (published June 11, 1998).

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 retroviral LTRs, 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).

Antibodies for use in the invention also include "kappabodies" (Ill et al. "Design and construction of a hybrid immunoglobulin domain with properties of both heavy and light chain variable regions" *Protein Eng* 10:949-57 (1997)), "minibodies" (Martin et al. "The affinity-selection of a minibody polypeptide inhibitor of human interleukin-6" *EMBO J* 13:5303-9 (1994)), "diabodies" (Holliger et al. "'Diabodies': small bivalent and bispecific antibody fragments" *PNAS USA* 90:6444-6448 (1993)), and "janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)) may also be prepared.

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:

Hybridoma	Deposit No.
2.12.1	PTA-2792
2.13.2	PTA-2788
2.14.3	PTA-2790
3.1.1	PTA-2791
4.9.2	PTA-2789

4.17.3 PTA-2793

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^{-9} 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, NSO_0, 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 via 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 ($5x10^6$) 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 H_2SO_4. We then quantitated the signal by measuring the OD_{450nm}. 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 mm^3, 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*.

SEQUENCE LISTING

<110> Cohen, Bruce D.
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Guyot, Deborah J.

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<213> Homo sapiens

<400> 28

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
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```
1               5                  10                  15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        115                 120                 125
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140
Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175
Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205
Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    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
    290                 295                 300
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
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305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 29
<211> 296
<212> DNA
<213> Homo sapiens

<400> 29
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagaga 296

<210> 30
<211> 98
<212> PRT
<213> Homo sapiens

<400> 30
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg

<210> 31
<211> 296
<212> DNA
<213> Homo sapiens

<400> 31
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaga 296

<210> 32
<211> 98
<212> PRT
<213> Homo sapiens

<400> 32
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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 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

<210> 33
<211> 296
<212> DNA
<213> Homo sapiens

<400> 33
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggggac cctgtccctc 60
acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120
cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180
aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagaga 296

<210> 34
<211> 98
<212> PRT
<213> Homo sapiens

<400> 34
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

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
     50                  55                  60

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

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                 85                  90                  95

Ala Arg
```

<210> 35
<211> 293
<212> DNA
<213> Homo sapiens

<400> 35
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 36
<211> 97
<212> PRT
<213> Homo sapiens

<400> 36

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
             20                  25                  30

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

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
```

<210> 37

<211> 290
<212> DNA
<213> Homo sapiens

<400> 37
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacctcc 290

<210> 38
<211> 96
<212> PRT
<213> Homo sapiens

<400> 38
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
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
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

<210> 39
<211> 288
<212> DNA
<213> Homo sapiens

<400> 39
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctccn 288

<210> 40
<211> 96
<212> PRT
<213> Homo sapiens

<400> 40
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

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

<210> 41
<211> 288
<212> DNA
<213> Homo sapiens

<400> 41
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccctcch 288

<210> 42
<211> 96
<212> PRT
<213> Homo sapiens

<400> 42
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu 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 Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

<210> 43
<211> 293
<212> DNA
<213> Homo sapiens

<400> 43
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 44
<211> 97
<212> PRT
<213> Homo sapiens

<400> 44
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

Ser Arg Val Thr Met 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

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

<400> 45
Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr
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 Asp Leu Gly Trp Ser Asp Ser 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
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

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
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 46
<211> 470
<212> PRT
<213> Homo sapiens

<400> 46
Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
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 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 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
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

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
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 47
<211> 236
<212> PRT
<213> Homo sapiens

<400> 47
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser
20 25 30

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

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu His Arg Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

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

His Asn Ser Tyr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

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

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 48
<211> 236
<212> PRT
<213> Homo sapiens

<400> 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

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

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

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

His Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

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

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 49
<211> 470
<212> PRT
<213> Homo sapiens

<400> 49
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Val Gln Cys Gln Ala Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
65 70 75 80

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
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
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

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
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 50
<211> 473
<212> PRT
<213> Homo sapiens

<400> 50
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80

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 Ala Arg Val Leu Arg Phe Leu Glu Trp Leu Leu Tyr Tyr
115 120 125

Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
210 215 220

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
245 250 255

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 51
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<212> PRT
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Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
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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, endocronological 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 milogenic 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 endocronological 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, αvß3 inhibitors, αvß5 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 x 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 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.

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, endocronological 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, endocronological 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

```
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A30       GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
2.14.3k   ---------- ---------- ----TCCTCC CTGTCTGCAT CTGTAGGAGA  26
2.12.1k   ---------- ---------- ---------- -----TGCAT CTGTAGGAGA  15
4.9.2k    GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
Consensus GACATCCAGA TGACCCAGTY TCCATCCTCC CTGTCTGCAT CTGTAGGAGA  50
                                                    CDR1

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A30       CAGAGTCACC ATCACTTGCC GGGCAAGTCA GGGCATTAGA AATGATTTAG 100
2.14.3k   CAGAGTCACC TTCACTTGCC GGGCAAGTCA GGACATTAGA CGTGATTTAG  76
2.12.1k   CAGAGTCACC TTCACTTGCC GGGCAAGTCA GGACATTAGA CGTGATTTAG  65
4.9.2k    CAGAGTCACC ATCACTTGCC GGGCAAGTCA GGGCATTAGA AGTGATTTAG 100
Consensus CAGAGTCACC WTCACTTGCC GGGCAAGTCA GGRCATTAGA MRTGATTTAG 100

2.13.2K   GCTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
A30       GCTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
2.14.3k   GCTGGTATCA GCAGAAACCA GGGAAAGCTC CTAAGCGCCT GATCTATGCT 126
2.12.1k   GCTGGTATCA GCAGAAACCA GGGAAAGCTC CTAAGCGCCT GATCTATGCT 115
4.9.2k    GCTGGTTTCA GCAGAAACCA GGGAAAGCCC CTAAGCGCCT GATCTATGCT 150
Consensus GCTGGTWTCA GCAGAAACCA GGGAAAGCYC CTAAGCGCCT GATCTATGCT 150
          CDR2

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2.14.3k   GCATCCCGTT TACAAAGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 176
2.12.1k   GCATCCCGTT TACAAAGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 165
4.9.2k    GCATCCAAAT TACACCGTGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200
Consensus GCATCCMRWT TRCAMMGWGG GGTCCCATCA AGGTTCAGCG GCAGTGGATC 200

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2.12.1k   TGGGACAGAA TTCACTCTCA CAATCAGCAG CCTGCAGCCT GAAGATTTTG 215
4.9.2k    TGGGACAGAA TTCACTCTCA CAATCAGCCG CCTGCAGCCT GAAGATTTTG 250
Consensus TGGGACAGAA TTCACTCTCA CAATCAGCMG CCTGCAGCCT GAAGATTTTG 250
                                          CDR3

2.13.2K   CAACTTATTA CTGTTTACAA CATAATAGTT ACCCGTGCAG TTTTGGCCAG 300
A30       CAACTTATTA CTGTCTACAG CATAATAGTT ACCC-TCCN- ---------- 288
2.14.3k   CAACTTATTA CTGTCTACAG CATAATAATT ATCCTCGGAC GTTCGGCCAA 276
2.12.1k   CAACTTATTA CTGTCTACAG CATAATAATT ATCCTCGGAC GTTCGGCCAA 265
4.9.2k    CAACTTATTA CTGTCTACAG CATAATAGTT ACCCTCGGAC TTTCGGCGGA 300
Consensus CAACTTATTA CTGTYTACAR CATAATARTT AYCCKYBSNS KTTYGGCSRR 300

2.13.2K   GGGACCAAGC TGGAGATCAA AC----                          322
A30       ---------- ---------- ------                          288
2.14.3k   GGGACCAAGC TGGAAATCAT ACGAAC                          302
2.12.1k   GGGACCAAGC TGGAAATCAT ACGAAC                          291
4.9.2k    GGGACCAAGC TGGAGATCAA AC----                          322
Consensus GGGACCRAGS TGGARATCAW ACGAAC                          326
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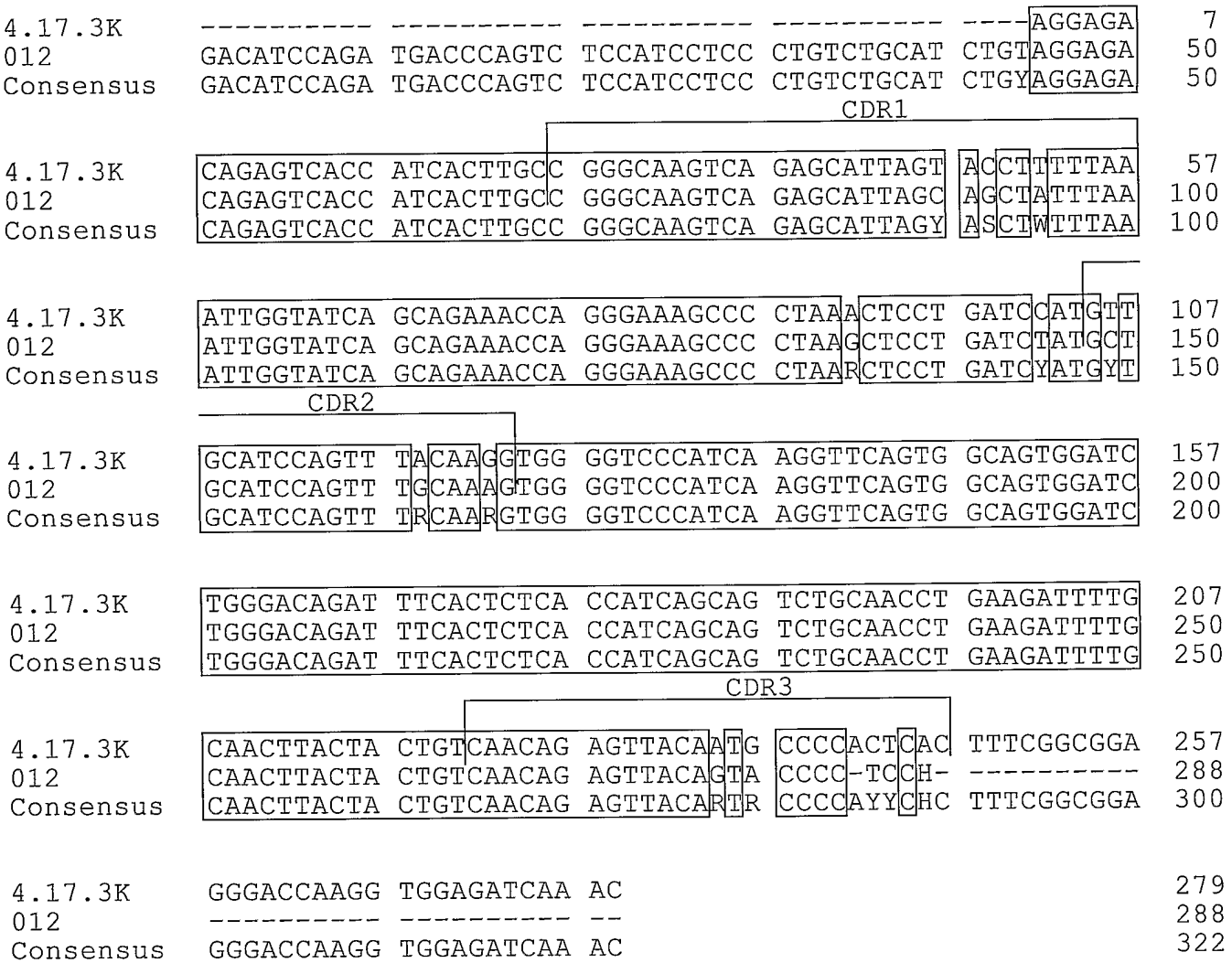
FIG. 1B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CDR1
4.17.3K CAGAGTCACC ATCACTTGCC GGGCAAGTCA GAGCATTAGT ACCTTTTTAA 57
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Consensus CAGAGTCACC ATCACTTGCC GGGCAAGTCA GAGCATTAGY ASCTWTTTAA 100
4.17.3K ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAACTCCT GATCCATGTT 107
012 ATTGGTATCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTATGCT 150
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CDR2
4.17.3K GCATCCAGTT TACAAGGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 157
012 GCATCCAGTT TGCAAAGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 200
Consensus GCATCCAGTT TRCAARGTGG GGTCCCATCA AGGTTCAGTG GCAGTGGATC 200
4.17.3K TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 207
012 TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 250
Consensus TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG 250
CDR3
4.17.3K CAACTTACTA CTGTCAACAG AGTTACAATG CCCCACTCAC TTTCGGCGGA 257
012 CAACTTACTA CTGTCAACAG AGTTACAGTA CCCC-TCCH- ---------- 288
Consensus CAACTTACTA CTGTCAACAG AGTTACARTR CCCCAYYCHC TTTCGGCGGA 300
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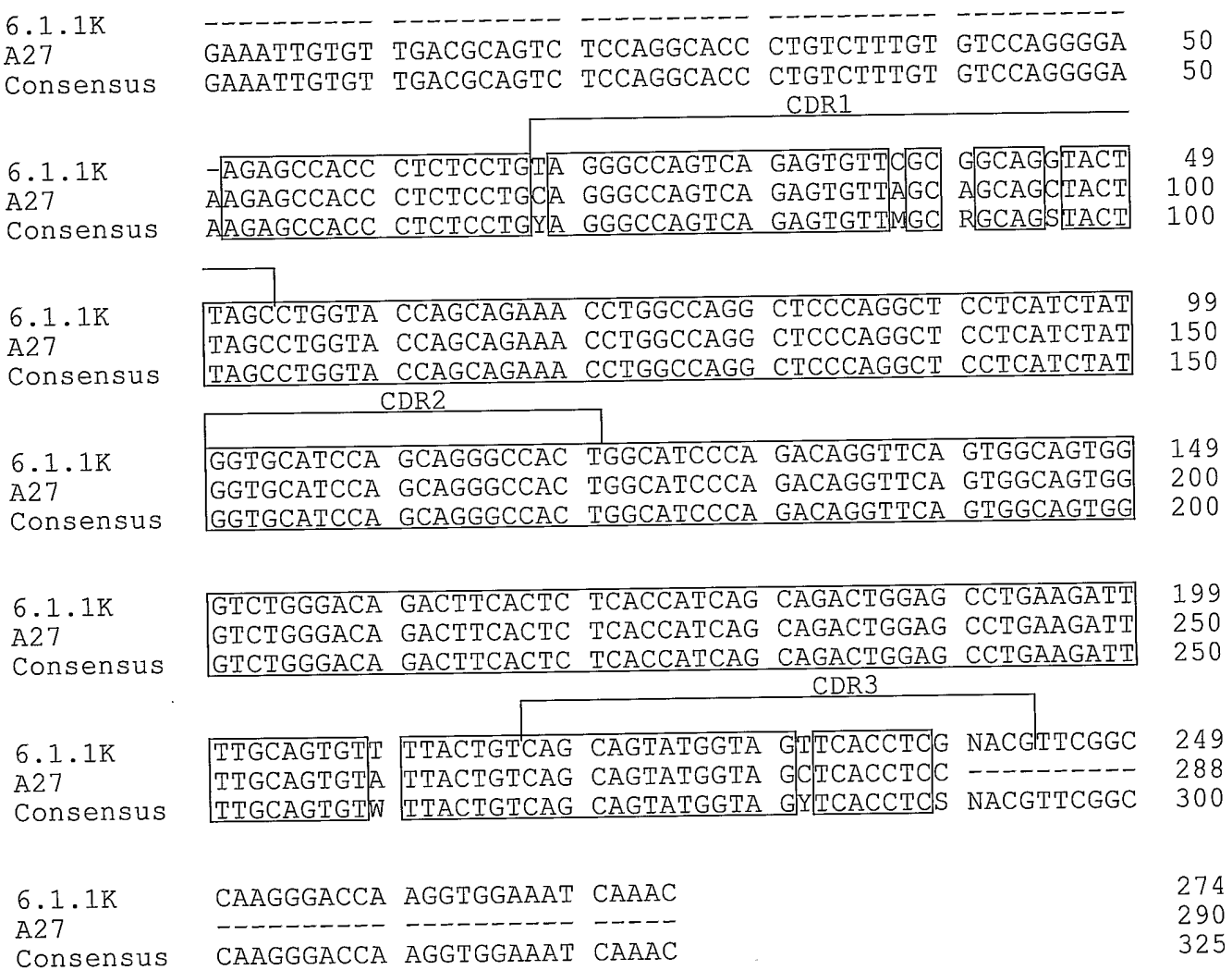
Consensus GGGACCAAGG TGGAGATCAA AC 322

FIG. 1C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CDR1
6.1.1K -AGAGCCACC CTCTCCTGTA GGGCCAGTCA GAGTGTTCGC GGCAGGTACT 49
A27 AAGAGCCACC CTCTCCTGCA GGGCCAGTCA GAGTGTTAGC AGCAGCTACT 100
Consensus AAGAGCCACC CTCTCCTGYA GGGCCAGTCA GAGTGTTMGC RGCAGSTACT 100
6.1.1K TAGCCTGGTA CCAGCAGAAA CCTGGCCAGG CTCCCAGGCT CCTCATCTAT 99
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Consensus TAGCCTGGTA CCAGCAGAAA CCTGGCCAGG CTCCCAGGCT CCTCATCTAT 150
CDR2
6.1.1K GGTGCATCCA GCAGGGCCAC TGGCATCCCA GACAGGTTCA GTGGCAGTGG 149
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A27 TTGCAGTGTA TTACTGTCAG CAGTATGGTA GCTCACCTCC ---------- 288
Consensus TTGCAGTGTW TTACTGTCAG CAGTATGGTA GYTCACCTCS NACGTTCGGC 300
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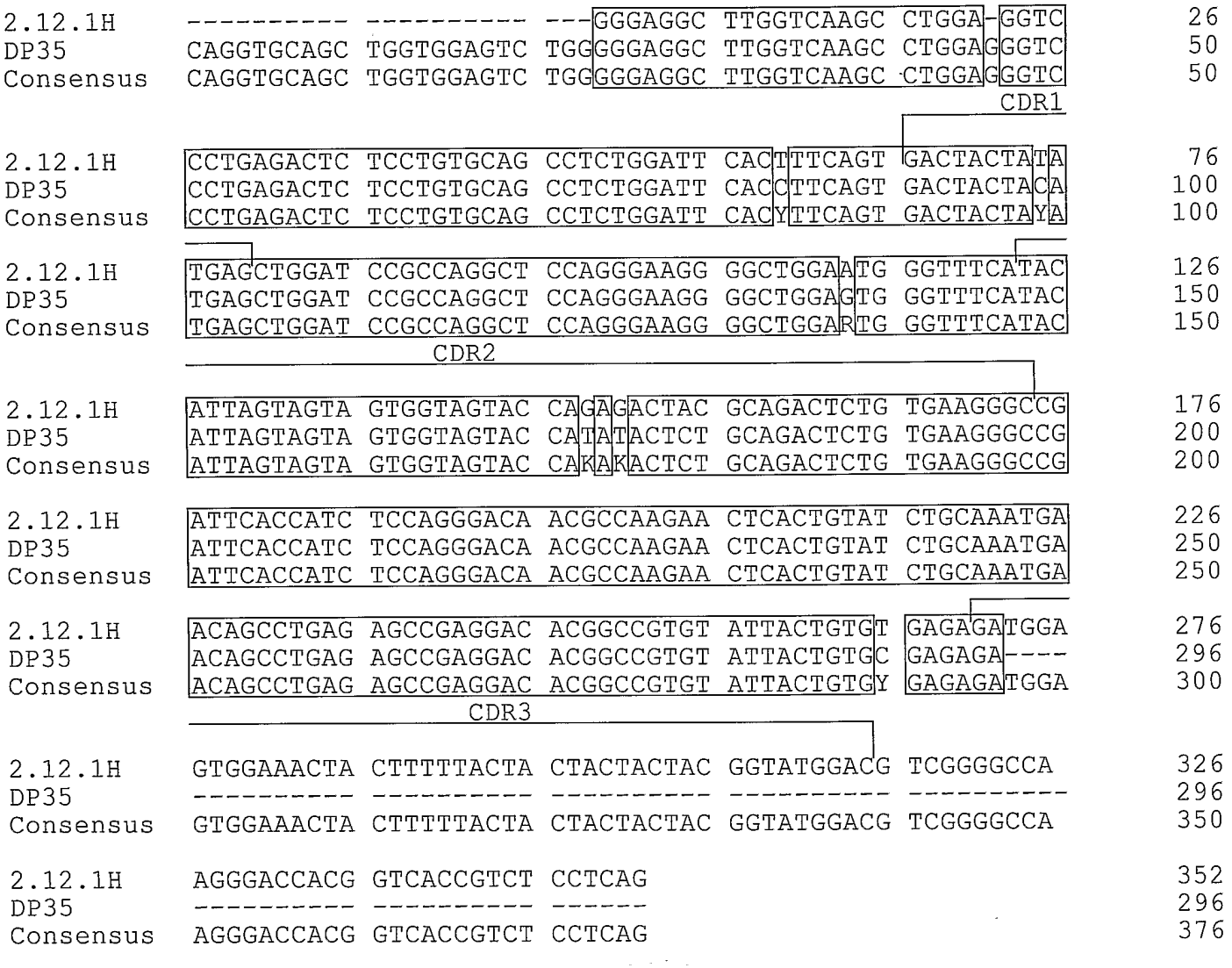
FIG. 2A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CDR1
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Consensus TGAGCTGGAT CCGCCAGGCT CCAGGGAAGG GGCTGGARTG GGTTTCATAC 150
CDR2
2.12.1H ATTAGTAGTA GTGGTAGTAC CAGAGACTAC GCAGACTCTG TGAAGGGCCG 176
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CDR3
2.12.1H GTGGAAACTA CTTTTTACTA CTACTACTAC GGTATGGACG TCGGGGCCA 326
DP35 ---------- ---------- ---------- ---------- ---------- 296
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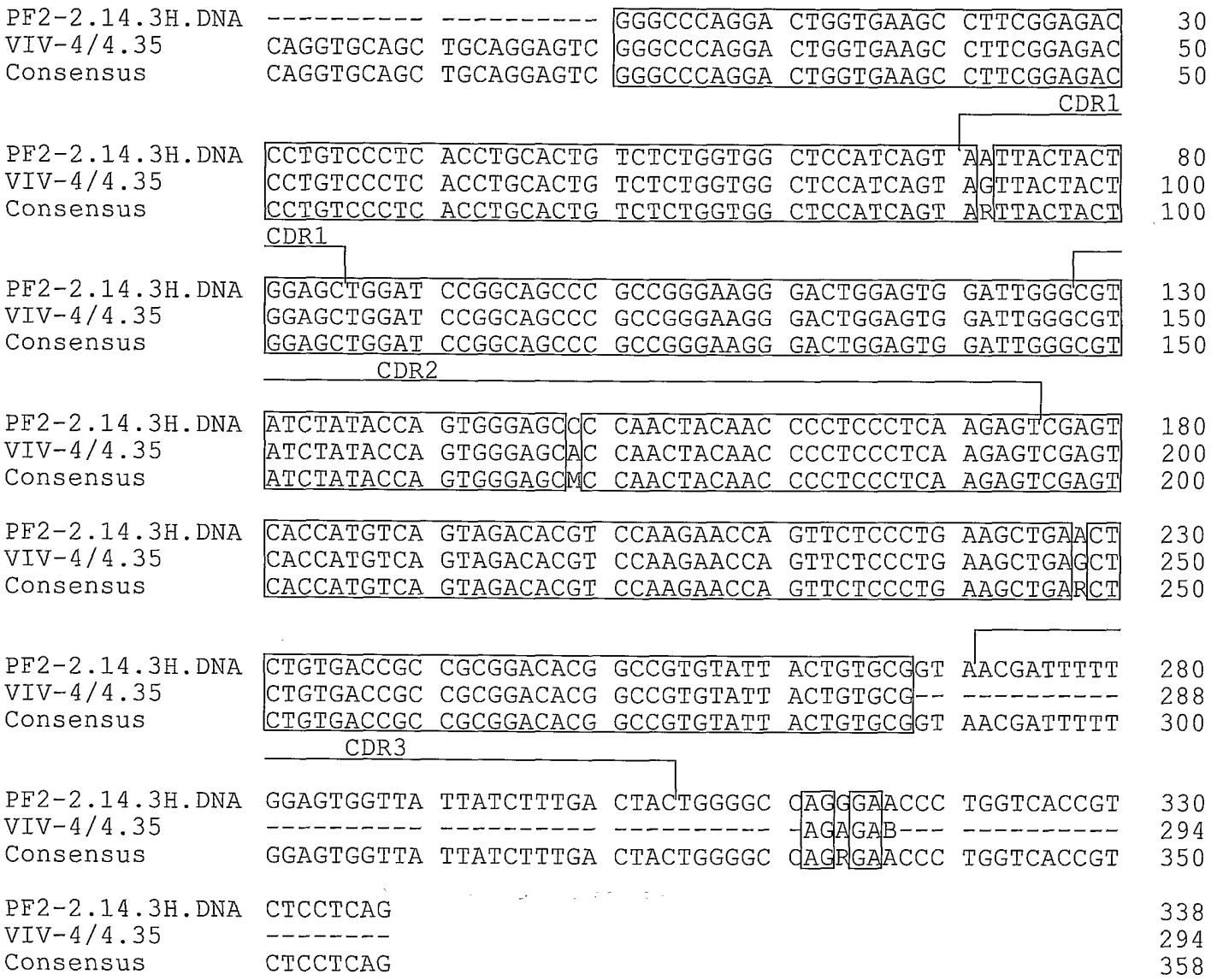
FIG. 2B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Consensus CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC 50
CDR1
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VIV-4/4.35 CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT 100
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CDR1
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Consensus GGAGCTGGAT CCGGCAGCCC GCCGGGAAGG GACTGGAGTG GATTGGGCGT 150
CDR2
PF2-2.14.3H.DNA ATCTATACCA GTGGGAGCCC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 180
VIV-4/4.35 ATCTATACCA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 200
Consensus ATCTATACCA GTGGGAGCMC CAACTACAAC CCCTCCCTCA AGAGTCGAGT 200
PF2-2.14.3H.DNA CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAACT 230
VIV-4/4.35 CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGCT 250
Consensus CACCATGTCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGARCT 250
PF2-2.14.3H.DNA CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCGGT AACGATTTTT 280
VIV-4/4.35 CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCG-- ---------- 288
Consensus CTGTGACCGC CGCGGACACG GCCGTGTATT ACTGTGCGGT AACGATTTTT 300
CDR3
PF2-2.14.3H.DNA GGAGTGGTTA TTATCTTTGA CTACTGGGGC CAGGGAACCC TGGTCACCGT 330
VIV-4/4.35 ---------- ---------- ---------- -AGAGAB--- ---------- 294
Consensus GGAGTGGTTA TTATCTTTGA CTACTGGGGC CAGRGAACCC TGGTCACCGT 350
PF2-2.14.3H.DNA CTCCTCAG 338
VIV-4/4.35 -------- 294
Consensus CTCCTCAG 358

FIG. 2C-1

```
6.1.1H     GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC  50
4.9.2H     GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC  50
DP47       GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC  50
2.13.2H    GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC  50
Consensus  GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC  50
                                                      CDR1

6.1.1H     CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
4.9.2H     CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
DP47       CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
2.13.2H    CCTGAGACTC TCCTGTACAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
Consensus  CCTGAGACTC TCCTGTRCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA 100
           CDR1                                                CDR2

6.1.1H     TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGGT 150
4.9.2H     TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
DP47       TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
2.13.2H    TGAACTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGCT 150
Consensus  TGARCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTC GGTCTCAGST 150
                                  CDR2

6.1.1H     ATTACTGGGA GTGGTGGTAG TACATACTAC GCAGACTCCG TGAAGGGCCG 200
4.9.2H     ATTAGTGGTA GTGGTGGTAT CACATACTAC GCAGACTCCG TGAAGGGCCG 200
DP47       ATTAGTGGTA GTGGTGGTAG CACATACTAC GCAGACTCCG TGAAGGGCCG 200
2.13.2H    ATTAGTGGTA GTGGTGGTAC CACATTCTAC GCAGACTCCG TGAAGGGCCG 200
Consensus  ATTASTGGKA GTGGTGGTAB YACATWCTAC GCAGACTCCG TGAAGGGCCG 200

6.1.1H     GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
4.9.2H     GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
DP47       GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT CTGCAAATGA 250
2.13.2H    GTTCACCATC TCCAGAGACA ATTCCAGGAC CACGCTGTAT CTGCAAATGA 250
Consensus  GTTCACCATC TCCAGAGACA ATTCCARGAM CACGCTGTAT CTGCAAATGA 250
                                                      CDR3

6.1.1H     ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATC-- 298
4.9.2H     ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATGTG 300
DP47       ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGA---- 296
2.13.2H    ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATCTT 300
Consensus  ACAGCCTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GAAAGATCTK 300
                          CDR3-for 4.9.2 and 2.13.2

6.1.1H     ---------- ---------- ---------- ---------- --------C- 299
4.9.2H     GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
DP47       ---------- ---------- ---------- ---------- ---------- 296
2.13.2H    GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
Consensus  GGCTACGGTG ACTTTTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA 350
                     CDR3-for 6.1.1

6.1.1H     AGGGACTACG GTGATTATGA GTTGGTTCGA CCCCTGGGGC CAGGGAACCC 349
4.9.2H     AGGGACTAC- ---------- ---------- ---------- ---------- 359
DP47       ---------- ---------- ---------- ---------- ---------- 296
2.13.2H    AGGGACTAC- ---------- ---------- ---------- ---------- 359
Consensus  AGGGACYACG GTGATTATGA GTTGGTTCGA CCCCTGGGGC CAGGGAACCC 400
```

FIG. 2C-2

```
6.1.1H     TGGTCACCGT CTCCTCAG                                    367
4.9.2H     -GGTCACCGT CTCCTCAG                                    376
DP47       ---------- --------                                    296
2.13.2H    -GGTCACCGT CTCCTCAG                                    376
Consensus  TGGTCACCGT CTCCTCAG                                    418
```

FIG. 2D

```
4.17.3H    ---------- ---------- ---CCCAGGA CTGGTGAAGC CTTCGGAGAC   27
DP71       CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC   50
Consensus  CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC   50
                                                        CDR1

4.17.3H    CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT   77
DP71       CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT  100
Consensus  CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGT AGTTACTACT  100
           CDR1

4.17.3H    GGAGTTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  127
DP71       GGAGCTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  150
Consensus  GGAGYTGGAT CCGGCAGCCC CCAGGGAAGG GACTGGAGTG GATTGGGTAT  150
                 CDR2

4.17.3H    ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  177
DP71       ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  200
Consensus  ATCTATTACA GTGGGAGCAC CAACTACAAC CCCTCCCTCA AGAGTCGAGT  200

4.17.3H    CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGTT  227
DP71       CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGCT  250
Consensus  CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG AAGCTGAGYT  250
                           CDR3

4.17.3H    CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGCCAG GACGTATAGC  277
DP71       CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGC--- GA--------  289
Consensus  CTGTGACCGC TGCGGACACG GCCGTGTATT ACTGTGCCAG GACGTATAGC  300

4.17.3H    AGTTCGTTCT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  327
DP71       ---------- ---------- ----GA---- ---------- -GA-------  293
Consensus  AGTTCGTTCT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  350

4.17.3H    CACCGTCTCC TCAG                                        341
DP71       ---------- ----                                        293
Consensus  CACCGTCTCC TCAG                                        364
```

FIG. 3A

Clone	C domain mutations	FR mutation	CDR mutation	Change in Cys	Change in glycosylation
2.13.2 Heavy	0	3	8	0	0
2.13.2 Light	0	1	4	1 (CDR3)	0
2.12.2 Heavy	0	2	8	0	0
2.12.2 Light	0	3	5	0	0

FIG. 3B

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

```
                                          +         *                    * *                 ++
MEFGLSWLFL VAILKGVQCE VQLLZSGGGL VQPGGSLRLS CTASGFTFSS YAMNWVRQAP GKGLEWVSAI SGSGGTTFYA DSVKGRFTIS RDNSRTTLYL
MEFGLSWLFL VAILKGVQCE VQLLZSGGGL VQPGGSLRLS CAASGFTFSS YAMSWVRQAP GKGLEWVSAI SGSGGTTFYA DSVKGRFTIS RDNSRTTLYL
                    * *  ***

QMNSLRAEDT AVYYCAK--D LGWSDSYYYY YGMDVWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP
QMNSLRAEDT AVYYCAKGYS SGW--YYYYY YGMDVWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP

AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVQF
AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVQF

NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS
NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS

DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
```

FIG. 3C

PF2 2.13.2 LC (A30/Jk2)

```
                                  +                                                  * *
MDMRVPAQLL GLLLLWFPGA RCDIQMTQFP SSLSASVGDR VTITCRASQG IRNDLGWYQQ KPGKAPKRLI YAASRLHRGV PSRFSGSGSG TEFTLTISSL
DMRVPAQLLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTITCRASQG IRNDLGWYQQ KPGKAPKRLI YAASSLQSGV PSRFSGSGSG TEFTLTISSL
                    **
QPEDFATYYC LQHNSYPCSF GQGTKLEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
QPEDFATYYC LQHNSYPYTF GQGTKLEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST

LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```


FIG. 3D

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

```
                      +                                                          **
MEFGLSWVFL VAIIKGVQCQ AQLVESGGGL VKPGGSLRLS CAASGFTFSD YYMSWIRQAP GKGLEWVSYI SSSGSTRDYA DSVKGRFTIS RDNAKNSLYL
MEFGLSWVFL VAIIKGVQCQ VQLVESGGGL VKPGGSLRLS CAASGFTFSD YYMSWIRQAP GKGLEWVSYI SSSGSTIYYA DSVKGRFTIS RDNAKNSLYL
                  +   * ** ***
QMNSLRAEDT AVYYCVR--D GVETTF-YYY YYGMDVWGQG TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF
QMNSLRAEDT AVYYCARVLR GVETTFYYYY YYGMDVWGQG TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALOCLVKDYF PEPVTVSWNS CALTSGVHTF

PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ
PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ

PNWYVDGVEV HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK TISKTKGQPRE PQVYTLPPS REEMTKNQVS LTCLVKGFYP
PNWYVDGVEV HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK TISKTKGQPRE PQVYTLPPS REEMTKNQVS LTCLVKGFYP

SDIAVEWESN GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLSP GK
SDIAVEWESN GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLSP GK
```

FIG. 3E

```
PF2.12.1 Light chain.  (A30/JK1)
                                    +     *   *                   *
MDMRVPAQLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTFTCRASQD IRRDLGWYQQ KPGKAPKRLI YAASRLQSGV PSRFSGSGSG TEFTLTISSL
MDMRVPAQLL GLLLLWFPGA RCDIQMTQSP SSLSASVGDR VTFTCRASQD IRRDLGWYQQ KPGKAPKRLI YAASRLQSGV PSRFSGSGSG TEFTLTISSL
                        +   +
QPEDFATYYC LQHNNYPRTF GQGTEVEIIR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
QPEDFATYYC LQHNNYPRTF GQGTEVEIIR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST

LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

FIG. 4

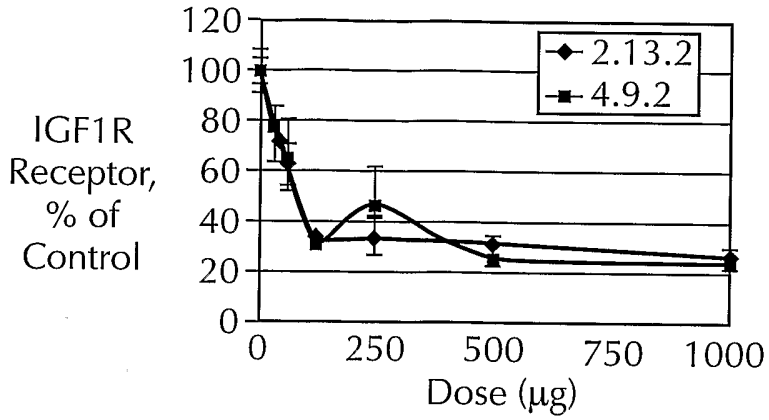
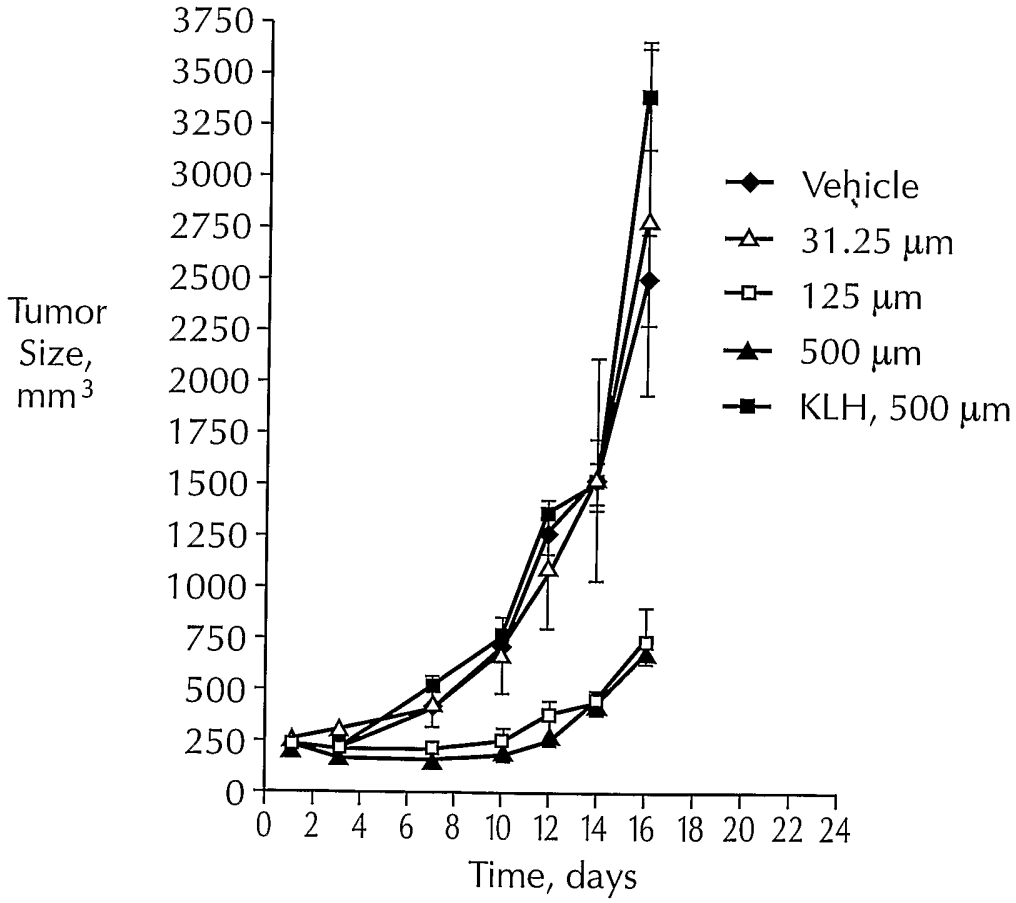

IGF1R Receptor, % of Control
120
100
80
60
40
20
0
0
250
500
750
1000
Dose (µg)
2.13.2
4.9.2

FIG. 5


Tumor Size, mm3
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time, days
Vehicle
31.25 µm
125 µm
500 µm
KLH, 500 µm

SEQUENCE LISTING

<110> Cohen, Bruce D.
Bedian, Vahe
Obrocea, Mihail
Gomez-Navarro, Jesus
Cusmano, John D.
Wang, Huifen F.
Page, Kelly L.
Guyot, Deborah J.

<120> USES OF ANTI-INSULIN-LIKE GROWTH FACTOR I RECEPTOR ANTIBODIES

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ccgtttacaa agtggggtcc catcaaggtt cagcggcagt ggatctggga cagaattcac 180
tctcacaatc agcagcctgc agcctgaaga ttttgcaact tattactgtc tacagcataa 240
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Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
20 25 30

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
     50                  55                  60

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn
 65                  70                  75                  80

Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile Ile Arg
                 85                  90                  95

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
        115                 120                 125

Pro Arg Glu Ala Lys Val Gln Trp
    130                 135
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  1               5                  10                  15

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
             20                  25                  30
```

```
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 Gln 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 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

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140

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

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ser Cys Ala
                165                 170
```

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 1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
            20                  25                  30

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

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
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Cys
                85                  90                  95

Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
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            20                  25                  30
```

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

Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala Asp Ser Val Lys
50 55 60

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

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
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Lys Asp Leu Gly Trp Ser Asp Ser Tyr Tyr Tyr Tyr Tyr Gly Met Asp
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acagaattca ctctcacaat cagcagcctg cagcctgaag attttgcaac ttattactgt 240
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20 25 30

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35 40 45

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
50 55 60

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
65 70 75 80

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1 5 10 15

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20 25 30

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

Ser Pro Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Val
50 55 60

Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Thr Ala
65 70 75 80

Ala Asp Thr Ala Val Tyr Tyr Cys Ala Val Thr Ile Phe Gly Val Val
85 90 95

Ile Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 13
<211> 322
<212> DNA
<213> Homo sapiens

<400> 13
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atcacttgcc gggcaagtca gggcattaga agtgatttag gctggtttca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccaaat tacaccgtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagccg cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa ac 322

<210> 14
<211> 107
<212> PRT
<213> Homo sapiens

<400> 14
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
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
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 15
<211> 376
<212> DNA
<213> Homo sapiens

<400> 15
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tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtat cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatctg 300
ggctacggtg acttttacta ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctcag 376

<210> 16
<211> 125
<212> PRT
<213> Homo sapiens

<400> 16
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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 Gly Ile 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 Asp Leu Gly Tyr Gly Asp Phe Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115 120 125

<210> 17
<211> 279
<212> DNA
<213> Homo sapiens

<400> 17
caggagacag agtcaccatc acttgccggg caagtcagag cattagtacc tttttaaatt 60
ggtatcagca gaaaccaggg aaagccccta aactcctgat ccatgttgca tccagtttac 120
aaggtggggt cccatcaagg ttcagtggca gtggatctgg gacagatttc actctcacca 180
tcagcagtct gcaacctgaa gattttgcaa cttactactg tcaacagagt tacaatgccc 240
cactcacttt cggcggaggg accaaggtgg agatcaaac 279

<210> 18
<211> 92
<212> PRT
<213> Homo sapiens

<400> 18
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr
1 5 10 15

Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
20 25 30

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
50 55 60

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Ala Pro
65 70 75 80

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
85 90

<210> 19
<211> 341
<212> DNA
<213> Homo sapiens

<400> 19
cccaggactg gtgaagcctt cggagaccct gtccctcacc tgcactgtct ctggtggctc 60

catcagtagt tactactgga gttggatccg gcagccccca gggaagggac tggagtggat 120
tgggtatatc tattacagtg ggagcaccaa ctacaacccc tccctcaaga gtcgagtcac 180
catatcagta gacacgtcca agaaccagtt ctccctgaag ctgagttctg tgaccgctgc 240
ggacacggcc gtgtattact gtgccaggac gtatagcagt tcgttctact actacggtat 300
ggacgtctgg ggccaaggga ccacggtcac cgtctcctca g 341

<210> 20
<211> 113
<212> PRT
<213> Homo sapiens

<400> 20
Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val
1 5 10 15

Ser Gly Gly Ser Ile Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro
20 25 30

Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser
35 40 45

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

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala
65 70 75 80

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Thr Tyr Ser Ser Ser Phe Tyr
85 90 95

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 21
<211> 274
<212> DNA
<213> Homo sapiens

<400> 21
agagccaccc tctcctgtag ggccagtcag agtgttcgcg gcaggtactt agcctggtac 60
cagcagaaac ctggccaggc tcccaggctc ctcatctatg gtgcatccag cagggccact 120
ggcatcccag acaggttcag tggcagtggg tctgggacag acttcactct caccatcagc 180
agactggagc ctgaagattt tgcagtgttt tactgtcagc agtatggtag ttcacctcgn 240

acgttcggcc aagggaccaa ggtggaaatc aaac 274

<210> 22
<211> 91
<212> PRT
<213> Homo sapiens

<400> 22
Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Gly Arg Tyr
1 5 10 15

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
20 25 30

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
35 40 45

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
50 55 60

Glu Asp Phe Ala Val Phe Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Arg
65 70 75 80

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
85 90

<210> 23
<211> 367
<212> DNA
<213> Homo sapiens

<400> 23
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt attactggga gtggtggtag tacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatcca 300
gggactacgg tgattatgag ttggttcgac ccctggggcc agggaaccct ggtcaccgtc 360
tcctcag 367

<210> 24
<211> 122
<212> PRT
<213> Homo sapiens

<400> 24
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ser Gly Ile Thr Gly Ser Gly 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 Asp Pro Gly Thr Thr Val Ile Met Ser Trp Phe Asp Pro Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 25
<211> 320
<212> DNA
<213> Homo sapiens

<400> 25
gaactgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg 60
gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt 120
ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca 180
gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga 240
aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga 300
gcttcaacag gggagagtgt 320

<210> 26
<211> 106
<212> PRT
<213> Homo sapiens

<400> 26
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 27
<211> 978
<212> DNA
<213> Homo sapiens

<400> 27
gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 60
agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120
tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc 240
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc 300
aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc 360
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc 420
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc 480
gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 540
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 600
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 660
cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 720
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 780
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 840
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 900
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 960
tccctgtctc cgggtaaa 978

<210> 28
<211> 326
<212> PRT

<213> Homo sapiens

<400> 28

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
  1               5                  10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
             20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
         35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
     50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                 85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

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

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240
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```
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
    290                 295                 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Lys
                325
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<210> 29
<211> 296
<212> DNA
<213> Homo sapiens

<400> 29
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagaga 296

<210> 30
<211> 98
<212> PRT
<213> Homo sapiens

<400> 30
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
  1               5                  10                  15

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

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

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
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50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg

<210> 31
<211> 296
<212> DNA
<213> Homo sapiens

<400> 31
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaga 296

<210> 32
<211> 98
<212> PRT
<213> Homo sapiens

<400> 32
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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 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

<210> 33
<211> 296
<212> DNA
<213> Homo sapiens

<400> 33
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggggac cctgtccctc 60
acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120
cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180
aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagaga 296

<210> 34
<211> 98
<212> PRT
<213> Homo sapiens

<400> 34
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

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
50 55 60

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

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg

<210> 35
<211> 293

<212> DNA
<213> Homo sapiens

<400> 35
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 36
<211> 97
<212> PRT
<213> Homo sapiens

<400> 36
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

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

<210> 37
<211> 290
<212> DNA
<213> Homo sapiens

<400> 37
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacctcc 290

<210> 38
<211> 96
<212> PRT
<213> Homo sapiens

<400> 38
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
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
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

<210> 39
<211> 288
<212> DNA
<213> Homo sapiens

<400> 39
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctccn 288

<210> 40
<211> 96
<212> PRT

<213> Homo sapiens

<400> 40

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
             20                  25                  30

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
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<210> 41
<211> 288
<212> DNA
<213> Homo sapiens

<400> 41

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccctcch              288
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<210> 42
<211> 96
<212> PRT
<213> Homo sapiens

<400> 42

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
```

```
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu 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 Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                 85                  90                  95
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<210> 43
<211> 293
<212> DNA
<213> Homo sapiens

<400> 43
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 44
<211> 97
<212> PRT
<213> Homo sapiens

<400> 44

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
             20                  25                  30

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
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Ser Arg Val Thr Met 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

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

<400> 45
Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr
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 Asp Leu Gly Trp Ser Asp Ser 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
325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
340 345 350

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

420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 46
<211> 470
<212> PRT
<213> Homo sapiens

<400> 46
Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
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 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 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
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350

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
420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 47
<211> 236
<212> PRT
<213> Homo sapiens

<400> 47
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser
20 25 30

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

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu His Arg Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

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

His Asn Ser Tyr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

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

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

```
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 48
<211> 236
<212> PRT
<213> Homo sapiens

<400> 48

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
  1               5                  10                  15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
             20                  25                  30

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

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
     50                  55                  60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
 65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                 85                  90                  95

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

His Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
```

130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 49
<211> 470
<212> PRT
<213> Homo sapiens

<400> 49
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Val Gln Cys Gln Ala Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
65 70 75 80

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
        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
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350

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
            420                 425                 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    450                 455                 460

Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 50
<211> 473
<212> PRT
<213> Homo sapiens

<400> 50

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
  1               5                  10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
             20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
         35                  40                  45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
     50                  55                  60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
 65                  70                  75                  80

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 Ala Arg Val Leu Arg Phe Leu Glu Trp Leu Leu Tyr Tyr
        115                 120                 125

Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
    130                 135                 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145                 150                 155                 160

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
                165                 170                 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
            180                 185                 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
        195                 200                 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
    210                 215                 220

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
225                 230                 235                 240

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
                245                 250                 255

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        355                 360                 365
```

```
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 51
<211> 236
<212> PRT
<213> Homo sapiens

<400> 51

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
  1               5                  10                  15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
             20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Phe Thr Cys Arg Ala Ser
         35                  40                  45

Gln Asp Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
     50                  55                  60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val
 65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                 85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
```

100 105 110

His Asn Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile
115 120 125

Ile Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 52
<211> 236
<212> PRT
<213> Homo sapiens

<400> 52
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

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

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

```
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                 85                  90                  95

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

His Asn Ser Tyr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

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

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 53
<211> 326
<212> DNA
<213> Artificial Sequence

<400> 53
gacatccaga tgacccagty tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
wtcacttgcc gggcaagtca ggrcattaga mrtgatttag gctggtwtca gcagaaacca 120
gggaaagcyc ctaagcgcct gatctatgct gcatccmrwt trcammgwgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcmg cctgcagcct 240
gaagattttg caacttatta ctgtytacar cataatartt aycckybsns kttyggcsrr 300
gggaccrags tggaratcaw acgaac 326

<210> 54
<211> 322
<212> DNA

<213> Artificial Sequence

<400> 54
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgyaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagy asctwtttaa attggtatca gcagaaacca 120
gggaaagccc ctaarctcct gatcyatgyt gcatccagtt trcaargtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacartr ccccayychc tttcggcgga 300
gggaccaagg tggagatcaa ac 322

<210> 55
<211> 325
<212> DNA
<213> Artificial Sequence

<400> 55
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgya gggccagtca gagtgttmgc rgcagstact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtw ttactgtcag cagtatggta gytcacctcs nacgttcggc 300
caagggacca aggtggaaat caaac 325

<210> 56
<211> 376
<212> DNA
<213> Artificial Sequence

<400> 56
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt cacyttcagt gactactaya tgagctggat ccgccaggct 120
ccagggaagg ggctggartg ggtttcatac attagtagta gtggtagtac cakakactac 180
gcagactctg tgaagggccc attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgy gagagatgga 300
gtggaaacta ctttttacta ctactactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctcag 376

<210> 57
<211> 358
<212> DNA
<213> Artificial Sequence

<400> 57
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt arttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcmc caactacaac 180
ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240
aagctgarct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcggt aacgattttt 300
ggagtggtta ttatctttga ctactggggc cagrganccc tggtcaccgt ctcctcag 358

<210> 58
<211> 418
<212> DNA
<213> Artificial Sequence

<400> 58
caggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
tcctgtrcag cctctggatt cacctttagc agctatgcca tgarctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagst attastggka gtggtggtab yacatwctac 180
gcagactccg tgaagggccc gttcaccatc tccagagaca attccargam cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatctk 300
ggctrsksyg actyttacta ctactactac ggtatggacg tctggggcca agggacyacg 360
gtgattatga gttggttcga cccctggggc cagggaaccc tggtcaccgt ctcctcag 418

<210> 59
<211> 364
<212> DNA
<213> Artificial Sequence

<400> 59
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagytggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180
ccctccctca agagtcgact caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagyt ctgtgaccgc tgcggacacg gccgtgtatt actgtgccag gacgtatagc 300
agttcgttct actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tcag 364

<210> 60
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 60
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15