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(54) ANTI-IGF-1 RECEPTOR HUMANIZED ANTIBODY

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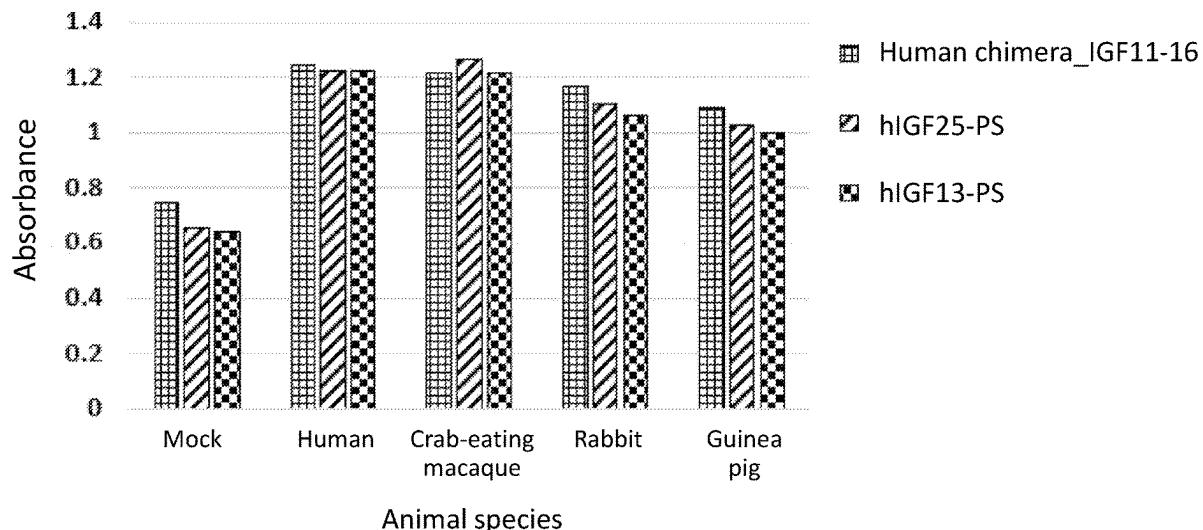
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(57)

ABSTRACT

Provided are: an anti-IGF-1 receptor humanized antibody which includes CDRs of a light chain and a heavy chain derived from mice parent antibody IGF11-16, and respective FRs of a light chain and a heavy chain derived from a human antibody, and in which at least one of the CDRs includes at least one amino acid residue substitution with respect to a corresponding CDR of the mice parent antibody; a fragment of the anti-IGF-1 receptor humanized antibody; or a derivative thereof.

Specification includes a Sequence Listing.



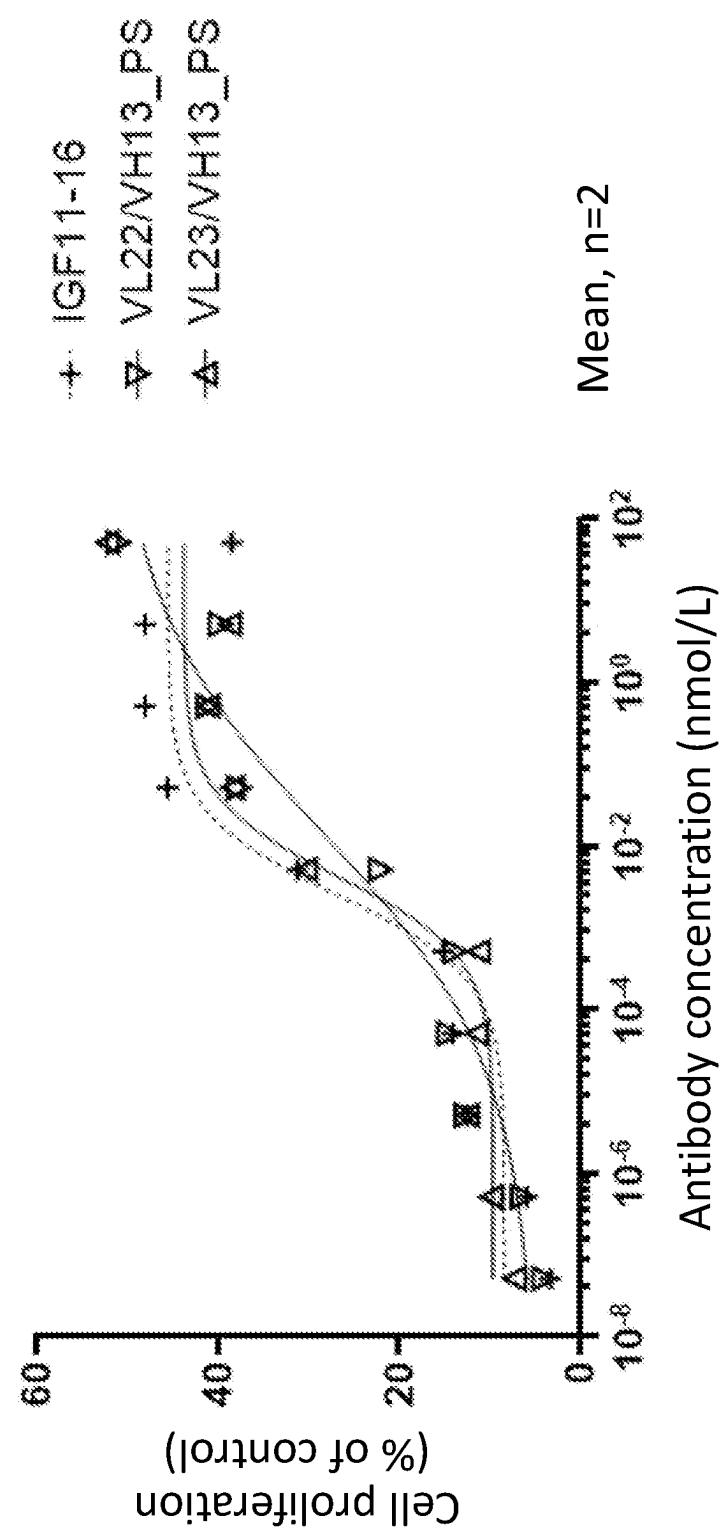


Figure 1A

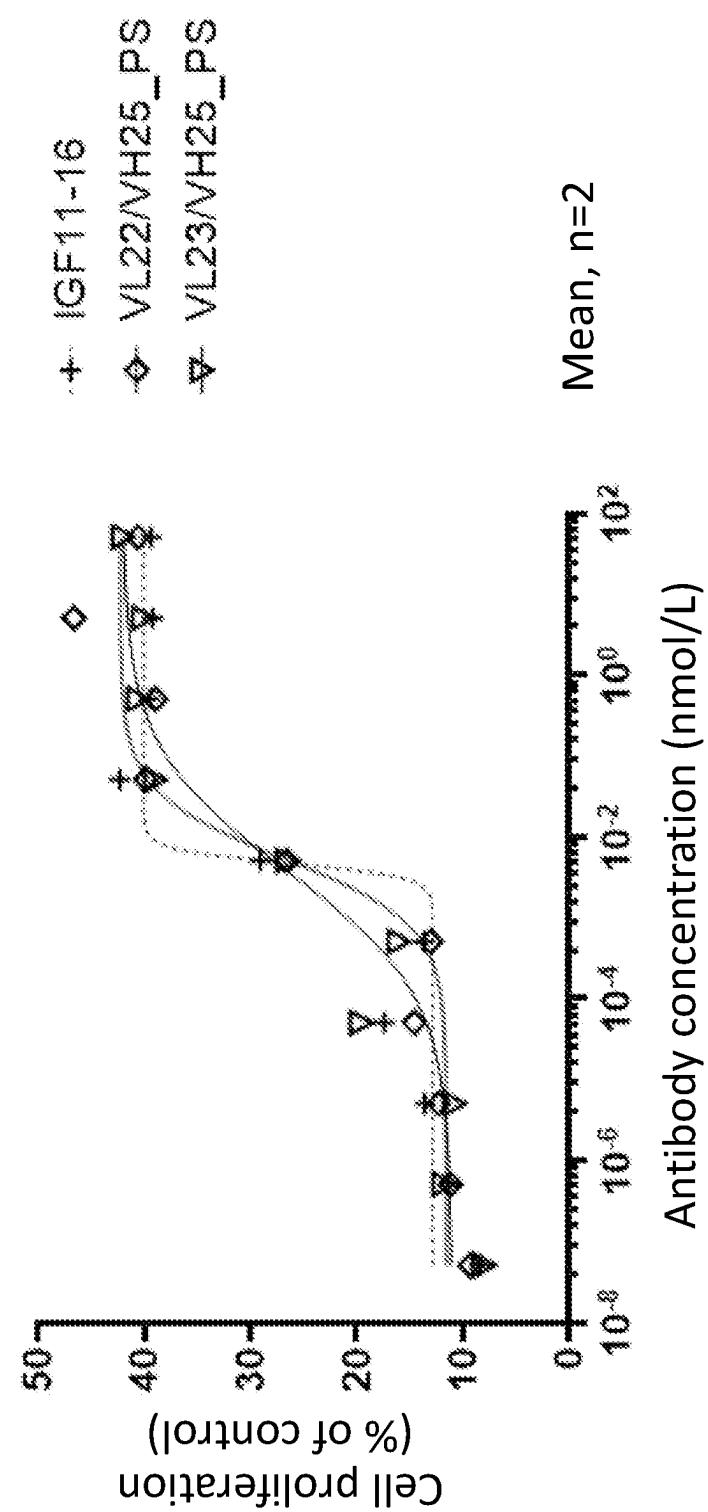


Figure 1B

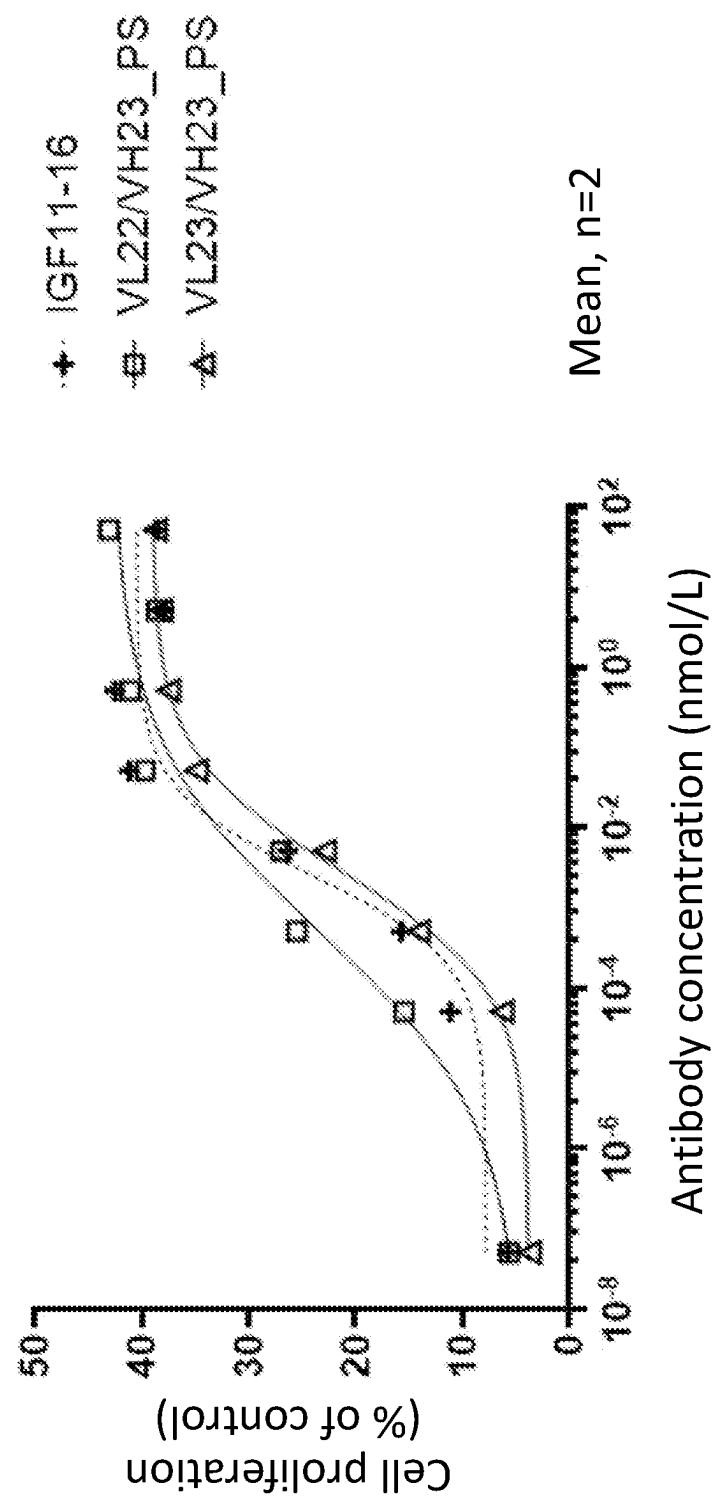
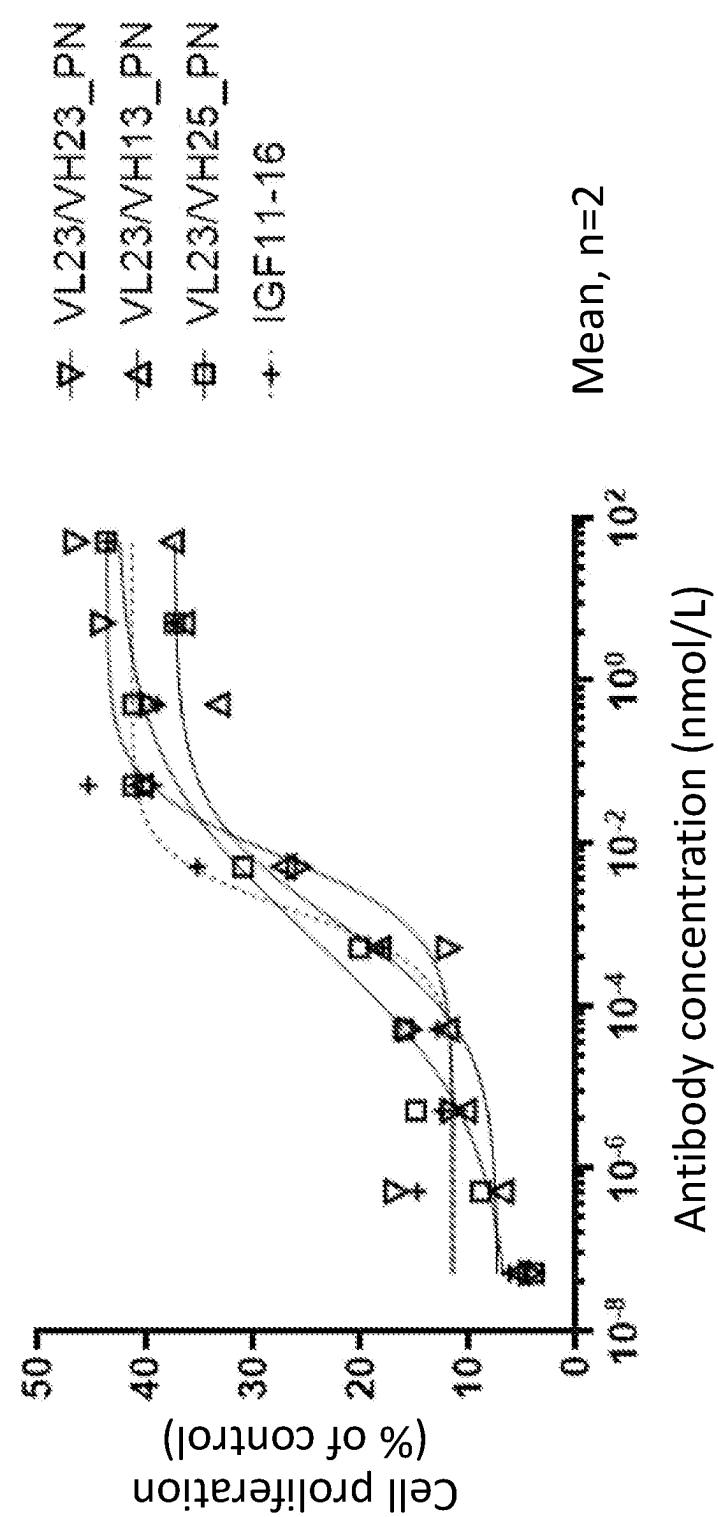


Figure 1C

Figure 1D



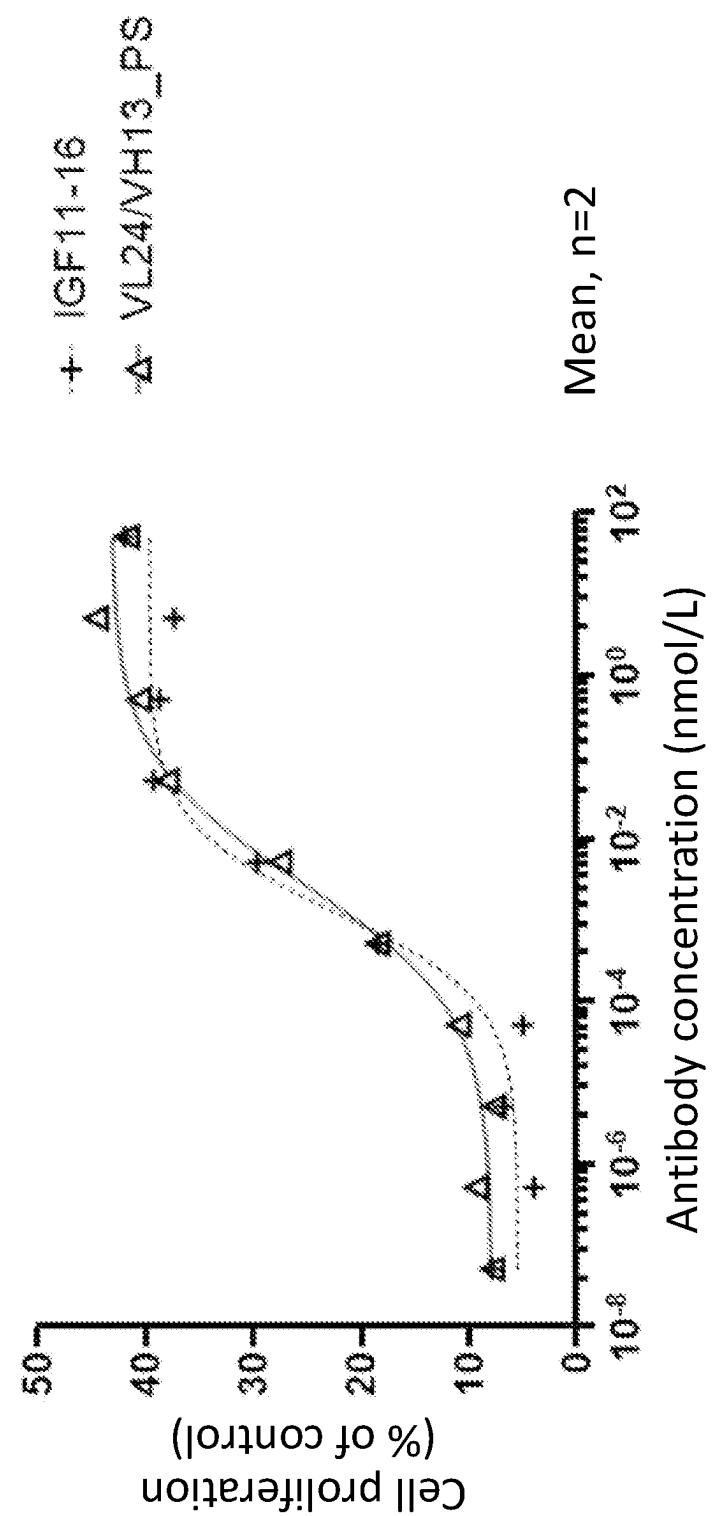


Figure 1E

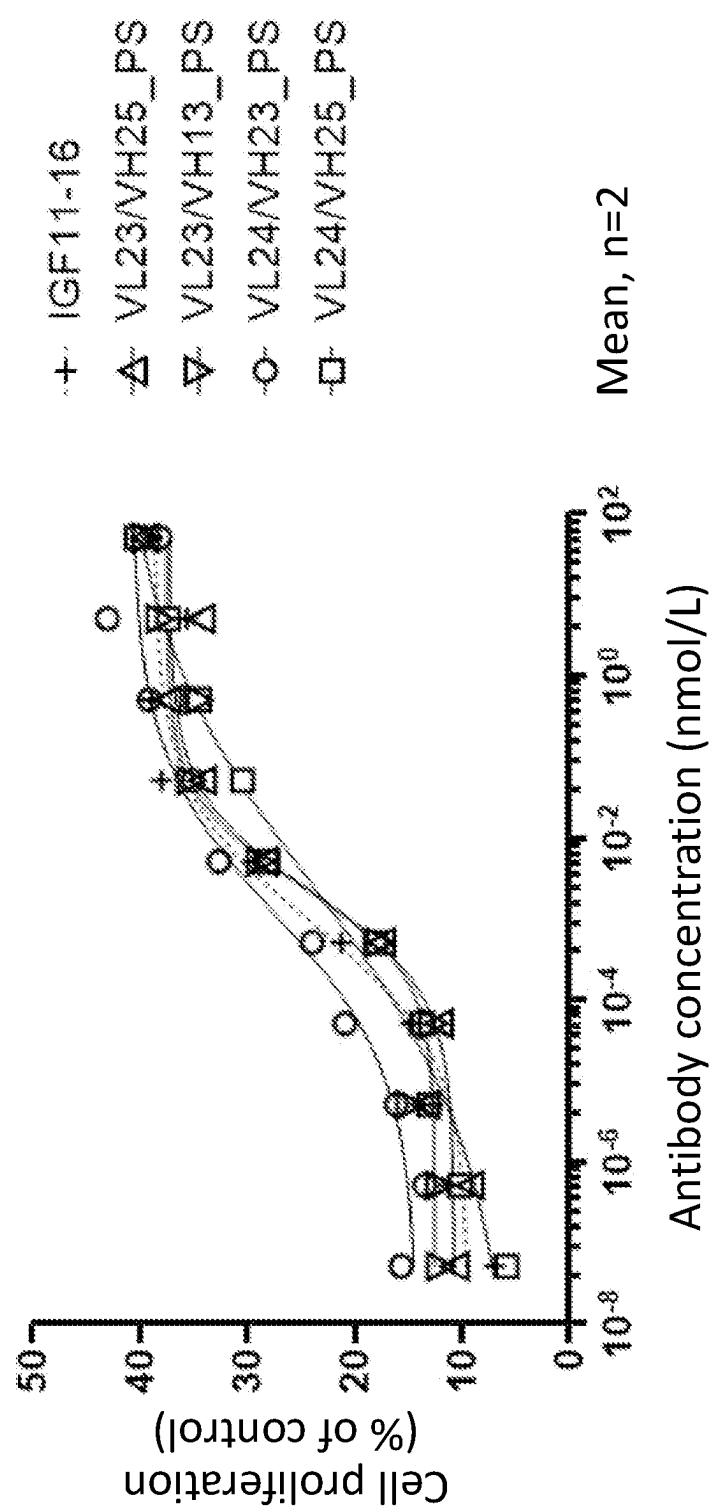


Figure 1F

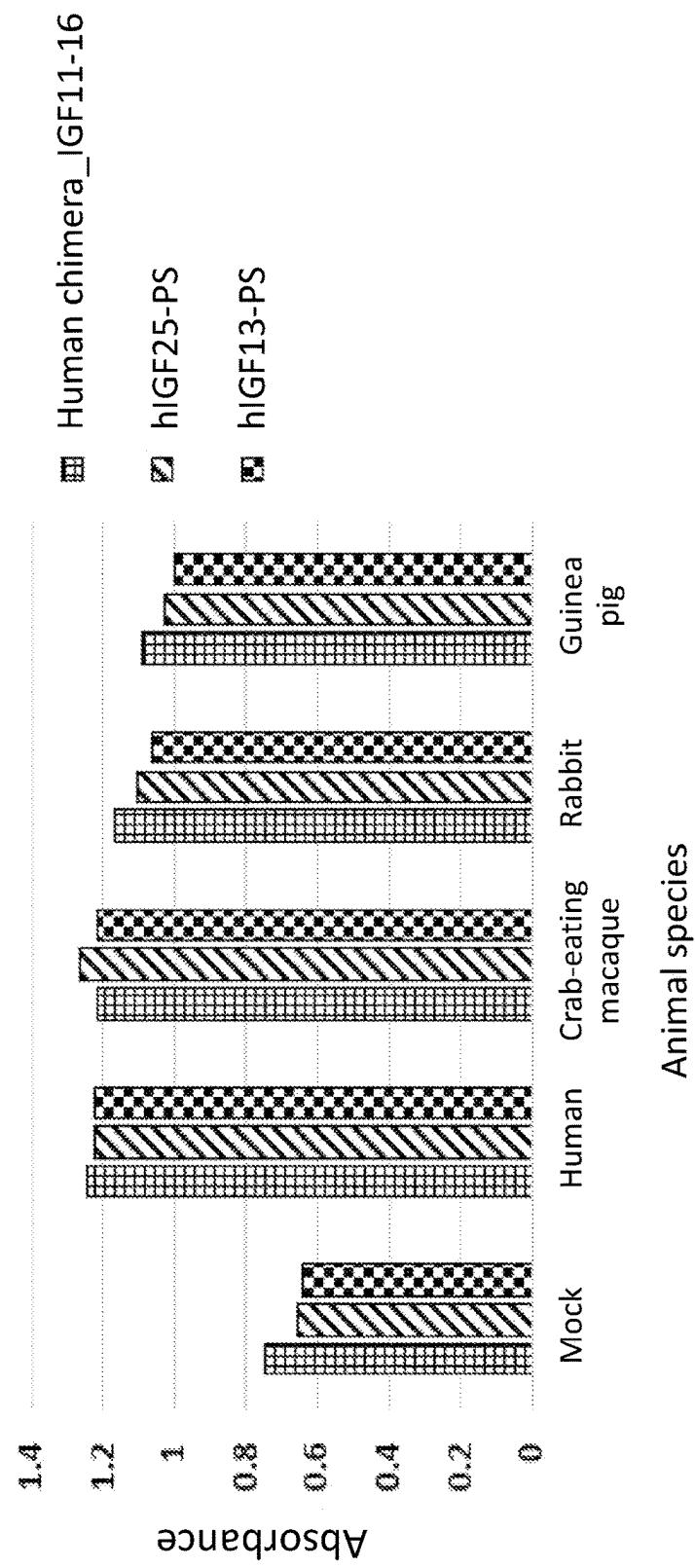


Figure 2

Figure 3A

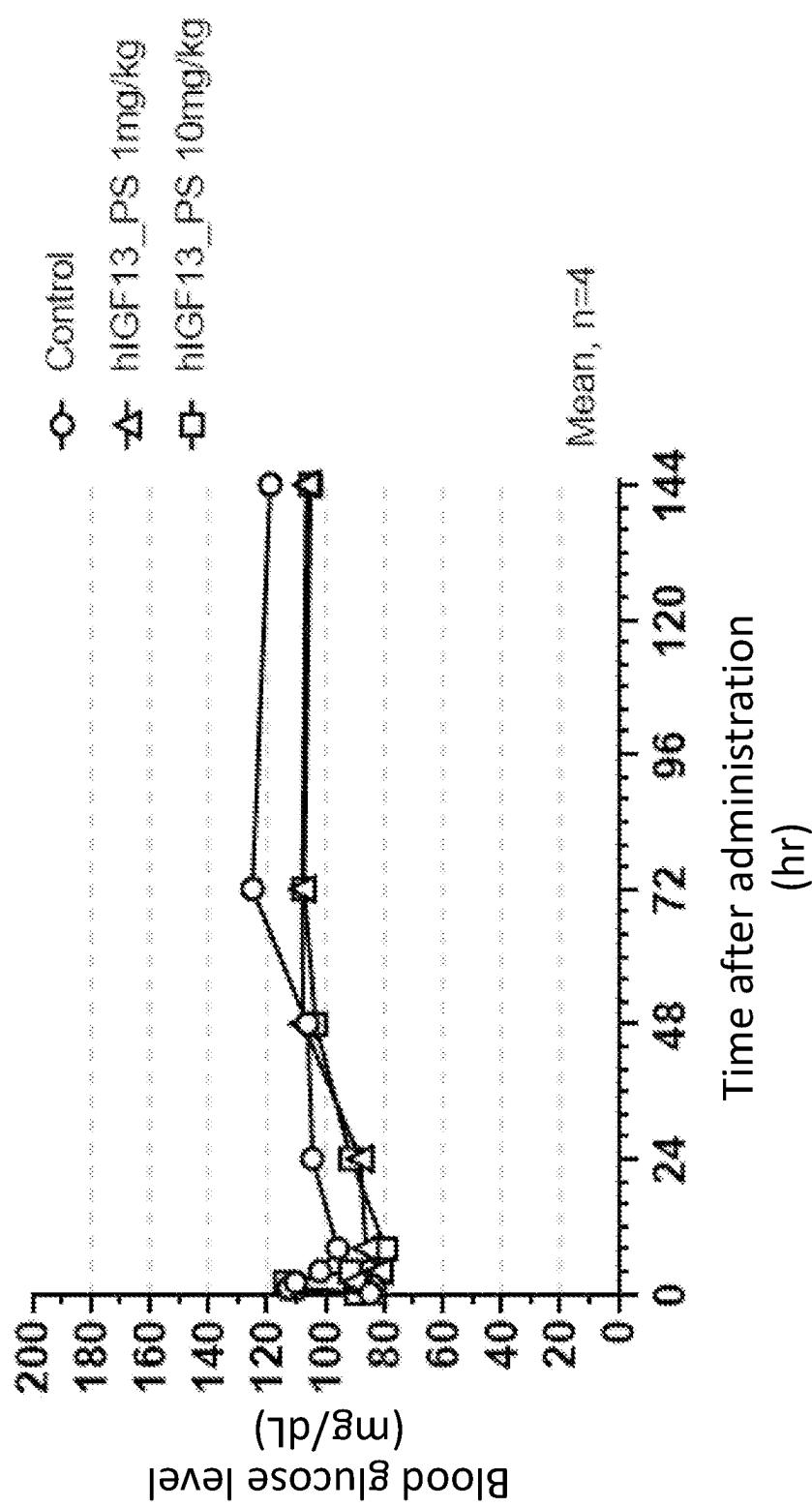
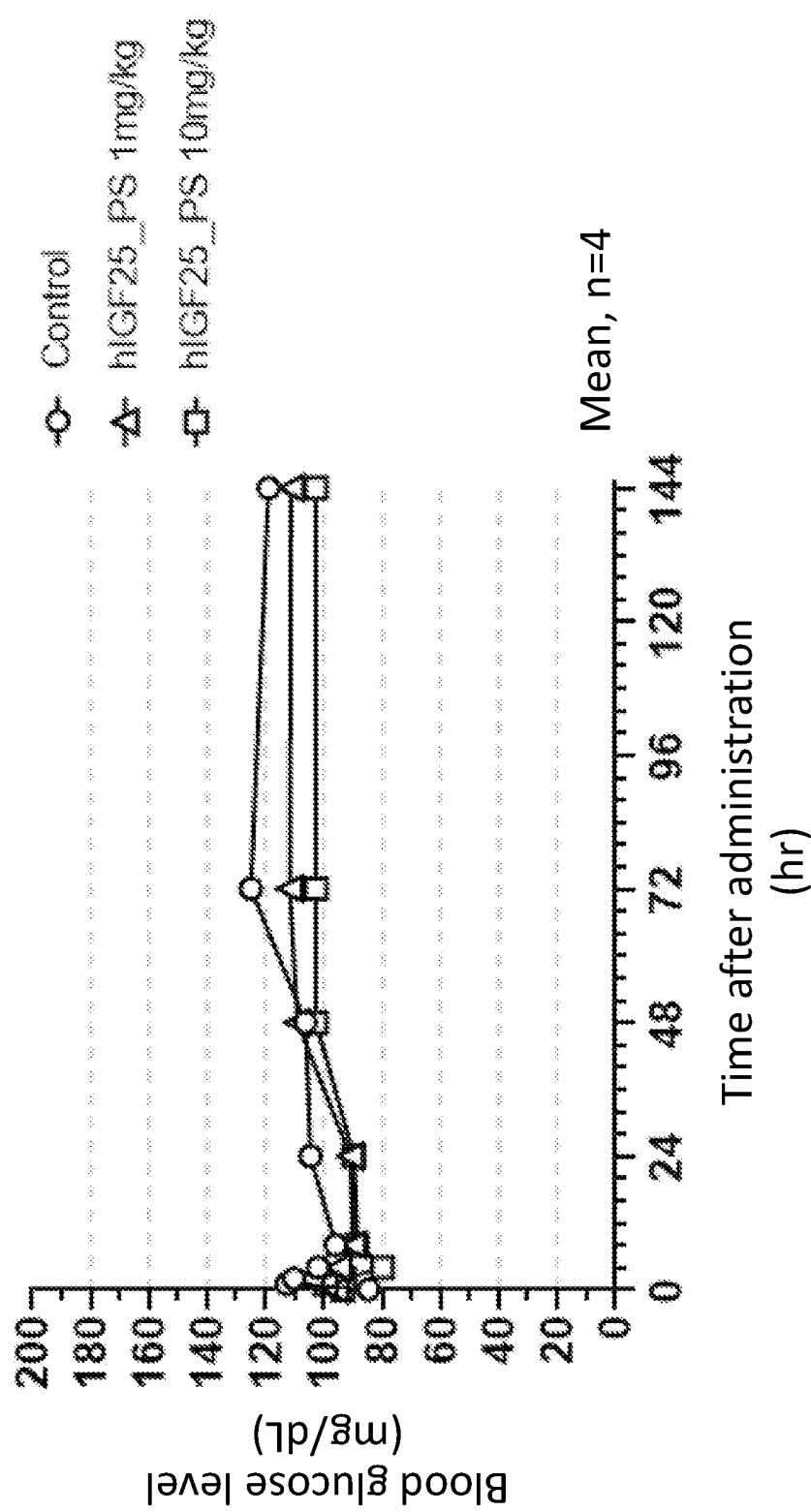


Figure 3B



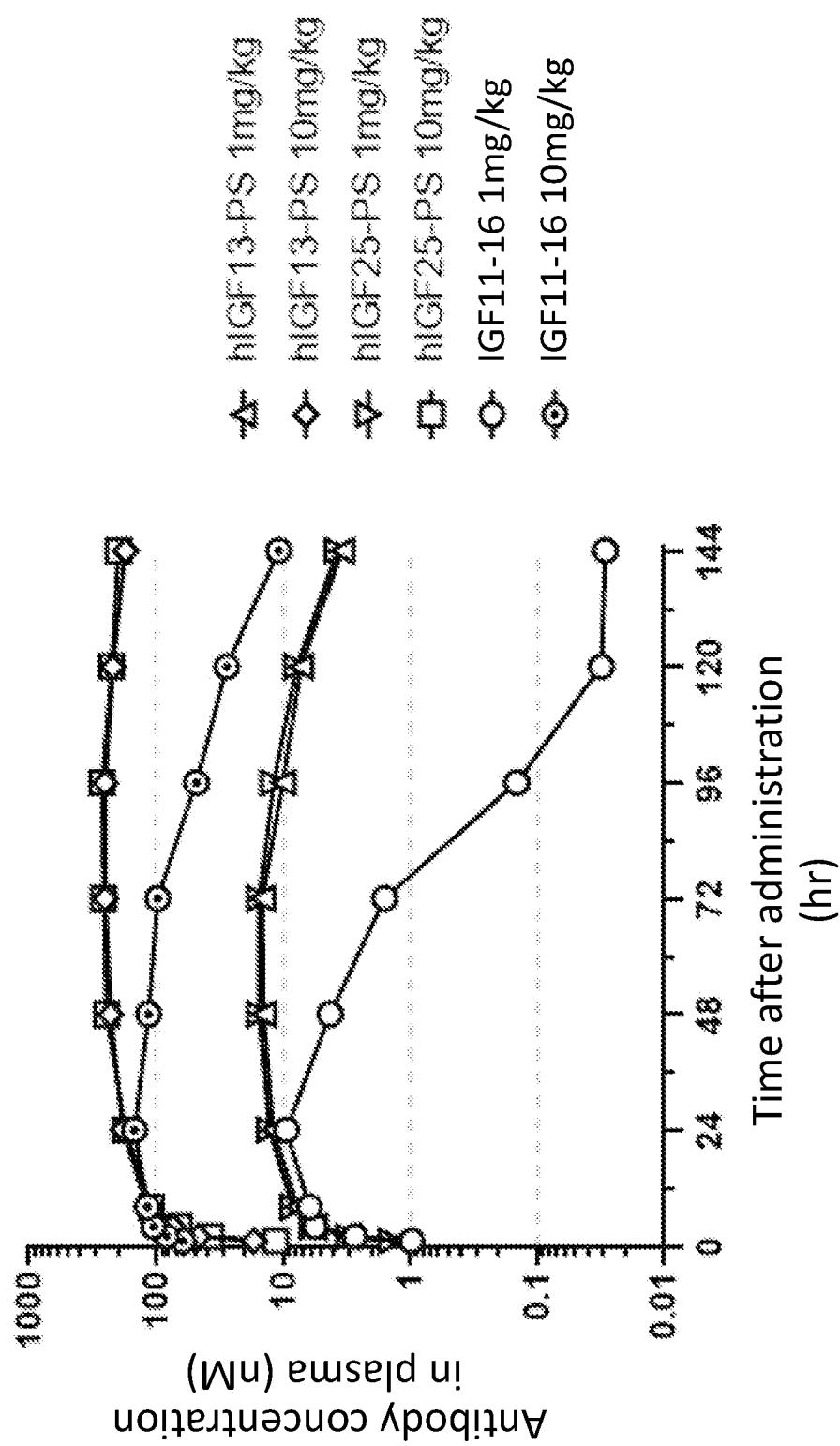


Figure 4

Figure 5

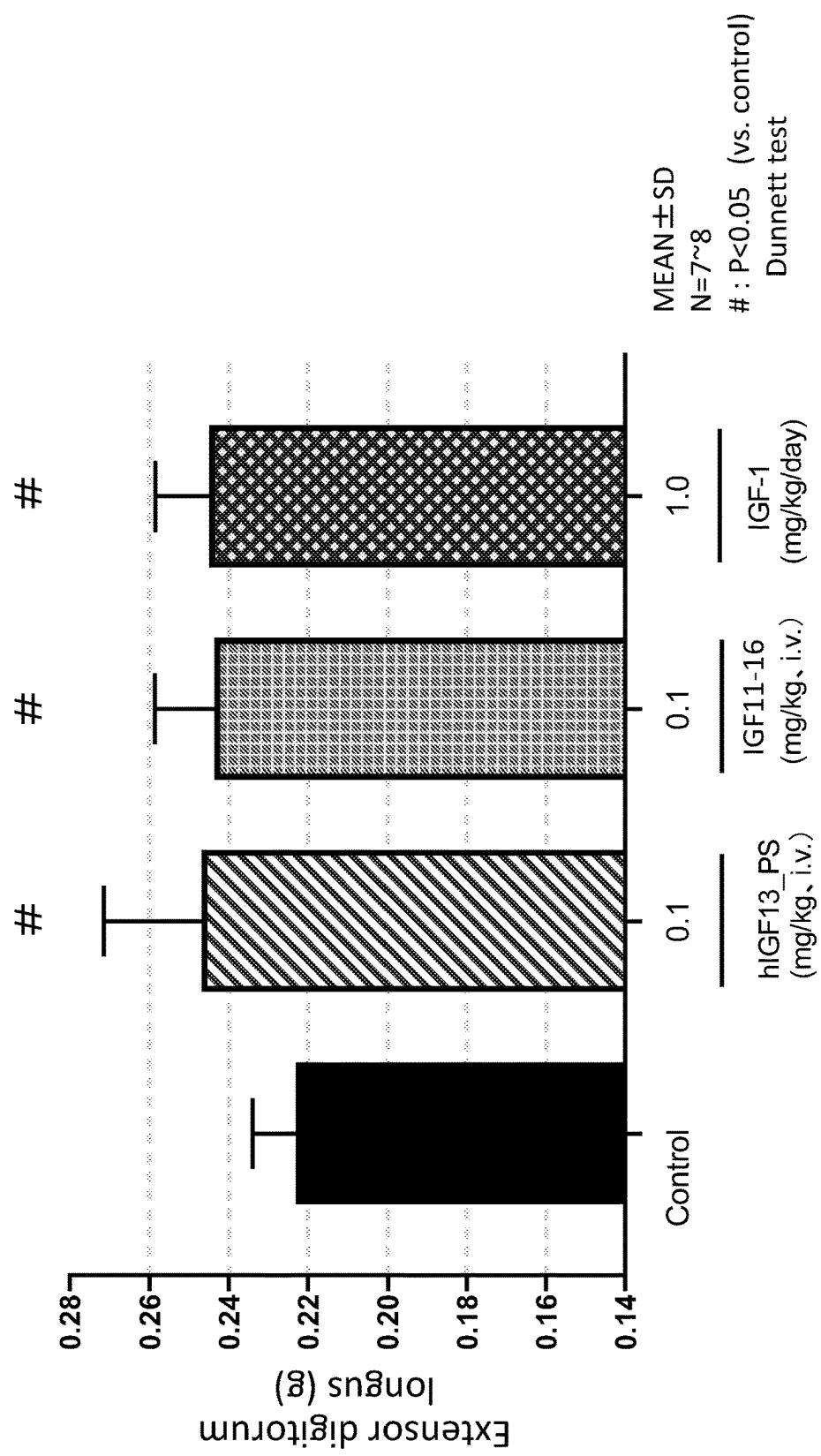
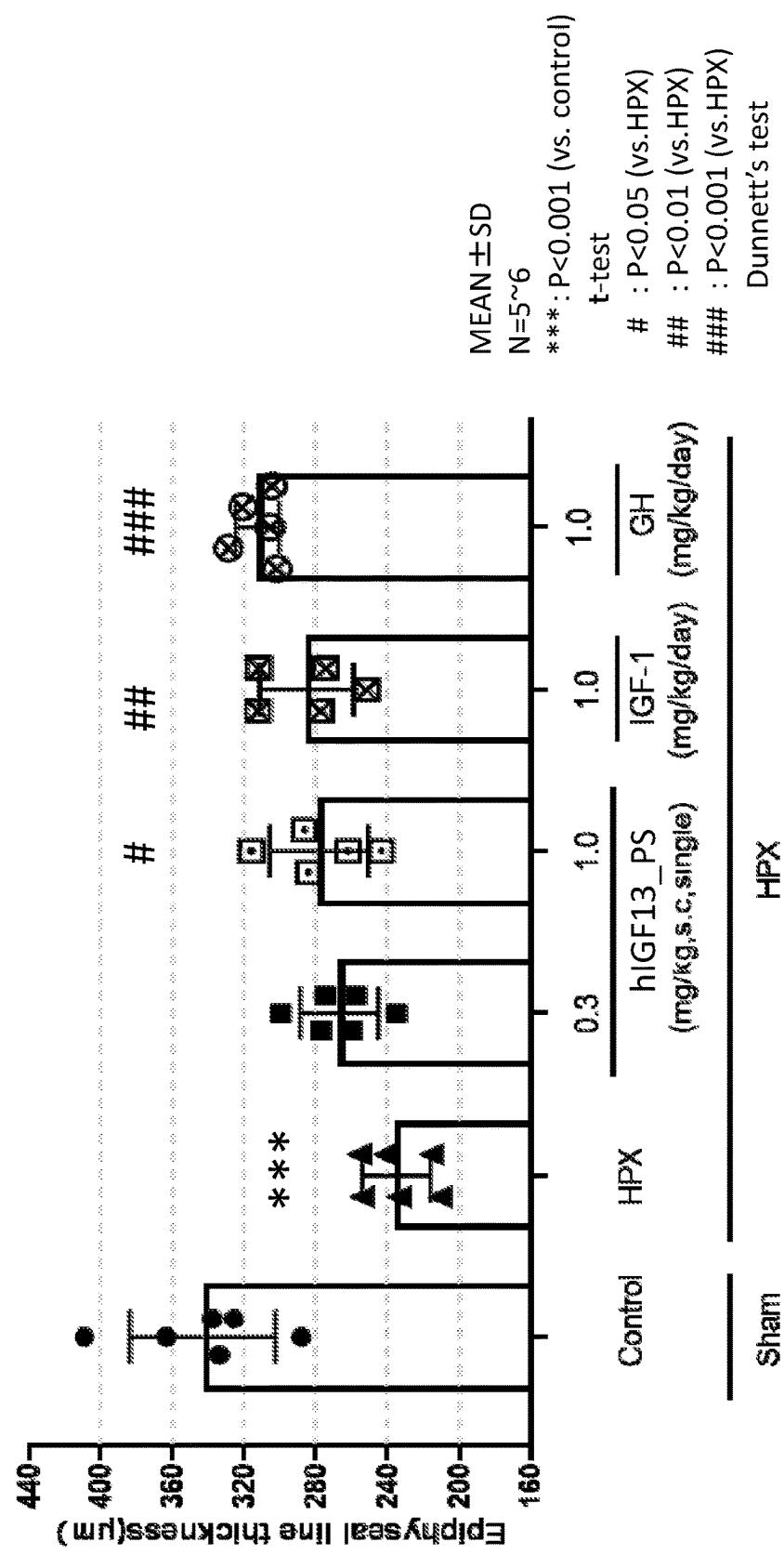


Figure 6



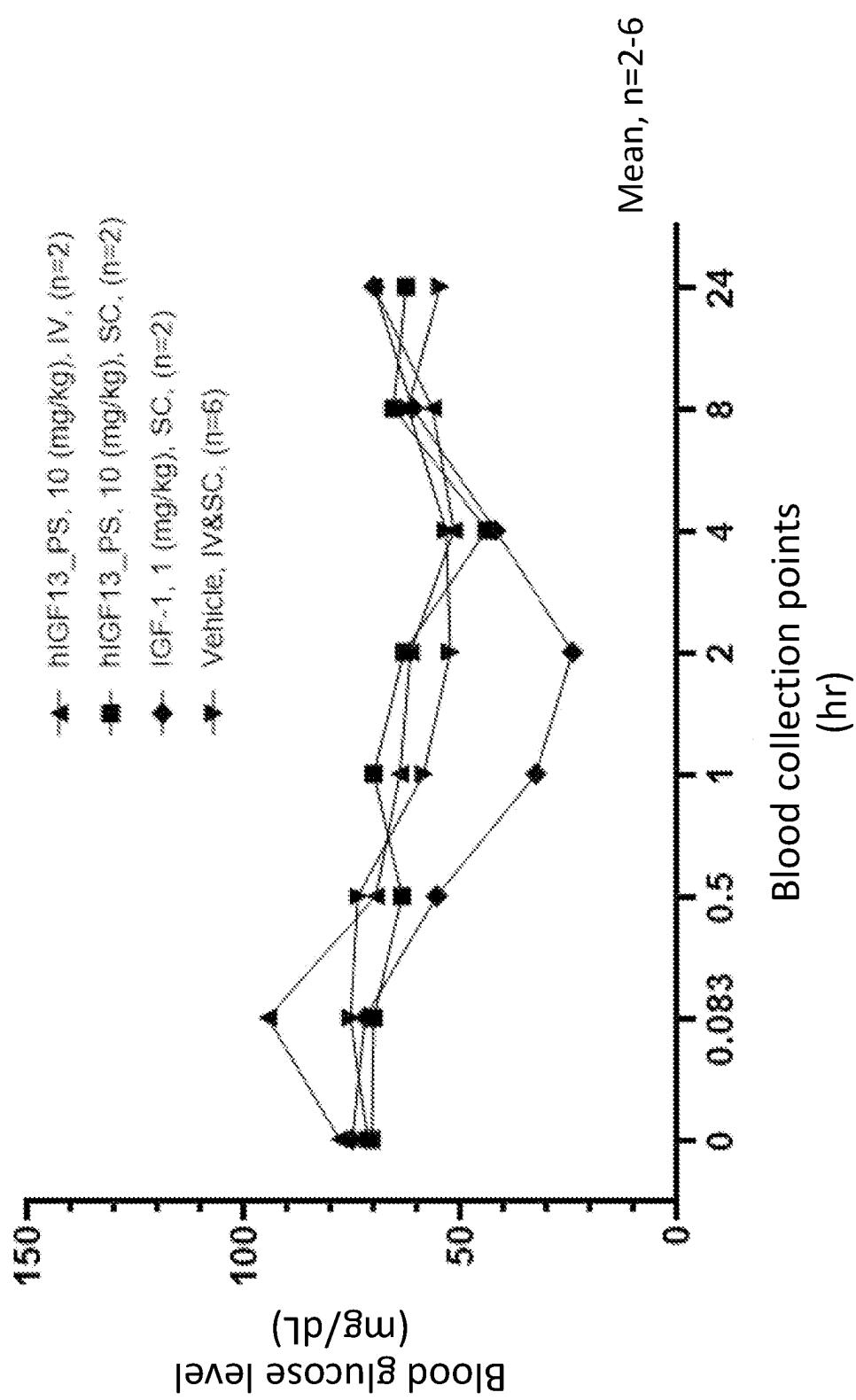


Figure 7

Figure 8

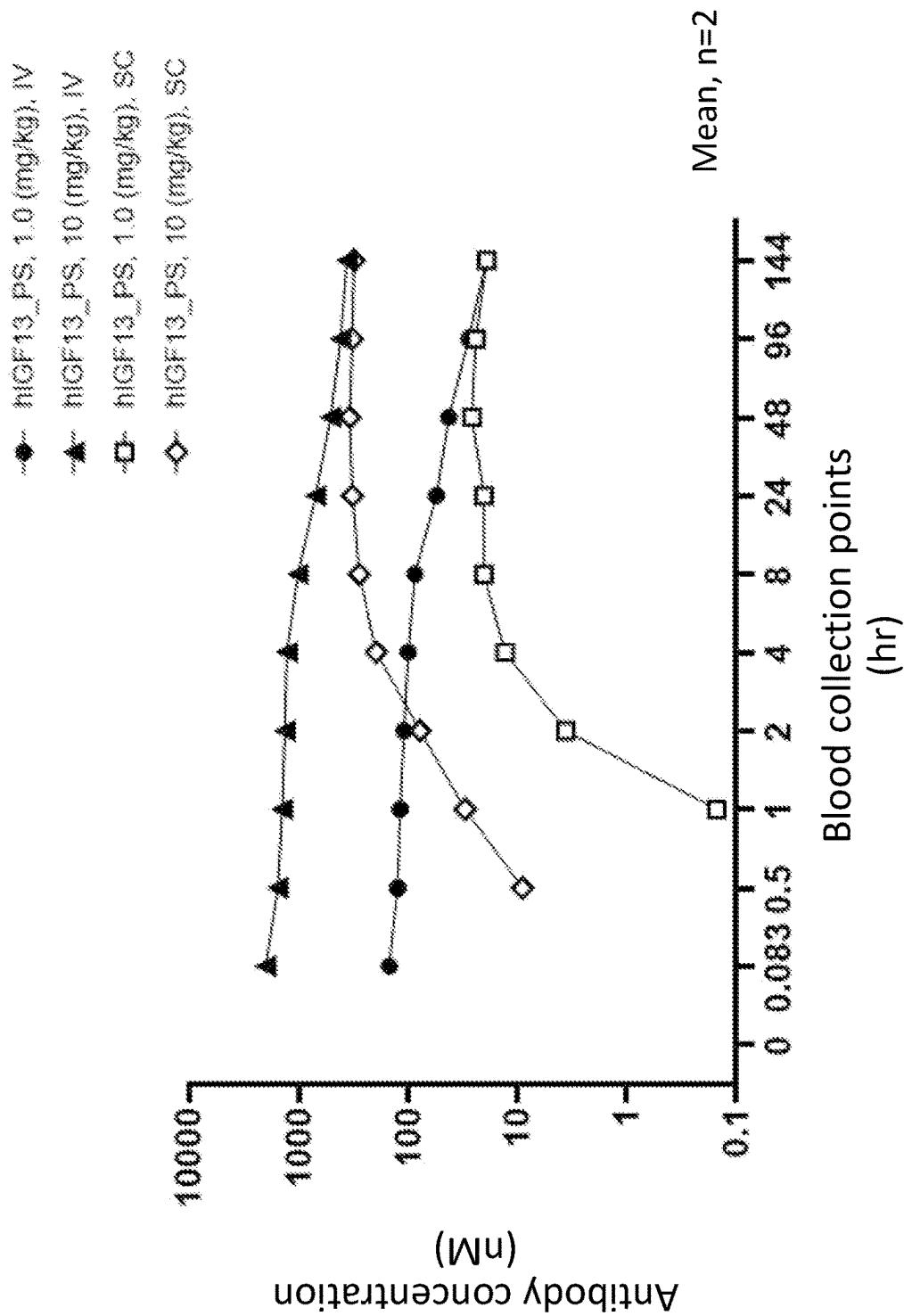
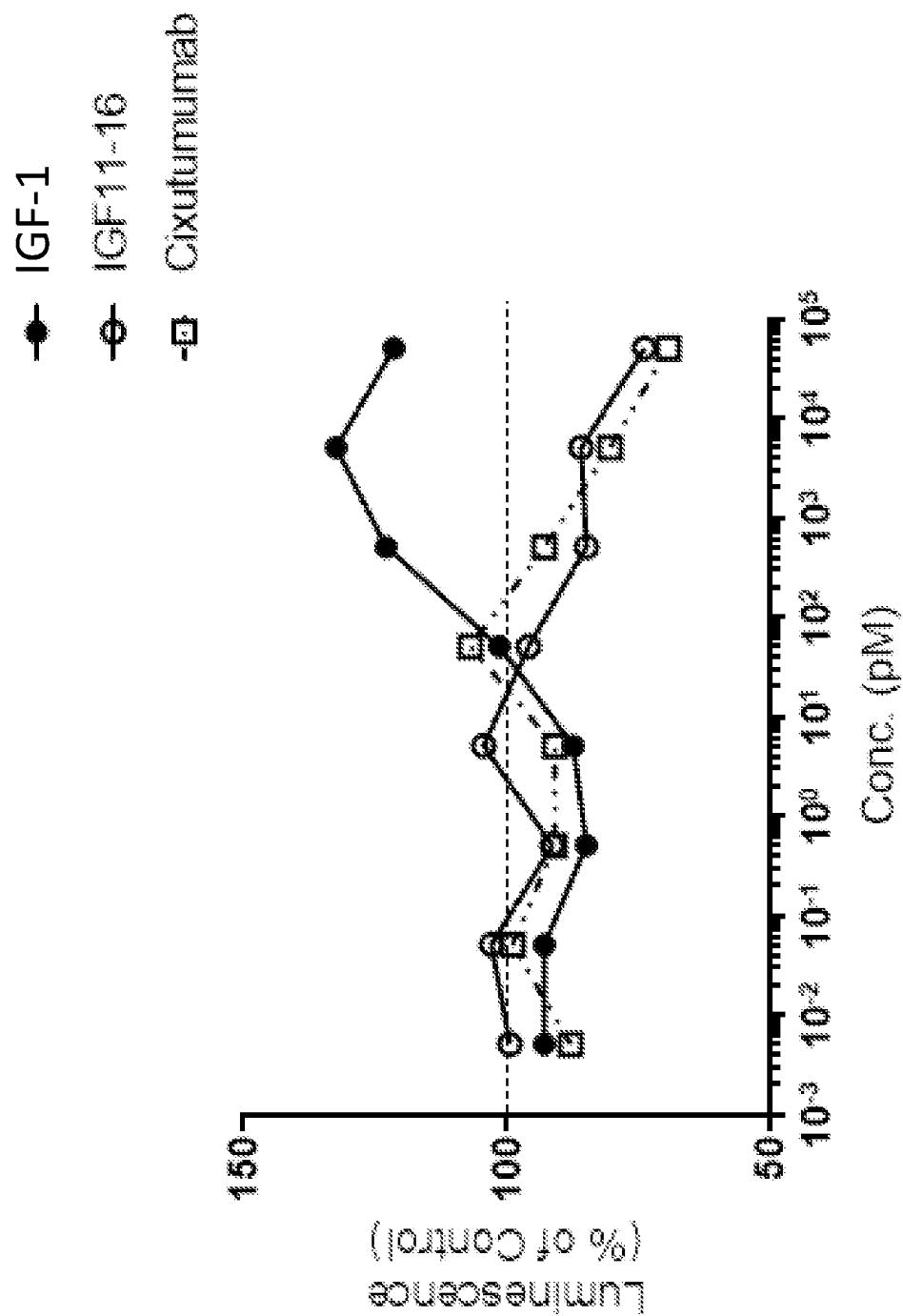


Figure 9



ANTI-IGF-1 RECEPTOR HUMANIZED ANTIBODY**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application is a National Stage of International Application No. PCT/JP2021/020890 filed Jun. 1, 2021, claiming priority based on Japanese Patent Application No. 2020-096344 filed Jun. 2, 2020.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been filed electronically in ASCII plain text format and is hereby incorporated by reference in its entirety. Said text copy, created on Apr. 27, 2023, is named Substitute Sequence Listing and is 166 KB in size.

TECHNICAL FIELD

[0003] The present invention relates to an anti-IGF-1 receptor humanized antibody and, more specifically, to an anti-IGF-1 receptor humanized antibody which specifically binds to an IGF-1 receptor.

BACKGROUND ART**1. IGF-1**

[0004] IGF-1 is an insulin-like growth factor secreted mainly from the liver through activation of a growth hormone (GH) receptor by the growth hormone secreted from the pituitary gland, and affects an IGF-1 receptor to thereby express a variety of physiological functions in various organs. Because of this, IGF-1 is expected to be used for the treatment of a variety of diseases. Since the amino acid sequence of IGF-1 has a high similarity of about 40% to that of proinsulin, IGF-1 can bind to an insulin receptor and thereby express insulin-like effects. In addition, since the amino acid sequence of the IGF-1 receptor has a high similarity of about 60% to that of an insulin receptor, these receptors can form a heterodimer and thereby exhibit physiological effects. Insulin can act on the insulin receptor to thereby express a strong effect of lowering the level of blood glucose, and is thus used as a hypoglycemic drug.

2. IGF-1 Receptor

[0005] An IGF-1 receptor is a transmembrane protein consisting of an alpha chain and a beta chain, and has six extracellular domains (L1, CR, L2, Fn1, Fn2, and Fn3), a transmembrane domain, and an intracellular domain. The intracellular domain of the IGF-1 receptor incorporates a tyrosine kinase. The extracellular domain participates in activation of the intracellular tyrosine kinase associated with conformational change of the IGF-1 receptor, which occurs when IGF-1 binds to the IGF-1 receptor. The IGF-1 receptor forms a homodimeric complex (homo-type). IGF-1 binding to the IGF-1 receptor (homo-type) triggers signaling via activation of the receptor kinase. The IGF-1 receptor also forms a heterodimeric complex (hetero-type) with the insulin receptor. Insulin or IGF-1 binding to the IGF-1 receptor (hetero-type) triggers signaling via activation of the receptor kinase.

3. Physiological Effects of IGF-1

[0006] IGF-1 has been shown to exhibit growth promoting effects, such as increasing the body length and the body mass, and insulin-like metabolic effects, such as glucose metabolism acceleration and hypoglycemic effects. It has been revealed that mecasermin, a human recombinant IGF-1, improves symptoms related to insulin receptor abnormality, such as hyperglycemia, hyperinsulinemia, acanthosis nigricans and hirsutism. IGF-1 has also been shown to improve growth disorder of dwarfism resistant to growth hormone (Non-Patent Literature 1).

4. Growth Promoting Effects of IGF-1

[0007] IGF-1 is a major growth-promoting factor (Non-Patent Literature 2, Non-Patent Literature 3). In fact, mecasermin, a human recombinant IGF-1, has been used clinically as a drug for treating dwarfism. IGF-1 is also known to enhance the DNA synthesis capacity of human chondrocytes. Administration of IGF-1 also increases the body mass and lengthens the femur bone length in pituitaryectomized rats.

5. Effect of IGF-1 on Increasing Muscle Mass

[0008] Enhancement of cell proliferation activity with IGF-1 requires continuous activation of the IGF-1 receptor. An animal engineered to overexpress the IGF-1 receptor exhibits increased muscle mass. Sustained administration of IGF-1/IGFBP3 to a patient with proximal femur fracture enhances her/his grip strength and improves her/his ability of standing from a seated position without assistance. The muscle IGF-1 levels of the elderly humans and mice are known to be lower than those of the young. Over expression of IGF-1 specifically in muscle tissues of elderly mice improved their muscle masses compared to wild-type mice (Non-Patent Literature 4).

6. Precedent Products for Increasing Muscle Mass

[0009] Anamorelin, a ghrelin receptor agonist, increased lean body mass in a clinical trial for cachexia, which is a disuse muscle atrophy. However, it involves adverse effects such as inducing nausea and hyperglycemia. Myostatin, a negative control factor of skeletal myogenesis, affects activin receptor II (ActRII) to thereby inhibit Akt/mTOR. LY2495655, an anti-myostatin antibody, increases the muscle masses of patients who received total hip replacement arthroplasty and those of elderly subjects. Bimagumab, an anti-ActRII antibody, increases the muscle mass of neuromuscular disease patients. However, there is no drug so far which promotes formation of skeletal muscles and can thereby be used for the treatment of a subject in need thereof.

7. Hypoglycemic Effect of IGF-1

[0010] IGF-1 is known to have hypoglycemic effect as an insulin-like effect. IGF-1 enhances glucose uptake effect of rat muscle-derived cells. Administration of IGF-1 also reduces the blood glucose level of rats. It has been reported that the glucose lowering effect of IGF-1 cause hypoglycemia as a clinical adverse effect. In addition, administration of IGF-1 to a human subject causes hypoglycemia. Therefore, at the onset of IGF-1 treatment, it is necessary to keep controlling the dosage starting from a low dosage with

observing various clinical findings including the blood glucose level after administration.

[0011] IGF-1 expresses hypoglycemic effect via, e.g., promotion of Akt phosphorylation. An active variant of Akt enhances glucose uptake by 3T3-L1 cells. On the other hand, an Akt2-deficient mouse exhibited elevated blood glucose level. An Akt inhibitor inhibits insulin-induced glucose uptake by rat muscle-derived cells. In addition, IGF-1 is also known to activate an insulin receptor which plays a role in hypoglycemic effect. These findings suggest that the hypoglycemic effect of IGF-1 involves overactivation of Akt and activation of the insulin receptor.

8. Short Half-Life of IGF-1 in Blood

[0012] IGF-1 has a short half-life in blood, and therefore requires frequent administrations when used in treatment. In fact, mecasermin, a human recombinant IGF-1, has a blood half-life of about 11 hours to about 16 hours, and therefore needs to be administered once to twice daily in the treatment of dwarfism. About 70 to 80% of IGF-1 is bound to IGFBP3 in blood, while a free form of IGF-1 exhibits physiological effect. Binding of IGF-1 to IGFBP3 maintains its half-life in blood to a time period of from about 10 hours to about 16 hours. IPLEX, a combination drug of IGF-1 with IGFBP3, exhibited a blood half-life extended from that of IGF-1 to a time period of about 21 hours to about 26 hours, and thereby allowed for reduction of administration frequency to once daily. However, IPLEX was already withdrawn from the market. There has been also an attempt to develop a PEGylated IGF-1 with improved IGF-1 kinetics, but no drug has successfully been developed so far and is currently available.

9. Therapeutic Effects Expected to be Achieved Via IGF-1's Effects

[0013] IGF-1 is known to affect various organs and exerts a wide variety of physiological functions. IGF-1 has been reported to have neuroprotective effect on the central nervous system by protecting mitochondria and antioxidant effect via activation of the IGF-1 receptor. IGF-1 promotes regeneration of injured neurites. IGF-1 is deemed to be effective in the treatment of hepatic cirrhosis, which evolves from liver damage or chronic liver disease and involves hepatic fibrosis. Administration of IGF-1 improved hepatic fibrosis in a model animal of hepatic cirrhosis. IGF-1 is also known to play a role in the development and functions of kidney. IGF-1 has protective effect against oxidative stress and apoptosis due to glucotoxicity in mesangial cells of kidney. IGF-1 is expected as a drug for the treatment of nephropathy.

[0014] Examples of conditions expected to be improved via IGF-1 administration include: sarcopenia, disuse muscle atrophy, cachexia, dwarfism, Laron syndrome, hepatic cirrhosis, hepatic fibrosis, aging, intrauterine growth restriction (IUGR), neurological disease, cerebral stroke, spinal cord injury, cardiovascular protection, diabetes, insulin resistant, metabolic syndrome, nephropathy, osteoporosis, cystic fibrosis, wound healing, myotonic dystrophy, AIDS-associated sarcopenia, HIV-associated fat redistribution syndrome, burn, Crohn's disease, Werner's syndrome, X-linked combined immunodeficiency disease, hearing loss, anorexia nervosa, and retinopathy of prematurity (Non-Patent Literature 19). Thus, IGF-1 is expected as a drug for the treatment

of a variety of diseases because of its wide spectrum of physiological effects. However, problems such as its adverse hypoglycemic effect and its short half-life requiring multiple administrations have prevented its clinical applications.

10. Anti-IGF-1 Receptor Agonist Antibody

[0015] In general, antibody formulations have long half-life, and prove effective if administered once to twice a month. Some IGF-1 receptor agonist antibodies have been reported to be effective in activating the receptor in vitro. Specifically, antibodies 3B7 and 2D1 enhance cellular DNA synthesis of recombinant IGF-1 receptor expression cells cultured for five hours in vitro (Non-Patent Literature 5). Anti-IGF-1 receptor antagonist antibodies 11A1, 11A4, 11A11, and 24-57, which has an activity to inhibit the proliferation of a cancer cell line, enhance, although very slightly, tyrosine phosphorylation of IGF-1 receptor in vitro (Non-Patent Literature 6). Antibodies 16-13, 17-69, 24-57, 24-60, and 24-31 are shown to be effective in promoting cellular DNA synthesis and glucose uptake in vitro in a short time, and have the potential to exhibit hypoglycemic effect (Non-Patent Literature 7).

[0016] However, IGF-1 receptor tyrosine phosphorylation has been observed even with anti-IGF-1 receptor antagonist antibodies which have an inhibitory effect on cancer cell proliferation, such as αIR-3, and is not an indicator of agonist action (Non-Patent Literatures 5, 6, 8). It cannot be an indicator of agonist antibodies with cell proliferation activity also, since in cell proliferation assays using DNA synthesis as an indicator, such as thymidine or BrdU uptake, thymidine uptake has also been observed for anti-IGF-1 receptor antagonist antibodies with cancer cell growth inhibitory activity (Non-Patent Literatures 5 to 8). Furthermore, all of these were short-term evaluations within 24 hours, and there have been no reports of IGF-1 receptor agonist antibodies for promoting cell proliferation in culture for several days (Non-Patent Literatures 5 to 8), let alone antibodies that showed agonist activity against the IGF-1 receptor in vivo. In addition, since IGF-1 exerts both hypoglycemic and cell proliferative effects, it is necessary to avoid hypoglycemic effects in order to administer anti-IGF-1 receptor agonist antibodies to humans as therapeutic agents, although there have been no reports of such anti-IGF-1 receptor agonist antibodies. In addition, antibodies have a large molecular mass and are known to exhibit low tissue distribution, with a brain distribution of about 0.1% and a muscle tissue distribution of about 2%. Therefore, antibodies that show sufficient pharmacological activity at extremely low concentrations (on the order of pM) are required in order to exert their effects in tissues where antibody migration is low. However, there have been no reports of anti-IGF-1 receptor agonist antibodies that can act at such extremely low concentrations.

[0017] Against this background, the present inventors have succeeded in producing an anti-IGF-1 receptor monoclonal mouse antibody, IGF11-16, which exerts myoblast proliferative activity at very low concentrations in vitro and does not induce glucose uptake by differentiated skeletal muscle cells at such concentrations. In addition, the obtained monoclonal antibody IGF11-16 can be used to induce glucose uptake by skeletal muscle cells. Furthermore, they have confirmed that the obtained monoclonal mouse antibody

induces muscle mass gain and growth plate elongation in vivo without causing hypoglycemic symptoms (Patent Literature 1).

11. Anti-IGF-1 Receptor Antagonist Antibody

[0018] There are attempts to use an antibody which binds to the IGF-1 receptor for the treatment of malignancies, based on its antagonist effect of inhibiting binding of IGF-1 to the IGF-1 receptor. However, existing IGF-1 receptor antagonist antibodies have various adverse effects such as hyperglycemia in monotherapy (Non-Patent Literature 9), and exhibit increased incidence of hyperglycemia when used in combination with other anticancer agents (Non-Patent Literature 10). Accordingly, their therapeutic applications are expected to be limited. Recently, teprotumumab was approved for the treatment of ophthalmopathy in hyperthyroidism (Non-Patent Literature 11).

LIST OF CITATIONS

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Non-Patent Literature

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Factor-1 Receptor Monoclonal Antibody, in Patients with Advanced Solid Tumors. *Clin Cancer Res.*, 2011.17(19): p. 6304-12.

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[0031] [Non-Patent Literature 12] Riechman, L., Clark, M., Waldmann, H., Winter, G.: Reshaping human antibodies for therapy. *Nature*, 1988. 332:p. 323-327.

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[0033] [Non-Patent Literature 14] Al-Lazikani et al., Journal of Molecular Biology, 1997, Vol. 273, No. 4, pp. 927-948

[0034] [Non-Patent Literature 15] Abhinandan, K. R. et al., Molecular Immunology, 2008, Vol. 45, pp. 3832-3839

[0035] [Non-Patent Literature 16] Jian, Y. et al., Nucleic Acids Research, 2013, Vol. 41, W34-W40

[0036] [Non-Patent Literature 17] Yamada, T. et al., Therapeutic monoclonal antibodies. *Keio Journal of Medicine*, 2011, Vol. 60, No. 2, pp37-46

[0037] [Non-Patent Literature 18] Burks, E. A., et al., Proc. Natl. Acad. Sci. USA, 1997, Vol. 94, No. 2, pp. 412-417

[0038] [Non-Patent Literature 19] Dumet, C., et al., MAbs, 2019, Vol. 11, No. 8, pp1341-1350

[0039] [Non-Patent Literature 20] Saunders, K. O., Frontiers in Immunology, 2019, Vol. 10, Article 1296

[0040] [Non-Patent Literature 21] Walle et al., Expert Opin. Biol. Ther., 2007, Vol. 7, No. 3, pp. 405-418

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SUMMARY OF INVENTION

Problem to be Solved by the Invention

[0042] An objective of the present invention is to provide an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof having a specificity and a binding affinity or activity equivalent to or higher than those of the previously reported anti-IGF-1 receptor mouse antibody IGF11-16 (Patent Literature 1), as well as a method of producing the same.

[0043] Specific objectives of the present invention include, but are not limited to, with an aim to obtain a humanized antibody having a specificity and a binding affinity or activity equivalent to or higher than those of the previously reported anti-IGF-1 receptor mouse antibody IGF11-16 (Patent Literature 1): (1) provision of amino acid residues essential for the design of a human framework; (2) provision of amino acid positions essential for maintaining activity in the CDR sequences, which are antigen binding sites (identified by the Kabat method in the present invention); (3) provision of amino acid substitutions to reduce immunogenicity; and (4) provision of amino acid substitutions to avoid the risk of deamidation.

[0044] Utilization and application of the present invention allows for provision of an anti-IGF-1 receptor humanized antibody that can increase muscle mas via, e.g., the human

IGF-1 receptor, without inducing hypoglycemic symptoms. This makes it possible to obtain an anti-IGF-1 receptor humanized antibody that can be administered to humans for the purpose of ameliorating or treating conditions or diseases related to IGF-1 receptor signaling such as, for example, sarcopenia, disuse muscular atrophy, or cachexia. It also makes it possible to provide a humanized antibody with low immunogenicity and physical stability that can be administered to humans.

Means to Solve the Problem

[0045] Thus, the present invention relates to, e.g., the following Aspects:

[Aspect 1]

[0046] An anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof comprising:

- [0047] heavy-chain and light-chain complementarity determining regions (CDRs) each derived from mouse parent antibody IGF11-16; and
- [0048] heavy-chain and light-chain framework regions (FRs) each derived from a human antibody,
- [0049] wherein at least one of the CDRs contains a substitution of at least one amino acid residue relative to the corresponding CDR of the mouse parent antibody IGF11-16.

[Aspect 2]

[0050] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, wherein the amino acid residue at the 25th position in Framework Region 1 of the heavy chain variable region (FR-H1) is a proline residue.

[Aspect 3]

[0051] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, comprising:

- [0052] as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), amino acid sequence defined in SEQ ID NO:1, or an amino acid sequence derived from SEQ ID NO:1 via substitution of any one amino acid residue thereof,
- [0053] as a sequence of CDR-2 of the heavy chain variable region (CDR-H2), SEQ ID NO:3 or amino acid sequence defined in SEQ ID NO:5, or amino acid sequence derived from SEQ ID NO:3 or SEQ ID NO:5 via substitution of any one, two, or three amino acid residues thereof,
- [0054] as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), amino acid sequence defined in SEQ ID NO:7, or an amino acid sequence derived from SEQ ID NO:7 via substitution of any one or two amino acid residues thereof,
- [0055] as a sequence of CDR-1 of the light chain variable region (CDR-L1), amino acid sequence defined in SEQ ID NO:9, or an amino acid sequence derived from SEQ ID NO:9 via substitution of any one or two amino acid residues thereof,
- [0056] as a sequence of CDR-2 of the light chain variable region (CDR-L2), amino acid sequence defined in SEQ ID NO:11, or an amino acid sequence

derived from SEQ ID NO:11 via substitution of any one amino acid residue thereof,

[0057] as a sequence of CDR-3 of the light chain variable region (CDR-L3), amino acid sequence defined in SEQ ID NO:13, or an amino acid sequence derived from SEQ ID NO:13 via substitution of any one or two amino acid residues thereof.

[Aspect 4]

[0058] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, comprising:

- [0059] as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), an amino acid sequence having a homology of 80% or more to SEQ ID NO:1,
- [0060] as a sequence of CDR-2 of the heavy chain variable region (CDR-H2), an amino acid sequence having a homology of 82% or more to SEQ ID NO:3 or SEQ ID NO:5,
- [0061] as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), an amino acid sequence having a homology of 75% or more to SEQ ID NO:7,
- [0062] as a sequence of CDR-1 of the light chain variable region (CDR-L1), an amino acid sequence having a homology of 81% or more to SEQ ID NO:9,
- [0063] as a sequence of CDR-2 of the light chain variable region (CDR-L2), an amino acid sequence having a homology of 85% or more to SEQ ID NO:11, and
- [0064] as a sequence of CDR-3 of the light chain variable region (CDR-L3), an amino acid sequence having a homology of 77% or more to SEQ ID NO:13.

[Aspect 5]

[0065] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, comprising:

- [0066] as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), an amino acid sequence derived from SEQ ID NO:1 in which Trp at the 3rd position of SEQ ID NO:1 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one amino acid residue other than the amino acid residue at the 3rd position or having a homology of 80% or more to SEQ ID NO:1,
- [0067] as a sequence of CDR-2 of the heavy chain variable region (CDR-H2),
- [0068] an amino acid sequence derived from SEQ ID NO:3 in which Glu at the 1st position and Asn at the 3rd position of SEQ ID NO:3 are each retained or substituted with a similar amino acid residue and Asn at the 6th position is retained or substituted with Ser or Gln, the amino acid sequence further including substitution of any one, two, or three amino acid residues other than the amino acid residues at the 1st position, the 3rd position, and the 6th position or having a homology of 82% or more to SEQ ID NO:3, or
- [0069] an amino acid sequence derived from SEQ ID NO:5 in which Glu at the 1st position and Asn at the 3rd position of SEQ ID NO:5 are each retained or substituted with a similar amino acid residue and Ser

at the 6th position of SEQ ID NO:5 is retained or substituted with Asn or Gln, the amino acid sequence further including substitution of any one, two, or three amino acid residues other than the amino acid residues at the 1st position, the 3rd position, and the 6th position or having a homology of 82% or more to SEQ ID NO:5,

[0070] as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), an amino acid sequence derived from SEQ ID NO:7 in which Arg at the 4th position of SEQ ID NO:7 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one or two amino acid residues other than the amino acid residue at the 4th position of SEQ ID NO:7 or having a homology of 75% or more to SEQ ID NO:7,

[0071] as a sequence of CDR-1 of the light chain variable region (CDR-L1), an amino acid sequence derived from SEQ ID NO:9 in which Trp at the 9th position of SEQ ID NO:9 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one or two amino acid residues other than the amino acid residue at the 9th position of SEQ ID NO:9 or having a homology of 81% or more to SEQ ID NO:9,

[0072] as a sequence of CDR-2 of the light chain variable region (CDR-L2), an amino acid sequence derived from SEQ ID NO:11 substitution of any one amino acid residue or having a homology of 85% or more to SEQ ID NO:11,

[0073] as a sequence of CDR-3 of the light chain variable region (CDR-L3), an amino acid sequence derived from SEQ ID NO:13 substitution of any one or two amino acid residues or having a homology of 77% or more to SEQ ID NO:13.

[Aspect 6]

[0074] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 5, which binds specifically to an extracellular domain of human IGF-1 receptor having the amino acid sequence defined in SEQ ID NO:71.

[Aspect 7]

[0075] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 6, comprising:

[0076] as a heavy chain variable region, an amino acid sequence defined in SEQ ID NO:43, 47, 49, 53, 55, or 59, an amino acid sequence derived from SEQ ID NO:43, 47, 49, 53, 55, or 59 via substitution, deletion, or addition of one or several amino acid residues, or an amino acid sequence having a homology of 90% or more to SEQ ID NO:43, 47, 49, 53, 55, or 59, and

[0077] as a light chain variable region, an amino acid sequence defined in SEQ ID NO:65, 67, or 69, an amino acid sequence derived from SEQ ID NO:65, 67, or 69 via substitution, deletion, or addition of one or several amino acid residues, or an amino acid sequence having a homology of 90% or more to SEQ ID NO:65, 67, or 69.

[Aspect 8]

[0078] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 7, comprising as a constant region of heavy and/or light chains, a constant region of heavy and/or light chains of any class of human immunoglobulin.

[Aspect 9]

[0079] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, wherein the heavy chain constant region is the heavy chain constant region of human IgG4 or a region derived therefrom via substitution of 1 to 10 amino acids.

[Aspect 10]

[0080] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, wherein the heavy chain constant region is the heavy chain constant region of human IgG1 or a region derived therefrom via substitution of 1 to 10 amino acids.

[Aspect 11]

[0081] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 10, which binds to an IGF-1 receptor with an affinity represented by an equilibrium dissociation constant (KD) of 1×10^{-7} M or less.

[Aspect 12]

[0082] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 11, which has an ability to activate IGF-1 receptor signaling.

[Aspect 13]

[0083] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 12, which exhibits a proliferative activity in a myoblast proliferation assay.

[Aspect 14]

[0084] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 13, which exhibits a binding affinity comparable to that of the mouse parent antibody IGF11-16 in a BIA-CORE binding assay to recombinant soluble IGF-1 receptor.

[Aspect 15]

[0085] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 14, which has an ability to induce muscle mass gain effect without inducing hypoglycemic symptoms in a normal mammal.

[Aspect 16]

[0086] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 15, which has an ability to induce growth plate cartilage elongation effect without inducing hypoglycemic symptoms in a hypophysectomized model animal.

[Aspect 17]

[0087] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 16, which, when administered to a vertebrate animal at a dose which induces an increase in muscle mass and/or body length, does not reduce the blood glucose level of the vertebrate animal.

[Aspect 18]

[0088] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 16, which, even at a blood exposure level 10 times higher than an effective dose sufficient to induce an increase in muscle mass and/or body length, does not reduce the blood glucose level of a vertebrate animal.

[Aspect 19]

[0089] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 18, which has an ability to inhibit the activation of IGF-1 receptor signaling.

[Aspect 20]

[0090] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 18, which inhibits the proliferative activity of at least one ligand of IGF-1, IGF-2 and insulin, which ligand can activate the IGF-1 receptor in a myoblast proliferation assay.

[Aspect 21]

[0091] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 18, which has an activity to inhibit cell proliferation in a cancer cell proliferation assay.

[Aspect 22]

[0092] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 18, which has at least one characteristic selected from:

[0093] (1) inhibiting the proliferation of vertebrate-derived cells induced by an IGF-1 receptor activating ligand;

[0094] (2) inhibiting the proliferation of cells in a vertebrate animal induced by an IGF-1 receptor activating ligand in a cell proliferative disorder;

[0095] (3) not affecting glucose uptake by differentiated muscle cells at a dose sufficient to inhibit the proliferation of vertebrate-derived cells induced by an IGF-1 receptor activating ligand; and

[0096] (4) not affecting the blood glucose level in a vertebrate animal even at a dose sufficient to inhibit cell proliferation in a vertebrate cell proliferative disorder caused by IGF-1 receptor activating ligand.

[Aspect 23]

[0097] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 22, which has an ability to induce an inhibitory

effect on cancer cell proliferation without affecting the blood glucose level in a cancer-bearing model animal.

[Aspect 24]

[0098] The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 23, which, even at a blood exposure level 10 times higher than an effective dose sufficient to induce an inhibitory effect on cancer cell proliferation in a cancer-bearing model animal, does not affect the blood glucose level of the model animal.

[Aspect 25]

[0099] A nucleic acid molecule comprising a polynucleotide sequence encoding an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 24.

[Aspect 26]

[0100] A cloning vector or expression vector comprising at least one nucleic acid molecule according to claim 25.

[Aspect 27]

[0101] A recombinant cell derived from a host cell via introduction of a vector according to claim 26.

[Aspect 28]

[0102] A process of producing an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 24, comprising:

[0103] culturing a recombinant cell according to claim 27; and

[0104] purifying the anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof produced by the recombinant cell.

[Aspect 29]

[0105] A pharmaceutical composition comprising, as an active ingredient, an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 24, a nucleic acid molecule according to claim 25, a vector according to claim 26, or a recombinant cell according to claim 27.

[Aspect 30]

[0106] The pharmaceutical composition according to claim 29, for use in the treatment of muscle atrophic disease or dwarfism.

[Aspect 31]

[0107] The pharmaceutical composition according to claim 30, wherein the muscle atrophic disease is disuse muscle atrophy, sarcopenia, or cachexia.

[Aspect 32]

[0108] The pharmaceutical composition according to claim 30, wherein the dwarfism is Laron-type dwarfism or growth-hormone resistant dwarfism.

[Aspect 33]

[0109] The pharmaceutical composition according to claim 29, for use in the treatment of an IGF-1 receptor associated disease.

[Aspect 34]

[0110] The pharmaceutical composition according to claim 33, wherein the IGF-1 receptor associated disease is selected from the group consisting of: liver cancer, neuroblastoma, rhabdomyosarcoma, bone cancer, pediatric cancer, acromegalia, ovary cancer, pancreas cancer, benign prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, neck cancer, synoviosarcoma, urinary bladder cancer, stomach cancer, Wilms' tumor, diarrhea associated with metastatic carcinoid and vasoactive intestinal peptide secreting tumor, vipoma, Verner-Morrison syndrome, Beckwith-Wiedemann syndrome, kidney cancer, renal-cell cancer, transitional cell cancer, Ewing's sarcoma, leukemia, acute lymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatous brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, undifferentiated neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendrogloma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic erythematosus, myasthenia gravis, autoimmune thyroiditis, Hashimoto's thyroiditis, thyroid ophthalmopathy, hyperthyroidism and Behcet's disease.

Advantageous Effects of Invention

[0111] The present invention allows for provision of an anti-IGF-1 receptor humanized antibody that binds to the human IGF-1 receptor, and that can be used for the treatment or prevention of diseases that act through the human IGF-1 receptor. The present invention also allows for provision of a humanized antibody with low immunogenicity and physical stability that can be administered to humans.

BRIEF DESCRIPTION OF DRAWINGS

[0112] FIGS. 1A to 1F show the human myoblast proliferative activity of various humanized antibodies of the present invention in comparison with the mouse parent antibody IGF11-16.

[0113] FIG. 1B Same as above.

[0114] FIG. 1C Same as above.

[0115] FIG. 1D Same as above.

[0116] FIG. 1E Same as above.

[0117] FIG. 1F Same as above.

[0118] FIG. 2 is a graph showing the reactivity of the humanized antibodies hIGF13_PS and hIGF25_PS of the present invention against IGF-1R of each animal species as measured by ELISA using HEK293T cells expressing IGF-1Rs of different animal species in comparison with that of the human mouse chimeric antibody IGF11-16.

[0119] FIG. 3A shows the transition of the blood glucose level over time in guinea pigs treated with the humanized antibody hIGF13_PS of the present invention.

[0120] FIG. 3B shows the transition of the blood glucose level over time in guinea pigs administered with the humanized antibody hIGF25_PS of the present invention.

[0121] FIG. 4 shows the transition of the blood concentration over time in guinea pigs treated with the humanized antibody hIGF13_PS or hIGF25_PS of the present invention in guinea pigs in comparison with those treated with the mouse parent antibody IGF11-16.

[0122] FIG. 5 shows the changes in the mass of extensor digitorum longus mass after 2 weeks of a single intravenous administration of the humanized antibody hIGF13_PS to normal guinea pigs, in comparison with continuous subcutaneous administration of IGF-1 and a single intravenous administration of the mouse parent antibody IGF11-16.

[0123] FIG. 6 shows the change in epiphyseal thickness of the proximal tibia after 2 weeks of a single intravenous administration of the humanized antibody hIGF13_PS to pituitary-ectomized guinea pigs in comparison with continuous subcutaneous administration of IGF-1 and continuous subcutaneous administration of a GH preparation.

[0124] FIG. 7 shows the change in the blood glucose level in crab-eating macaques treated with administration of the humanized antibody hIGF13_PS in comparison with those treated with IGF-1 administration.

[0125] FIG. 8 shows the change in the blood concentration in crab-eating monkeys treated with administration of the humanized antibody hIGF13_PS.

[0126] FIG. 9 shows the concentration-dependent effect of the mouse parent antibody IGF11-16 on HepG2 cell proliferation.

DESCRIPTION OF EMBODIMENTS

[0127] The present invention will now be described below with reference to specific embodiments, although the present invention should not be limited in any way to these embodiments. All references cited herein, including patent publications, patent application publications, and non-patent documents, are hereby incorporated by reference in their entirety for all purposes.

[0128] The unit "M," which refers to concentration, is used herein synonymously with the unit "mol/L," which refers to molar concentration.

[0129] The present invention relates to an anti-IGF-1 receptor humanized antibody that specifically binds to the IGF-1 receptor. The antibody of the present invention has a function to increase muscle mass acts via the human IGF-1 receptor without inducing hypoglycemic symptoms. This makes it possible to ameliorate or treat conditions or diseases involving IGF-1 receptor signaling, such as sarcopenia, disuse muscular atrophy, and keratoconus. In addition, the antibody of the present invention is a humanized antibody that ensures low immunogenicity and physical stability.

[IGF]

[0130] In the present disclosure, IGF refers to as an insulin-like growth factor, which may be either IGF-1 or IGF-2. Both IGF-1 and IGF-2 are biological ligands having agonist activities which bind to an IGF-1 receptor (insulin-like growth factor-I receptor) and transduce signals such as cell division and metabolism into the cell. IGF-1 and IGF-2 are also known to have cross-avidity to an insulin receptor (INSR), which is structurally similar to the IGF-1 receptor. The present specification will mainly discuss IGF-1, since its properties such as physiological functions are known more than those of IGF-2. However, in the context of

discussion about various effects and diseases mediated via binding of a ligand to the IGF-1 receptor, both IGF-1 and IGF-2 may collectively be mentioned.

[0131] IGF-1, also referred to as somatomedin C, is a single polypeptide hormone consisting of 70 amino acids. The sequence of human IGF-1 is available, e.g., with NCBI Reference Sequence number: NP_000609, or, on the EMBL-EBI, with UniProtKB accession number P05019. The amino acid sequence of mature human IGF-1 is shown in SEQ ID NO:83, and an example of the corresponding nucleotide sequence is shown in SEQ ID NO:84. This sequence consisting of 70 amino acids is conserved in many species. In the present invention, the term "IGF-1" without any limitation means an IGF-1 protein having such hormone activity, unless specified otherwise.

[0132] IGF-1 is produced by a variety of cells in the living body, including liver cells, and exists in blood and other body fluids. Therefore, wild-type IGF-1 can be obtained via purification from body fluid of an animal or from a primary cultured cell or a cultured cell line derived from an animal. Since a growth hormone induces IGF-1 production by cells, IGF-1 can also be purified from body fluid of an animal to which a growth hormone has been administered, or from a primary cultured animal cell or an animal cell line incubated in the presence of a growth hormone. As a different method, IGF-1 can also be obtained from a recombinant cell prepared by transfection of an expression vector carrying a nucleic acid molecule encoding an amino acid sequence of IGF-1 into a host such as a prokaryotic organism (e.g., *E. coli*) or a eukaryotic cell including a yeast, an insect cell, or a cultured mammal-derived cell, or from a transgenic animal or a transgenic plant into which an IGF-1 gene has been transfected. Human IGF-1 is also available as a research reagent (Enzo Life Sciences, catalog: ADI-908-059-0100, Abnova, catalog: P3452, etc.) or as a pharmaceutical product (Somazon® mecasermin, INCRELEX®, etc.). The *in vivo* and *in vitro* activities of IGF-1 for use can be evaluated as specific activities relative to an IGF-1 standard substance under NIBSC code: 91/554, whose activity corresponds to one international unit/microgram. The standard substance is available from World Health Organization's National Institute for Biological Standards and Control (NIBSC). In the context of the present invention, IGF-1 is considered as having a specific activity equivalent to the IGF-1 of NIBSC code: 91/554.

[IGF-1 Receptor]

[0133] In the present disclosure, the term "IGF-1 receptor" or "IGF-1R" refers to as an insulin-like growth factor-I receptor. The term "IGF-1 receptor" used herein means an IGF-1 receptor protein, unless specified otherwise. The IGF-1 receptor is a protein formed with two subunits, each consisting of an alpha chain and a beta chain. The amino acid sequence of a human IGF-1 receptor is indicated in SEQ ID NO:71, of which a subsequence consisting of the amino acid residues at positions 31 to 735 represents the alpha chain, while a subsequence starting from the amino acid residue at position 740 represents the beta chain. The alpha chain of the IGF-1 receptor has a portion to which IGF-1 binds, while the beta chain has a transmembrane structure and exhibits a function to transmit signals into the cell. The alpha chain of the IGF-1 receptor can be divided into L1, CR, L2, FnIII-1, and FnIII-2a/ID/FnIII-2b domains. According to the amino acid sequence of the human IGF-1

receptor defined in SEQ ID NO:71, the residues at position 31 to position 179 correspond to the L1 domain, the residues at position 180 to position 328 correspond to the CR domain, the residues at position 329 to position 491 correspond to the L2 domain, the residues at position 492 to position 607 correspond to the FnIII-1 domain, and the residues at position 608 to position 735 correspond to the FnIII-2a/ID/FnIII-2b domain. The amino acid sequence of human IGF-1 receptor is available, e.g., on EMBL-EBI with UniProtKB-accession number P08069, and is also indicated in the sequence listing as SEQ ID NO:71.

[0134] The IGF-1 receptor is known to be expressed in a wide range of tissues and cells in the living body, and receives various stimuli via IGF-1, such as induction of cell proliferation and activation of intracellular signals. In particular, effects of IGF-1 on myoblasts via the IGF-1 receptor can be evaluated using cell proliferation activities as indicators. For this reason, myoblasts are useful in analyzing the effects of antibodies binding to the IGF-1 receptor. Cells expressing an IGF-1 receptor derived from human or any other vertebrate can be prepared artificially, by transfection of an expression vector carrying a nucleic acid molecule encoding the amino acid sequence of an IGF-1 receptor derived from human or any other vertebrate into a eukaryotic host cell, such as a cultured insect cell or a mammal-derived cell, to prepare a recombinant cell expressing the IGF-1 receptor encoded by the transfected nucleic acid on its cell membrane. The resultant cell expressing the IGF-1 receptor can be used for analysis of the binding ability and intracellular signal transmissibility of antibodies.

[Mouse Parent Antibody IGF11-16]

[0135] The amino acid sequence of CDR-H1 of IGF11-16 is shown in SEQ ID NO:85, the amino acid sequence of CDR-H2 in SEQ ID NO:86, the amino acid sequence of CDR-H3 in SEQ ID NO:87, the amino acid sequence of CDR-L1 in SEQ ID NO:88, the amino acid sequence of CDR-L2 in SEQ ID NO:89, and the amino acid sequence of CDR-L3 in SEQ ID NO:90. The amino acid sequence of the heavy chain variable region is shown in SEQ ID NO:39 (an example of the corresponding nucleotide sequence is shown in SEQ ID NO:40), and the amino acid sequence of the light chain variable region is shown in SEQ ID NO:41 (an example of the corresponding nucleotide sequence is shown in SEQ ID NO:42). The full-length amino acid sequence of the light chain of IGF11-16 is shown in SEQ ID NO:91 (an example of the corresponding nucleotide sequence is shown in SEQ ID NO:92), and the full-length amino acid sequence of the heavy chain is shown in SEQ ID NO:93 (an example of the corresponding nucleotide sequence is shown in SEQ ID NO:94). All antibodies having names including the expression IGF11-16 refer to this mouse parent antibody IGF11-16.

[Anti-IGF-1 Receptor Humanized Antibody]

[0136] One aspect of the present invention provides a novel anti-IGF-1 receptor humanized antibody (hereinafter referred to as "the antibody of the present invention" as appropriate).

[0137] In the present disclosure, the term "an antibody" indicates a glycoprotein containing at least two heavy (H) chains and two light (L) chains coupled together via disulfide bindings. Each heavy chain has a heavy chain variable

region (abbreviated as VH) and a heavy chain constant region. The heavy chain constant region contains three domains, i.e., CH1, CH2, and CH3. Each light chain contains a light chain variable region (abbreviated as VL) and a light chain constant region. A light chain constant region has one domain, i.e., CL. There are two types of light chain constant regions, i.e., λ (lambda) chain and κ (kappa) chain. Heavy chain constant regions are classified into γ (gamma) chain, μ (mu) chain, α (alpha) chain, δ (delta) chain and ϵ (epsilon) chain, and different types of heavy chain constant regions result in different isotypes of antibodies, i.e., IgG, IgM, IgA, IgD, and IgE, respectively. Each of the VH and VL is also divided into four relatively conserved regions (FR-1 (FR1), FR-2 (FR2), FR-3 (FR3), and FR-4 (FR4)), collectively referred to as framework regions (FR), and three highly variable regions (CDR-1 (CDR1), CDR-2 (CDR2), and CDR-3 (CDR3)), collectively referred to as complementarity determining regions (CDR). The VH region includes the three CDRs and the four FRs arranged in the order of FR-1 (FR-H1), CDR-1 (CDR-H1), FR-2 (FR-H2), CDR-2 (CDR-H2), FR-3 (FR-H3), CDR-3 (CDR-H3), and FR-4 (FR-H4) from the amino terminal to the carboxyl terminal. The VL includes the three CDRs and the four FRs arranged in the order of FR-1 (FR-L1), CDR-1 (CDR-L1), FR-2 (FR-L2), CDR-2 (CDR-L2), FR-3 (FR-L3), CDR-3 (CDR-L3), and FR-4 (FR-L4) from the amino terminal to the carboxyl terminal. The variable region of each of the heavy chain and the light chain includes a binding domain, which interacts with an antigen.

[0138] The antibody of the present invention may be a fragment and/or derivative of an antibody. Examples of antibody fragments include F(ab')², Fab, and Fv. Examples of antibody derivatives include: antibodies to which an amino acid mutation has been introduced in its constant region; antibodies in which the domain arrangement of the constant regions has been modified; antibodies having two or more Fc's per molecule; antibodies consisting only of a heavy chain or only of a light chain; antibodies with modified glycosylation; bispecific antibodies; conjugates of antibodies or antibody fragments with compounds or proteins other than antibodies; antibody enzymes; nanobodies; tandem scFv's; bispecific tandem scFv's; diabodies; and VHJs. The term "antibody" used herein encompasses such fragments and/or derivatives of antibodies, unless otherwise specified.

[0139] The term monoclonal antibody classically refers to an antibody molecule obtained from a clone derived from a single antibody-producing cell, but in the present disclosure, refers to a single type of antibody molecule containing a combination of VH and VL consisting of a specific amino acid sequence. It is also possible to obtain from a monoclonal antibody a nucleic acid molecule having a gene sequence encoding the amino acid sequence of the antibody protein, which nucleic acid molecule can be used to produce a genetically engineered antibody. It is also well known to those skilled in the art to use genetic information of the sequences of an H chain and an L chain, or their variable regions or CDR sequences, for modifying an antibody to improve its binding ability and specificity, or for modifying an antibody derived from an animal such as mouse to a human-type antibody having a structure suitable for use as a therapeutic agent. It is also possible to obtain a human monoclonal antibody by preparing a non-human transgenic animal into which a human antibody gene has been intro-

duced and sensitizing the animal with an antigen. In addition, as a method that does not require sensitization of animals, a person skilled in the art can also employ a technique including using a phage library expressing antigen-binding regions of human antibodies or parts thereof (human antibody phage display) can be used to obtain phage clones presenting antibodies that specifically bind to the corresponding antigen or specific amino acid sequences, and producing a human antibody using the information from the obtained phage clones (see, e.g., Non-Patent Literature 17). A person skilled in the art can also design an antibody to be administered to a non-human animal by using the amino acid sequence information of CDRs and variable regions as appropriate, in a similar manner to humanization techniques.

[0140] According to one aspect, the antibody of the present invention is an anti-IGF-1 receptor humanized antibody that contains complementarity determining regions (CDRs) in each of the heavy and light chains derived from the mouse parent antibody IGF11-16, and framework regions (FRs) in each of the heavy and light chains derived from a human antibody, wherein at least one of the CDRs contains a substitution of at least one amino acid residue relative to the corresponding CDR of the mouse parent antibody IGF11-16.

[0141] Specifically, according to the present aspect, each of the complementarity determining regions (CDRs) of the heavy and light chains is derived from the corresponding CDR of the mouse parent antibody IGF11-16. The mouse parent antibody "IGF11-16" herein refers to an anti-IGF-1 receptor monoclonal mouse antibody previously produced by the inventors, as explained above (Patent Literature 1). The term "derived" from the CDR of the mouse parent antibody herein means that the amino acid sequence of each CDR of the antibody of this aspect is homologous (preferably, identical) to the amino acid sequence of the corresponding CDR of the mouse parent antibody IGF11-16 with a homology (preferably, an identity) of typically 75% or more, particularly 80% or more, or 85% or more, or even particularly 90% or more, and/or with the exception of a difference of typically four amino acid residues or less, particularly three amino acid residues or less, and even particularly two amino acid residues or less (Non-Patent Literature 18). However, the antibody of the present aspect requires that at least one of its CDRs contains a substitution of at least one amino acid residue relative to the corresponding CDR of the mouse parent antibody IGF11-16. In addition, the amino acid sequence of the heavy chain CDR-2 (CDR-H2) should only be homologous (preferably identical) to either the amino acid sequence of the CDR-H2 of the mouse parent antibody IGF11-16 or the CDR-H2 of the humanized antibody hIGF13_PS derived from the mouse parent antibody IGF11-16 as described below, with a homology (preferably, an identity) of typically 75% or more, particularly 80% or more, or 85% or more, or even particularly 90% or more, and/or with the exception of a difference of typically four amino acid residues or less, particularly three amino acid residues or less, and even particularly two amino acid residues or less.

[0142] In addition, each framework region (FR) of the heavy and light chains is derived from the corresponding FR of each class of human immunoglobulin, respectively. The term "derived from" the FR of a human immunoglobulin herein means that the amino acid sequence of each FR of the antibody of this form is homologous (preferably identical) to the amino acid sequence of the corresponding FR of the

human immunoglobulin, with a homology (preferably, an identity) of typically 80% or more, particularly 85% or more, or even particularly 90% or more, and/or with the exception of a difference of typically four amino acid residues or less, particularly three amino acid residues or less, and even particularly two amino acid residues or less. Human immunoglobulin frameworks are available from public databases, and can be used for selecting frameworks with high homology to mouse immunoglobulin frameworks. Amino acid sequences having high homology can be identified using, e.g., IgBLAST (Non-Patent Literature 16).

[0143] The amino acid residue at position 25 of the heavy chain FR1 herein may preferably be proline. Although there are several different amino acid residues between the heavy chain FR1 of the mouse parent antibody IGF11-16 and the heavy chain FR1 of the humanized antibody, the inventors' investigation revealed that the amino acid residue at position 25 of the heavy chain FR1, which is serine in the humanized antibody, may preferably be replaced with proline, as in the mouse parent antibody IGF11-16, since as described later in Example 3, the humanized antibody can exhibit activity equivalent to or higher than that of the mouse parent antibody IGF11-16 (the "equivalent" activity herein means that the ratio of the activity is within the range of $\pm 20\%$).

[0144] The heavy and light chains having the above homology can be obtained via, e.g., evolutionary engineering of antibodies, using the sequences of the heavy and light chains derived from the humanized antibodies of the present invention as templates. Specific examples include site-directed mutagenesis, random mutagenesis of CDRs, chain shuffling, CDR walking, etc.

[0145] "Random mutagenesis" is a method of generating mutants by introducing random mutations into specific genetic DNA. According to PCR mutagenesis, mutations are introduced by DNA amplification under specific conditions with low replication stringency (error-prone PCR), whereby mutations are introduced at arbitrary sites throughout the DNA amplified by PCR. According to DNA shuffling, the target gene is first fragmented, and mutations are introduced to the resulting fragments in the same manner as the PCR mutagenesis. Random mutations can also be introduced in an intended region or in a site-specific manner by mixing several bases in a specific synthetic step during DNA synthesis.

[0146] "Chain shuffling" is a method in which one of the VH or VL genes of the antibody variable regions is immobilized, and the other is combined with a V gene library to construct a library. The constructed library is expressed on phages, and then screened for combinations of antibody variable regions having high specificity for the original antigen. This method is the first choice for in vitro affinity maturation of antibodies obtained from naive/non-immune libraries.

[0147] "CDR walking" is a method in which random mutations are introduced into each CDR of the VH and VL genes, and the resulting population of mutants is subjected to screening using specific conditions to select antibodies having strong binding activity. The selected CDRs are then combined to obtain a clone having even stronger binding activity. In general, random mutations may be introduced only in CDR3 for further investigation.

[0148] Once a humanized parent antibody having specific activity is thus obtained, the parent antibody can then be used as a template and modified into a new humanized

antibody with maintaining its activity using a methodology which has almost completely been established, and such a process can be outsourced to, e.g., CRO.

[0149] According to one aspect, the antibody of the present invention may preferably have a specific amino acid sequence as each CDR sequence. Specific examples are described below. The "identity" between amino acid sequences herein refers to the percentage of identical amino acid residues between the sequences, and the "similarity" between amino acid sequences herein refers to the percentage of identical or similar amino acid residues between the sequences. The homology and identity between amino acid sequences can be determined by, e.g., the BLAST method (the default conditions of NCBI's PBLAST). The term "similar amino acid residues" herein refers to amino acid residues that have side chains with similar chemical properties (e.g., charge or hydrophobicity). Examples of groups of similar amino acid residues are shown below. The groups below mean that in the case of replacing, e.g., an alanine residue with a similar amino acid residue, it should be replaced with a valine, leucine, isoleucine, or methionine residue.

[0150] (1) Amino acid residues with aliphatic side chains: alanine (Ala or A), valine (Val or V), leucine (Leu or L), isoleucine (Ile or I), and methionine (Met or M) residues.

[0151] (2) Amino acid residues with aliphatic hydroxyl side chains: serine (Ser or S) and threonine (Thr or T) residues.

[0152] (3) Amino acid residues with amide-containing side chains: asparagine (Asn or N) and glutamine (Gln or Q) residues.

[0153] (4) Amino acid residues with aromatic side chains: phenylalanine (Phe or F), tyrosine (Tyr or Y), tryptophan (Trp or W), and histidine (His or H) residues.

[0154] (5) Amino acid residues with basic side chains: lysine (Lys or K), arginine (Arg or R), and histidine (His or H) residues.

[0155] (6) Amino acid residues with acidic side chains: aspartic acid (Asp or D) and glutamic acid (Glu or E) residues.

[0156] (7) Amino acid residues with sulfur-containing side chains: cysteine (Cys or C) and methionine (Met or M) residues.

[0157] The CDR-1 sequence of the heavy chain variable region (CDR-H1) may preferably be the amino acid sequence of SEQ ID NO:1, or an amino acid sequence derived from SEQ ID NO:1 via substitution of one amino acid residue. Alternatively, the CDR-H1 sequence may preferably have 80% or more homology (preferably, identity) with SEQ ID NO:1. Particularly preferable among them as the CDR-H1 sequence are amino acid sequences having the Trp residue at position 3 of SEQ ID NO:1 maintained or replaced with a similar amino acid residue, and also having any one amino acid residue other than the residue at position 3 maintained or replaced with a similar amino acid residue, or also having 80% or more homology (preferably, identity) with SEQ ID NO:1. An example of the nucleic acid sequence corresponding to SEQ ID NO:1 is shown in SEQ ID NO:2.

[0158] The CDR-2 sequence of the heavy chain variable region (CDR-H2) may preferably be the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, or an amino

acid sequence derived from SEQ ID NO:3 or SEQ ID NO:5 via substitution of one, two, or three amino acid residues. Alternatively, the CDR-H2 sequence may preferably have 82% or more homology (preferably, identity) with SEQ ID NO:3 or SEQ ID NO:5. Particularly preferable among them as the CDR-H2 sequence are amino acid sequences having the Glu residue at position 1 and the Asn residue at position 3 of SEQ ID NO:3 each maintained or replaced with a similar amino acid residue, and the Asn residue at position 6 of SEQ ID NO:3 maintained or replaced with Ser or Gln, and also having any one, two, or three amino acid residues other than the residues at positions 1, 3, and 6 each maintained or replaced with a similar amino acid residue, or also having 82% or more homology (preferably, identity) with SEQ ID NO:3. Alternatively, particularly preferable as the CDR-H2 sequence are amino acid sequences having the Glu residue at position 1 and the Asn residue at position 3 of SEQ ID NO:5 each maintained or replaced with a similar amino acid residue, and the Ser residue at position 6 of SEQ ID NO:5 maintained or replaced with Asn or Gln, and also having any one, two, or three amino acid residues other than the residues at positions 1, 3, and 6 each maintained or replaced with a similar amino acid residue, or also having 82% or more homology (preferably, identity) with SEQ ID NO:5. Examples of the nucleic acid sequences corresponding to SEQ ID NO:3 and SEQ ID NO:5 are shown in SEQ ID NO:4 and SEQ ID NO:6, respectively.

[0159] The CDR-3 sequence of the heavy chain variable region (CDR-H3) may preferably be the amino acid sequence of SEQ ID NO:7, or an amino acid sequence derived from SEQ ID NO:7 via substitution of one or two amino acid residues. Alternatively, the CDR-H3 sequence may preferably have 75% or more homology (preferably, identity) with SEQ ID NO:7. Particularly preferable among them as the CDR-H3 sequence are amino acid sequences having the Arg residue at position 4 of SEQ ID NO:7 maintained or replaced with a similar amino acid residue, and also having any one or two amino acid residues other than the residue at position 4 each maintained or replaced with a similar amino acid residue, or also having 75% or more homology (preferably, identity) with SEQ ID NO:7. An example of the nucleic acid sequence corresponding to SEQ ID NO:7 is shown in SEQ ID NO:8.

[0160] The CDR-1 sequence of the light chain variable region (CDR-L1) may preferably be the amino acid sequence of SEQ ID NO:9, or an amino acid sequence derived from SEQ ID NO:9 via substitution of one or two amino acid residues. Alternatively, the CDR-L1 sequence may preferably have 81% or more homology (preferably, identity) with SEQ ID NO:9. Particularly preferable among them as the CDR-L1 sequence are amino acid sequences having the Trp residue at position 9 of SEQ ID NO:9 maintained or replaced with a similar amino acid residue, and also having any one or two amino acid residues other than the residue at position 9 each maintained or replaced with a similar amino acid residue, or also having 81% or more homology (preferably, identity) with SEQ ID NO:9. An example of the nucleic acid sequence corresponding to SEQ ID NO:9 is shown in SEQ ID NO:10.

[0161] The CDR-2 sequence of the light chain variable region (CDR-L2) may preferably be the amino acid sequence of SEQ ID NO:11, or an amino acid sequence derived from SEQ ID NO:11 via substitution of one amino acid residue. Alternatively, the CDR-L2 sequence may pref-

erably have 85% or more homology (preferably, identity) with SEQ ID NO:11. An example of the nucleic acid sequence corresponding to SEQ ID NO:11 is shown in SEQ ID NO:10.

[0162] The CDR-3 sequence of the light chain variable region (CDR-L3) may preferably be the amino acid sequence of SEQ ID NO:13, or an amino acid sequence derived from SEQ ID NO:13 via substitution of one amino acid residue. Alternatively, the CDR-L3 sequence may preferably have 77% or more homology (preferably, identity) with SEQ ID NO:13. An example of the nucleic acid sequence corresponding to SEQ ID NO:13 is shown in SEQ ID NO:14.

[0163] The antibody of the present invention may particularly preferably have specific combinations of CDR sequences indicated below. Specifically, the antibody of the present invention may preferably have the combination of the amino acid sequence of SEQ ID NO:1 as the CDR-H1 sequence, the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 as the CDR-H2 sequence, the amino acid sequence of SEQ ID NO:7 as the CDR-H3 sequence, the amino acid sequence of SEQ ID NO:9 as the CDR-L1 sequence, the amino acid sequence of SEQ ID NO:11 as the CDR-L2 sequence, and the amino acid sequences of SEQ ID NO:13 as the CDR-L3 sequence.

[0164] Examples of methods for identifying the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 sequences in antibody sequences include the Kabat method (Non-Patent Literature 13) and the Chothia method (Non-Patent Literature 14), as well as methods improved from these methods (Non-Patent Literature 15). These methods are well-known to those skilled in the art, and can be learnt from, e.g., from the Internet homepage of Dr. Andrew C. R. Martin's Group (<http://www.bioinf.org.uk/abs/>).

[0165] In addition, as shown in Example 4, an alanine scan can be performed to identify the sites in the amino acid sequence of the CDR that are important for binding activity. From the results, it is clear that the amino acid residues shown in Table 7 and Table 8 below are extremely important. Substitution of at least these amino acid residues in this site with amino acids which do not have similar properties is expected to lead to decreased binding ability. In contrast, substitution with amino acids having similar properties may lead to an increase in binding affinity. On the other hand, among the 54 alanine substituted CDR sites, 44 sites maintained more than 80% of the binding activity even after alanine substitution. This suggests that the amino acid substitutions at these sites do not significantly affect the binding activity. Thus, scanning through the amino acid sequences of the CDR regions to identify the sites playing a role in binding to the antigen may serve to reduce immunogenicity, improve physical properties, and enhance binding while maintaining the binding property.

[0166] The antibody of the present invention should preferably have specific amino acid sequences as the sequences of heavy chain and light chain variable regions. Specific examples of the sequences are shown below. The phrase "one or several positions" herein refers to one, two, three, four, five, six, seven, eight, nine, or ten positions, unless otherwise noted.

[0167] The antibody of the present invention may preferably have, as the heavy chain variable region, the amino acid sequence of SEQ ID NO:47, or an amino acid sequence derived from SEQ ID NO:47 via substitution, deletion, or

addition of one or more amino acid residues. Alternatively, the antibody of the present invention may preferably have, as the heavy chain variable region, an amino acid sequence having 90% or more homology (preferably, identity) with SEQ ID NO:47. Particularly preferred among them as the heavy chain variable region are the amino acid sequence of VH13_PN (SEQ ID NO:43), VH13_PS (SEQ ID NO:47), VH23_PN (SEQ ID NO:49), VH23_PS (SEQ ID NO:53), VH25_PN (SEQ ID NO:55), or VH25_PS (SEQ ID NO:59). Examples of nucleic acid sequences corresponding to the amino acid sequences of SEQ ID NOS:43, 47, 49, 53, 55, and 59 are shown in SEQ ID NOS:44, 48, 50, 54, 56, and 60, respectively.

[0168] The antibody of the present invention may preferably have, as the light chain variable region, the amino acid sequence of SEQ ID NO:67, or an amino acid sequence derived from SEQ ID NO:67 via substitution, deletion, or addition of one or more amino acid residues. Alternatively, the antibody of the present invention may preferably have, as the light chain variable region, an amino acid sequence having 90% or more homology (preferably, identity) with SEQ ID NO:67. Particularly preferred among them as the light chain variable region are the amino acid sequence of VL13 (SEQ ID NO:61), VL14 (SEQ ID NO:63), VL22 (SEQ ID NO:65), VL23 (SEQ ID NO:67), or VL24 (SEQ ID NO:69) as the light chain variable region. Even more preferred are the amino acid sequence of VL22 (SEQ ID NO:65), VL23 (SEQ ID NO:67), or VL24 (SEQ ID NO:69). Examples of nucleic acid sequences corresponding to the amino acid sequences of SEQ ID NOS:61, 63, 65, 67, and 69 are shown in SEQ ID NOS:62, 64, 66, 68, and 70, respectively.

[0169] The antibody of the present invention may more preferably have any of the amino acid sequences described above as the heavy chain variable region and the light chain variable region. Particularly preferred as the antibody of the present invention are: the antibody having the amino acid sequence of VH13_PS (SEQ ID NO:47) as the heavy chain variable region and the amino acid sequence of VL23 (SEQ ID NO:67) as the light chain variable region (hereinafter referred to as "hIGF13_PS"); and the antibody having the amino acid sequence of VH25_PS (SEQ ID NO:59) as the heavy chain variable region and the amino acid sequence of VL23 (SEQ ID NO:67) as the light chain variable region (hereinafter referred to as "hIGF25_PS").

[0170] The amino acid sequence of each of the constant regions of the heavy and light chains of the antibody of the invention can be selected from, e.g., the amino acid sequences of the human IgG, IgA, IgM, IgE, and IgD classes as well as their variants. According to one aspect, the amino acid sequence of the heavy chain constant region of the antibody of the present invention may preferably have the amino acid sequence of the heavy chain constant region of the human IgG4 class, or an amino acid sequence derived therefrom via one to ten amino acid residues thereof (Non-Patent Literatures 19 and 20). According to another aspect, the amino acid sequence of the heavy chain constant region of the antibody of the present invention may preferably have the amino acid sequence of the heavy chain constant region of the human IgG1 class, or an amino acid sequence derived therefrom via one to ten amino acid residues thereof (Non-Patent Literatures 19 and 20).

[0171] The antibody of the present invention causes an antigen-antibody reaction with the human IGF-1 receptor.

The term "antigen-antibody reaction" herein refers to the binding of an antibody to the IGF-1 receptor with an affinity of an equilibrium dissociation constant (KD) of 1×10^{-7} M or less. The antibodies of the present invention usually bind to the IGF-1 receptor with a KD of 1×10^{-7} M or less, preferably 1×10^{-8} M or less, and even 1×10^{-9} M or less. Most preferably, it is 1×10^{-10} M or less.

[0172] The antibody of the present invention may preferably have the ability to specifically bind to the extracellular domain of the human IGF-1 receptor having the amino acid sequence of SEQ ID NO:71. The term "specificity" of an antibody to an antigen herein means that a high antigen-antibody reaction occurs between the antibody and the antigen. The term "IGF-1 receptor-specific antibody" herein refers to an antibody whose antigen-antibody reactivity to INSR, which has high similarity to the higher-order structure of IGF-1 receptor, is less than $1/100$ at a concentration that causes significant antigen-antibody reaction with cells expressing IGF-1 receptor.

[0173] A person skilled in the art can measure the antigen-antibody reaction employing a binding assay in a solid-phase or liquid-phase system selected as appropriate. Examples of such methods include, although not limited to: enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), surface plasmon resonance (SPR), fluorescence resonance energy transfer (FRET), luminescence resonance energy transfer (LRET), etc. Antigen-antibody reaction can also be detected by labelling the antibody and/or the antigen with an appropriate label substance such as enzymes, fluorescent substances, luminescent substances, radioisotopes, etc., and detecting the reaction employing a measurement method suitable for the physical and/or chemical properties of the label substance.

[0174] According to one aspect, the antibody of the present invention may preferably have an IGF-1 receptor signaling activity equivalent to or greater than that of the mouse parent antibody IGF11-16. The term "equivalent" in terms of IGF-1 receptor signaling activity herein means that the value is within 2-fold and/or the E_{max} value is within $\pm20\%$.

[0175] According to one aspect, the antibody of the present invention may preferably have a proliferative activity equivalent to or greater than that of the mouse parent antibody IGF11-16. The term "equivalent" in terms of proliferative activity herein means that the EC_{50} value is within 2-fold and/or the E_{max} value is within $\pm20\%$ in a myoblast proliferation assay.

[0176] According to one aspect, the antibody of the present invention may preferably have a binding affinity to a recombinant soluble IGF-1 receptor that is equivalent to or higher than the mouse parent antibody IGF11-16. The term "equivalent" in terms of proliferative activity in terms of binding affinity to the recombinant soluble IGF-1 receptor herein means that the KD value is within the range of from $1/3$ to 3 times that of the mouse parent antibody IGF11-16.

[0177] According to one aspect, the antibody of the present invention may preferably have a long half-life in blood, and exhibit muscle mass increasing effect via a single administration to an animal. Actually, according to the inventors' study, the anti-IGF-1 receptor humanized antibody of the present invention, when administered as a single dose to a guinea pig or a crab-eating macaque, exhibited a muscle mass-increasing effect equivalent to that achieved via continuous administration of IGF-1, as explained in the Examples below.

[0178] According to one aspect, the antibody of the present invention may preferably induce muscle mass increasing effect without inducing hypoglycemic symptoms in a normal mammal. According to one aspect, the antibody of the present invention may preferably induce growth plate cartilage elongation effect without inducing hypoglycemic symptoms in a hypophysectomized model animal. The term "hypoglycemic symptoms" herein refers to, in the case of the human, symptoms such as cold sweat, palpitations, disturbance of consciousness, convulsions, and tremors of limbs that occur with hypoglycemia. In the case of vertebrates such as monkeys, spontaneous movements decrease as an initial symptom, movements almost completely disappear as symptoms grow stronger, and consciousness is impaired as the blood glucose level drops further, leading to death.

[0179] When administered to a vertebrate at a dose that causes an increase in muscle mass, IGF-1 exhibits a marked hypoglycemic effect and usually induces hypoglycemic symptoms. However, according to one aspect, the antibody of the present invention may not induce such a hypoglycemic effect on a vertebrate, even when administered at a dose that induces an increase in muscle mass and/or body length, or more preferably at a dose 10 times higher than that dose. According to one aspect, the antibody of the present invention may not have the effect of lowering the blood glucose level in a vertebrate even when administered at a blood exposure level that is 10 times higher than the effective dose that induces an increase in muscle mass and/or body length of the vertebrate. In fact, according to the inventors' examination, the antibody of the present invention did not induce hypoglycemic symptoms in a guinea pig or a crab-eating macaque even when administered at a dose of 10 mg/kg, as shown in the Examples below.

[0180] In summary, the anti-IGF-1 receptor humanized antibody of the present invention has the potential to be a therapeutic or prophylactic agent for various diseases related to the IGF-1 receptor, such as disuse muscle atrophy and dwarfism, while overcoming the problematic hypoglycemic effect expected to be caused by IGF-1, and thereby allowing for prolonged half-life in blood.

[0181] The antibody of the present invention is deemed to activate both the homo-type receptor, in which IGF-1 receptor molecules form a dimer, and the hetero-type receptor, in which an IGF-1 receptor molecule and an INSR molecule form a dimer, by binding to the extracellular domain of the IGF-1 receptor molecule(s).

[Evaluation of Immunogenicity]

[0182] Since Anti-Drug Antibodies (ADAs) may affect the efficacy and pharmacokinetics of therapeutic antibodies and sometimes result in serious side effects, thus the utility and efficacy of therapeutic antibodies in clinical practice can be limited by their ADA production. Although many factors influence the immunogenicity of therapeutic antibodies, the importance of effector T-cell epitopes present in therapeutic proteins has been widely reported. Various in silico tools for predicting T cell epitopes have been developed, such as Epibase (Lonza), iTope/TCED (Antitope), and EpiMatrix (EpiVax). Employing these in silico tools allows for prediction of the presence of T-cell epitopes in each amino acid sequence (Non-Patent Literature 21), whereby potential immunogenicity can be evaluated. For the anti-IGF-1 recep-

tor humanized antibody of the present invention, potential immunogenicity was assessed using Epibase (Lonza).

[Deamidation Risk]

[0183] Among possible sequences of amino acids that make up proteins, NG, NT, NS, and NN are known to be prone to deamidation. The presence of any of these sequences may cause deamidation of the asparagine residue therein to an aspartic acid residue, resulting in a possible decrease in the activity of the antibody as well as a loss of uniformity in quality. In order to maintain quality during the manufacture and storage process, amino acids at risk of deamidation may be replaced with other amino acids to thereby prevent any loss of its activity and maintain its uniform quality. With regard to the antibody of the present invention, since the heavy chain CDR-2 (CDR-H2) region of the mouse parent antibody IGF11-16 includes an NS sequence (positions 55 and 56 of the heavy chain), the asparagine (N) residue at position 55 of the heavy chain was replaced with serine (S), in order to avoid the risk of this asparagine (N) being deamidated and converted to aspartic acid (D).

[Evaluation of Stability of Physical Properties]

[0184] In general, in order to ensure that the activity of the antibody is stably maintained for a long period of time, the stability of physical properties is examined by increasing the temperature or changing the pH. In the case of the anti-IGF-1 receptor humanized antibody of the present invention, the stability of physical properties was confirmed using a PBS solution of this antibody as a sample, by incubating it for one month at 37° C., and confirming that the purity was 95% or more and that no aggregates were produced.

[Epitope of the Anti-IGF-1 Receptor Humanized Antibody]

[0185] According to one aspect, the antibody of the present invention recognizes the CR domain of the IGF-1 receptor as an epitope. It is preferable that the antibody of the present invention may bind to an epitope that contains a peptide having the amino acid sequence corresponding to the amino acid residues from position 308 to position 319 (ProSerGlyPheIleArgAsnGlySerGlnSerMet) in the amino acid sequence of the human IGF-1 receptor (SEQ ID No:71), or to a sequence in the vicinity thereof. The antibody of the present invention is deemed to activate both the homo-type receptor, in which IGF-1 receptor molecules form a dimer, and the hetero-type receptor, in which an IGF-1 receptor molecule and an INSR molecule form a dimer, by binding to the CR domain of the IGF-1 receptor molecule(s).

[Anti-IGF-1 Receptor Humanized Agonist Antibody]

[0186] The agonist antibody of the present invention may preferably be in the form of human IgG class or variants thereof, human IgG4 subclass or variants thereof, or human IgG1 subclass or variants thereof. In one example, the stabilized IgG4 constant region contains a proline at position 241 of the hinge region by Kabat's system (Non-Patent Literature 22). This position corresponds to position 228 in the hinge region according to the EU numbering scheme (Non-Patent Literature 13). In human IgG4, this residue is generally serine, while stabilization can be induced by replacing this serine with proline. In one example, the N297A mutation can be incorporated into the constant

region of IgG1 to suppress as much as possible its abilities to bind to the Fc receptor and/or to anchor a complement. According to another aspect, an amino acid substitution can be introduced in the constant region in order to modulate its ability to bind to FeRn and thereby increase its half-life in blood. However, possible amino acid substitutions that can be introduced in the constant region are not limited to these examples.

[0187] The agonist antibody of the present invention may bind specifically and potently to the IGF-1 receptor and have the effect of increasing myoblast proliferation from very low concentrations *in vitro*.

[0188] The agonist antibody of the present invention may exhibit, when administered as a single dose to an animal, an effect of increasing muscle mass which is comparable to that of continuous administration of IGF-1. The agonist antibody of the present invention may also have a long half-life in the blood, and exhibit an effect of increasing muscle mass after a single administration to an animal. In fact, when administered as a single dose to a guinea pig or crab-eating macaque, the agonist antibody of the present invention exhibited the same level of muscle mass-increasing effect as that caused by continuous administration of IGF-1.

[0189] The agonist antibody of the present invention may also be characterized by not inducing a hypoglycemic effect at doses that induce muscle mass gain. IGF-1 has a marked hypoglycemic effect when administered at doses that induce muscle mass gain. However, the agonist antibody of the present invention may not have a hypoglycemic effect in a vertebrate at doses that induce an increase in muscle mass and/or body length in the vertebrate. It is preferred that the agonist antibody of the present invention may not have the effect of lowering the blood glucose level in a vertebrate, even when administered at a blood exposure level that is 10 times higher than the effective dose that induces an increase in muscle mass and/or body length in the vertebrate. In fact, even when the agonist antibody of the present invention was administered to a guinea pig or crab-eating macaque at a blood exposure level that is 10 times higher than the effective dose to induce an increase in muscle mass, no symptoms associated with an decrease in the blood glucose level or hypoglycemia were observed.

[0190] Based on the findings above, the agonist antibody of the present invention has the potential to be a therapeutic or prophylactic agent for various diseases related to the IGF-1 receptor, such as sarcopenia, disuse muscular atrophy, cathexis, and dwarfism, while overcoming the problematic hypoglycemic effect expected to be caused by IGF-1, and thereby allowing for prolonged half-life in blood.

[Anti-IGF-1 Receptor Humanized Antagonist Antibody]

[0191] The anti-IGF-1 receptor humanized antibody of the present invention can be made into an anti-IGF-1 receptor antagonist antibody with excellent activity and specificity, by taking advantage of the extremely high binding ability and specificity of its variable regions. In this aspect, the antibody of the present invention may be used not only as IgG but also in any other form such as, although not limited to, Fab, Fv, scFv, or VH.

[0192] The anti-IGF-1 receptor antagonist antibodies produced in this manner can be evaluated based on, e.g., its ability to inhibit IGF-1-dependent cell proliferation activity in a cancer cell line. The anti-IGF-1 receptor antagonist antibody selected in this manner is expected to be used as an

anti-cancer agent and as a drug for improving and treating diseases and conditions associated with abnormal cell proliferation.

[0193] This antibody can also be used for constructing bispecific or multispecific antibodies by fusing it directly or via a linker with various antibodies that recognize other antigens or epitopes. In this case, the antibody may be used not only as IgG but also in any other forms such as, although not limited to, Fab, Fv, scFv, or VH.

[0194] The bispecific or multispecific antibody containing the anti-IGF-1 receptor antagonist antibody produced in this manner can be evaluated based on, e.g., its ability to inhibit IGF-1-dependent cell proliferation activity in a cancer cell line. The bispecific or multispecific antibody containing the anti-IGF-1 receptor antagonist antibody produced in this manner is expected to be used as an anti-cancer agent and as a drug for improving and treating diseases and conditions associated with abnormal cell proliferation.

[0195] The anti-IGF-1 receptor antagonist antibody of the present invention is expected to be a therapeutic agent for the treatment of diseases whose pathological conditions can be induced by the activation of IGF-1 receptor signaling. Ligands that can activate IGF-1 receptors include IGF-1, IGF-2, and Insulin, as well as ligands for RTKs (receptor-type tyrosine kinases) that form heterodimers with IGF-1 receptors (e.g., EGF) and ligands for other receptors that cross-talk (e.g., TSH). The antibody of the present invention may have the activity to suppress IGF-1 receptor signaling activated by these ligands (allosteric antagonist action). In other words, the antibody of the present invention may suppress the excessively induced IGF-1 receptor signaling activity by binding to the IGF-1 receptor, and may be used for the treatment or prevention of diseases induced by the abnormal activation of the IGF-1 receptor. The antibody of the present invention may preferably have the ability to suppress signal activation in a level that is equivalent to or greater than that of the mouse parent antibody IGF11-16. The phrase "equivalent to mouse antibody IGF11-16" herein refers to an activity to inhibit by 10% or more, preferably 25% or more, particularly preferably 35% or more of the maximum cell proliferative activity that can be induced by ligands that can activate IGF-1 receptors such as IGF-1, IGF-2, or Insulin in a myoblast proliferation assay.

[0196] Specific examples of diseases induced by abnormal activation of IGF-1 receptors include: liver cancer, neuroblastoma, rhabdomyosarcoma, bone cancer, pediatric cancer, acromegalia, ovary cancer, pancreas cancer, benign prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, neck cancer, synoviosarcoma, urinary bladder cancer, stomach cancer, Wilms' tumor, diarrhea associated with metastatic carcinoid and vasoactive intestinal peptide secreting tumor, vipoma, Verner-Morrison syndrome, Beckwith-Wiedemann syndrome, kidney cancer, renal-cell cancer, transitional cell cancer, Ewing's sarcoma, leukemia, acute lymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatous brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, undifferentiated neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendrogloma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic erythematoses, myasthenia gravis, autoimmune thyroiditis, Hashimoto's

thyroiditis, thyroid ophthalmopathy, hyperthyroidism and Behcet's disease. These effects can be confirmed by using a cancer-bearing model animal.

[Anti-IGF-1 Receptor Humanized Antibody as a Local Delivery Tool]

[0197] The anti-IGF-1 receptor antibody can be used for local delivery of drugs and antibodies to IGF-1 receptor-expressing cells and tissues by utilizing its extremely high binding ability and specificity. In this case, the antibody may be used not only as IgG but also in any other forms such as, although not limited to, Fab, Fv, scFv, or VH. An antibody-drug conjugate containing the anti-IGF-1 receptor antibody of the present invention conjugated to a drug can deliver the drug to a local target, whereby the drug can specifically exert its efficacy at a lower dose, leading to a reduction in side effects.

[0198] The thus-produced conjugate of a drug or antibody with the anti-IGF-1 receptor humanized antibody of the present invention as a delivery tool can be evaluated based on, if the drug is an apoptosis-inducing agent, its ability to induce apoptosis in IGF-1 receptor-expressing cancer cell line. The thus-selected conjugate of a drug or antibody with the anti-IGF-1 receptor humanized antibody of the present invention is expected to be used as an anti-cancer agent and as a drug for improving and treating diseases and conditions associated with abnormal cell proliferation.

Alternatively, the anti-IGF-1 receptor antibody of the present invention can be labeled with a radioactive or fluorescent compound for use in detecting cancer cells expressing IGF-1 receptors. Use of such a diagnostic technique allows for efficient treatment using an anti-IGF-1 receptor antagonist antibody.

[Competitive Binding]

[0199] Antibodies that bind to the IGF-1 receptor in a competitive manner with the anti-IGF-1 receptor antibody of the present invention are also included in the scope of the present invention. The term "competitive binding" herein refers to a phenomenon in which when two or more monoclonal antibodies co-exist with an antigen, the binding of one of the antibodies to the antigen is inhibited by the binding of another of the antibodies to the antigen. In general, it can be measured by adding to a fixed amount (concentration) of a monoclonal antibody a different monoclonal antibody with increasing the amount (concentration) of the latter antibody, and measuring the amount (concentration) of the latter antibody at which the binding of the former antibody to the antigen decreases. The degree of its inhibition can be expressed in terms of IC₅₀ or K_i.

[0200] The phrase "a monoclonal antibody that binds to the antigen in a competitive manner with the anti-IGF-1 receptor antibody of the present invention" means an antibody that has, when antigen-antibody binding is detected using the anti-IGF-1 receptor antibody of the present invention at 10 nM, an IC₅₀ of usually 1000 nM or less, particularly 100 nM or less, or even particularly 10 nM or less. When measuring competitive binding, one or more of the antibodies used can be labelled with an appropriate label substance such as enzymes, fluorescent substances, luminescent substances, radioisotopes, etc., and the reaction can

be detected by employing a measurement method suitable for the physical and/or chemical properties of the label substance.

[Cross-Reactivity]

[0201] The antibody of the present invention may have cross-reactivity with the IGF-1 receptors of other vertebrates. The term "cross-reactivity" of an antibody herein refers to the binding ability of the antibody to the IGF-1 receptor of another animal species different from the target animal species (e.g., human) to which the antibody is designed to cause antigen-antibody reaction. The anti-IGF-1 receptor humanized antibody of the present invention may exhibits cross-reactivity with, in addition to the human IGF-1 receptor, IGF-1 receptors of other animals such as guinea pigs, monkeys, rabbits, etc. On the other hand, it does not cause cross-reaction with mouse and rat IGF-1 receptors.

[0202] It is also possible to use an animal species that do not cross-react with the antibody of the present invention, and genetically engineer a cell or animal of that species to produce a cell or animal expressing IGF-1 receptors with which the antibody of the present invention can cross-react.

[Evaluation of Binding Affinity]

[0203] The anti-IGF-1 receptor humanized antibody of the present invention may have an extremely strong binding affinity at a level equivalent to or higher than that of the mouse parent antibody IGF11-16 (Patent Literature 1). The binding affinity can be evaluated by, e.g., SPR (surface plasmon resonance) analysis using the extracellular region of the recombinant IGF-1 receptor as an antigen. In the Examples below, the binding affinity of monovalent is analyzed by using BIACORE, raising the reaction temperature to 40° C. and keeping the amount of fixed antigens low, although the methods for analyzing the binding affinity are not limited to this specific method, but may be any analytical methods that can quantitatively evaluate strong binding affinity.

[Evaluation of IGF-1 Receptor Signaling]

[0204] The anti-IGF-1 receptor humanized antibody of the present invention has been obtained by selecting humanized antibodies with levels equivalent to or higher than that of the mouse parent antibody IGF11-16 (Patent Literature 1) by using their ability to activate IGF-1 receptor signal as a primary evaluation system.

[0205] For the evaluation of IGF-1 receptor signal activation, we used the commercially available PathHunter® IGF1R Functional Assay (manufactured by DiscoverX). This system allows for evaluation of phosphorylation directly under the IGF-1 receptor signal in terms of enzymatic activity, by using a chemiluminescent substance as substrate, and measuring the signal intensity based on the luminescence intensity.

[0206] Specifically, a cell line used was HEK293 cells engineered to forcedly express an adapter protein SHC1-Enzyme Acceptor (EA) fusion protein with an SH2 domain that binds to the IGF-1 receptor and the intracellular tyrosine kinase of the IGF-1 receptor. In this cell line, ligand binding to the IGF-1 receptor leads to receptor dimerization, followed by receptor phosphorylation, which recruits an adapter protein with an SH2 domain to form a receptor signaling complex, whereby the binding of EA to the spa-

tially adjacent tyrosine kinase is promoted, and an active β -galactosidase is reconstituted. The level of chemiluminescence signal of the substrate hydrolyzed by this β -galactosidase activity can be measured for identifying the action of the drug on the receptor-type tyrosine kinase.

[0207] Humanized antibody variants with signal-inducing activity equivalent to or higher than that of the mouse parent antibody IGF11-16 were selected and then subjected to a secondary evaluation based on human myoblast proliferation. The means to evaluate IGF-1 receptor signaling is not limited to this specific method, but may be any system that can detect IGF-1 receptor tyrosine phosphorylation directly or indirectly and quantitatively.

[Proliferation-Inducing Activity of Vertebrate-Derived Cells and Muscle Mass-Increasing Activity]

[0208] Human myoblast cell proliferation assay was carried out as a secondary evaluation system for the humanized antibody of the present invention, whereby humanized antibodies with agonist activity equivalent to or higher than that of the mouse parent antibody IGF11-16 (Patent Document 1) in the same concentration range were narrowed down. The humanized antibodies selected in this manner were confirmed not to exhibit hypoglycemic effects in vivo, but to have the effect of increasing muscle mass. In other words, the anti-IGF-1 receptor humanized antibody of the present invention in one form has the ability to induce proliferation of vertebrate-derived cells.

[0209] The term "vertebrate-derived cells" in the context of the present disclosure should preferably be cells derived from mammals, birds, reptiles, amphibia, or fish, more preferably cells derived from mammals or birds, further more preferably cells derived from human, monkey, rabbit, guinea pig, cow, pig, sheep, horse, dog, rat, or mouse. Cells derived from these species which express an IGF-1 receptor with which the antibody of the present invention cross-reacts can be induced to proliferate by the antibody of the present invention. The "vertebrate-derived cells" according to the present disclosure also encompass: cells and animals engineered to express an IGF-1 receptor of a species with which the antibody of the present invention cross-reacts; and modified animal cells derived from such engineered cells and animals.

[0210] An antibody's proliferation-inducing activity of vertebrate-derived cells can be analyzed in vitro using primary cultured cells, established cell lines, or transformants derived from such cells.

[0211] In the present disclosure, the term "primary cultured cells" means cells which were isolated from an organ or a tissue of a living organism, and can typically be subcultured for some passages. Primary cultured cells derived from a vertebrate can be obtained from an organ or a tissue of the vertebrate via enzyme treatment, dispersion with physical means, or explant method. An organ or a tissue or its fragment obtained from the vertebrate can also be used for analyzing the antibody's activity above. Preferable examples of organs and tissues from which primary cells are prepared include: endocrine tissues such as thyroid, parathyroid, and adrenal gland; immune tissues such as appendix, tonsil, lymph nodes, and spleen; respiratory organs such as trachea and lung; digestive organs such as stomach, duodenum, small intestine, and large intestine; urinary organs such as kidney and urinary bladder; male genital organs such as vas deferens, testicle, and prostate; female

genital organs such as breast and fallopian tube; and muscle tissues such as heart muscle and skeletal muscles. More preferred examples include liver, kidney, or digestive organs or muscle tissues, among which muscle tissues are still more preferred. Primary cultured cells which can be used for analyzing the proliferation-inducing activity of an antibody of the present invention are cells which express an IGF-1 receptor and can be induced to proliferate by IGF-1 binding to the IGF-1 receptor. Typical examples thereof are skeletal muscle myoblasts, which are primary cultured cells isolated from muscle tissue. Human- or animal-derived primary cultured cells available by assignment or commercially on the market can also be obtained and used. Human primary cultured cells are available from various institutions and companies, e.g., ATCC®, ECACC, Lonza, Gibco®, Cell Applications, ScienCell research laboratories, and Promocell.

[0212] Methods for determining the cell proliferation-inducing activity by the antibody of the present invention in vertebrate-derived cells include: cell counting, measurement of DNA synthesis, and measurement of change in the metabolic enzyme activity. Methods for cell counting include methods using blood cell counting plates or cell counting devices such as Coulter counters. Methods for measuring DNA synthesis include methods based on uptake of [³H]-thymidine or 5-bromo-2'-deoxyuridine (BrdU). Method for measuring the change in metabolic enzyme activity include colorimetric quantitative methods such as MTT method, XTT method, and WST method. A person skilled in the art could also employ other methods as appropriate.

[0213] The cell proliferation-inducing activity can be determined by that the proliferation of cultured cells reacted with the antibody of the present invention increases compared to that of cultured cells not reacted with the antibody. In this case, the inducing activity can favorably be normalized through the measurement using IGF-1, an original ligand of the IGF-1 receptor, that is reacted under the same conditions as a control. An EC₅₀ value indicates a concentration at which 50% of the maximum proliferation-inducing activity is given in the case that the antibody of the present invention and IGF-1 are reacted with various concentrations to the cultured cells. In the case that the proliferation-inducing activity is evaluated with human skeletal muscle myoblast cells, the antibody of the present invention may preferably have an EC₅₀ value in the cell proliferation-inducing activity equivalent to or lower than that of IGF-1, more preferably an EC₅₀ value of 1/10 or less, further more preferably 1/20 or less, most preferably 1/50 or less than that of IGF-1. In addition, in the case that the proliferation-inducing activity is evaluated with human skeletal muscle myoblast cells, the antibody of the present invention may preferably have an EC₅₀ value of preferably 0.5 nM or less, more preferably 0.3 nM or less, most preferably 0.1 nM or less.

[0214] Methods for measuring the activity to induce cell growth in vivo include: a method involving administering the antibody of the present invention to a vertebrate and measuring changes in the mass, size, cell count, etc., for the entire body of the individual which received the administration or for an organ or a tissue isolated from the individual; and a method involving using an animal with a graft of vertebrate cells and measuring changes in the mass, size, cell count, etc., of the graft including vertebrate cells. Measurements for the entire body of an individual include:

measurements of the body mass, the body length, and the circumferences of four limbs; measurement of the body composition, using impedance method; and measurement of the creatinine height coefficient. Measurements for an organ, a tissue, or a graft from an individual include: in the case of a non-human animal, a method involving directly recovering the target organ, tissue or graft and measuring its mass, size, or the number of cells included therein. Non-invasive measurements for an organ, a tissue, or a graft from an individual include: image analysis using X-ray photography represented by Dual-energy X-ray absorptiometry (DXA), CT, and MRI; and contrast methods using tracers with isotopes or fluorescent substances. If the target tissue is skeletal muscle, then a change in the muscle force can also be used as an indicator. A person skilled in the art could also employ any other methods as appropriate for analyzing the activity of the antibody of the present invention to induce growth of vertebrate-derived cells in vivo. Methods for measuring the activity of the antibody of the present invention to induce growth of vertebrate-derived cells in vivo include: carrying out measurements using, e.g., the methods mentioned above for individuals who received administration of the antibody of the present invention and individuals who received administration of a different antibody other than the antibody of the present invention or any other control substance, and comparing the resultant measurements between these individuals.

[0215] With regard to the hemodynamics of antibodies, Example 14 below indicates comparison of the guinea pig hemodynamics of the hIGF13_PS and hIGF25_PS antibodies, which are the antibodies of the present invention, with those of the mouse IGF11-16 antibody (Patent Literature 1), which was the basis for designing the antibodies of the present invention. This example shows that the antibodies of the present invention have improved hemodynamics compared to IGF11-16.

[0216] One of the in vivo effects achieved by the antibody of the present invention is the effect of increasing the muscle mass and/or the body length. Specifically, IGF-1 has an effect of inducing the growth and differentiation of myoblasts in skeletal muscles as mentioned above, as well as an effect of broadening muscle fibers. It is expected that these effects collectively lead to the effect of increasing the muscle mass. Like IGF-1, when the antibody of the present invention is administered to an animal, it also exhibits an effect of increasing the muscle mass of the animal.

[0217] Methods for measuring the activity of the antibody of the present invention to increase the muscle mass include: for the entire body of the individual which received the administration, measurement of the body mass, the body length, and the circumferences of four limbs; measurement of the body composition, using impedance method; and measurement of the creatinine, and height coefficient. Other methods include: image analysis using X-ray photography represented by Dual-energy X-ray absorptiometry (DXA), CT, and MRI; contrast methods using tracers with isotopes or fluorescent substances; and measurement of a change in the muscle force. In the case of a non-human animal, a method involving directly recovering the target organ, tissue or graft and measuring its mass and/or size can also be used.

[0218] The effect of increasing the muscle mass can be evaluated by: comparing the muscle mass increases between an individual to which the antibody of the present invention was administered and an individual to which the antibody

was not administered; or comparing the muscle masses of an individual before and after administration of the antibody of the present invention. The effect of increasing the muscle mass can be determined if there is any increase in the muscle mass of an individual before and after the administration of the antibody of the present invention. IGF-1 also plays a role in the bone growth, and has an effect of increasing the body length (the body height in the case of the human). Therefore, the antibody of the present invention also exhibits an effect of increasing the body length when administered to an animal. The effect of the antibody of the present invention in increasing the body length of an individual can be determined by measuring the body weight, the body length, and the circumferences of four limbs of the individual.

[Effects on Blood Glucose Levels in Animals]

[0219] According to one aspect, the antibody of the present invention may have the feature of not affecting the blood glucose level in a vertebrate. IGF-1 is known to have the activity to lower the blood glucose level as a part of its agonist actions on the IGF-1 receptor. However, the agonist antibody of the present invention, which functions as an anti-IGF-1 receptor agonist antibody, exhibits the feature of not altering the blood glucose level even at a blood exposure that is 10 times higher than the effective dose that induces an increase in muscle mass when administered parenterally to an animal.

[0220] The feature of not inducing hypoglycemia in a vertebrate, which feature is characteristic of the antibody of the present invention, can also be evaluated in vitro. The antibody of the present invention does not affect glucose uptake by a vertebrate-derived cell in vitro. Primary cultured cells, strain cells, or transformed cells of these cells can be used as cells for evaluating this feature of the antibodies of the present invention.

[0221] Examples of methods for determining the effect of the antibody of the present invention on the glucose uptake by vertebrate-derived cells include: measurement of the intracellular glucose concentration; measurement of the intracellular uptake of a glucose analog tracer substance; and measurement of a change in the amount of a glucose transporter. Methods for measuring the glucose concentration include absorbance measurement methods such as enzyme method. Methods for measuring the intracellular uptake amount of a glucose analog tracer substance include measurement of the uptake amount of, e.g., [3H]-2'-deoxy-glucose. Methods for measuring a change in the amount of a glucose transporter include immunocytostaining and western blotting. A person skilled in the art could also employ other methods as appropriate. The fact that there is no effect on the intracellular glucose uptake can be confirmed if the intracellular glucose uptake of the cultured cells reacted with the antibody of the present invention is almost the same of the intracellular glucose uptake of the cultured cells in the absence of the antibody. In this case, it is convenient to also carry out the measurement under the same conditions using IGF-1, which is an original ligand for the IGF-1 receptor, as a control.

[0222] Methods for determining the glucose uptake by vertebrate-derived cells in vivo include: methods involving parenterally administering the antibody of the present invention to a vertebrate and determining a change in the glucose content of an organ or a tissue of the individual. Methods of measurement for the entire body of the individual which

received the administration include: measurement of the blood glucose level; and hemoglobin A1C using glycosylated proteins as indicators. Methods of measuring the glucose uptake for an organ or a tissue of an individual include: in the case of a non-human animal, directly recovering the target organ or tissue, and calculating the concentration of glucose or a tracer. Non-invasive methods for measuring the glucose uptake individual for an organ or a tissue of an individual include: image analysis using X-ray photography, CT, and MRI; and contrast methods using tracers with isotopes or fluorescent substances. If the target tissue is a skeletal muscle, then the glucose clamp can also be used as an indicator. A person skilled in the art could also employ any other methods as appropriate for analyzing the effect of the antibody of the present invention on the glucose uptake by vertebrate-derived cells *in vivo*.

[0223] The antibody of the present invention is also characterized in that when administered to a vertebrate even at an effective dosage sufficient to increase the muscle mass of the vertebrate, preferably at a dosage of 10 times or more the effective dosage, it does not change the blood glucose level of the vertebrate. When evaluating the effect of the antibody of the present invention in changing the blood glucose level of a vertebrate, it is preferred to use an animal belonging to mammals, birds, reptiles, amphibia or fish, more preferably an animal belonging to mammals or birds, still more preferably human, monkey, rabbit, guinea pig, cow, pig, sheep, horse, dog, rat, or mouse. An animal engineered to express an IGF-1 receptor of a species which has cross-reactivity with the antibody of the present invention can also be used as an animal for evaluating the effect of the antibody of the present invention in changing the blood glucose level. Invasive methods for measuring the blood glucose level include colorimetric method and electrode method. Examples of enzyme methods used for detection include glucose oxidase method (GOD method) and glucose dehydrogenase method (GDH method). Non-invasive methods include optical measurement methods. A person skilled in the art can also select any other method as appropriate. In the case of human, the normal range of fasting blood glucose level is from 100 mg/dL to 109 mg/dL. With regard to adverse events in the blood glucose level resulting from a drug administration (Common Terminology Criteria for Adverse Events v4.0), the blood glucose level of lower than the range of from 77 mg/dL to 55 mg/dL is defined as an indicative of low blood glucose, while a blood glucose level of higher than the range of from 109 mg/dL to 160 mg/dL is defined as an indicative of high blood glucose. A drug administration is considered as not affecting the blood glucose level when the blood glucose level after the drug administration is higher than 55 mg/dL and lower than 160 mg/dL, more preferably higher than 77 mg/dL and lower than 109 mg/dL. However, the normal value of blood glucose level and its range of fluctuation vary depending on the animal to which a drug is administered, and even a human subject may not always have a blood glucose level within a normal range at the time of the drug administration. Accordingly, in the context of the present invention, the antibody of the present invention should preferably be considered as not changing the blood glucose level of a vertebrate to which the antibody is administered when the change in the blood glucose level of the vertebrate is

preferably 30% or less, more preferably 20% or less, still more preferably 10% or less, compared to the solvent-administered control group.

[Process for Producing Anti-IGF-1 Receptor Humanized Antibody]

[0224] The antibody of the present invention can be obtained by humanizing the mouse monoclonal antibody against the IGF-1 receptor, IGF11-16 (Patent Literature 1). Humanization is a process of using a monoclonal antibody derived from non-human animal species and grafting its CDR regions into human frameworks by CDR grafting (Non-Patent Literature 12). Subsequently, based on three-dimensional structural analysis, the resulting antibody is subjected to introduction of amino acid substitutions intended to reduce immunogenicity to humans (T-cell antigenicity) and/or amino acid substitutions intended to avoid the risk of post-translational modifications such as deamination and oxidation, while maintaining its three-dimensional structure. Thus, a humanized antibody can be produced that maintains its activity while ensuring manufacturability and clinical safety.

[0225] It is very important for the humanization process to obtain information on (1) what kind of human framework design is needed in order to maintain its activity and (2) which amino acids in the CDR sequences are essential. Examples of methods for obtaining such humanized antibodies are described in Examples 1 to 9 below. The humanized antibodies thereby obtained include: humanized antibodies having VH13_PN (SEQ ID NO:43), VH13_PS (SEQ ID NO:47), VH23_PN (SEQ ID NO:49), VH23_PS (SEQ ID NO:53), VH25_PN (SEQ ID NO:55), or VH25_PS (SEQ ID NO:59) as the heavy chain variable region, and VL13 (SEQ ID NO:61), VL14 (SEQ ID NO:63), VL22 (SEQ ID NO:65), VL23 (SEQ ID NO:67), or VL24 (SEQ ID NO:69) as the light chain variable region, and more preferably, VL22 (SEQ ID NO:65), VL23 (SEQ ID NO:67), or VL24 (SEQ ID NO:69) as the light chain variable region. However, the antibodies of the present invention are not limited to these specific antibodies.

[0226] A nucleic acid molecule having a base sequence encoding the amino acid of the protein in the resultant anti-IGF-1 receptor humanized antibody can be produced, and such a nucleic acid molecule is also genetically engineered to produce an antibody. The H chain, L chain, or their variable regions in gene information of the antibody can be modified to improve the avidity and specificity of the antibody with reference to information of, for example, CDR sequences.

[0227] In a method of producing the antibody of the present invention, for example, mammalian cells, insect cells, and *Escherichia coli* into which genes encoding the amino acids of proteins in target antibodies are introduced are cultured, and thereby the antibody can be produced through purification of the resultant culture supernatant by a conventional process. A specific method is illustrated below.

[0228] A nucleic acid molecule encoding an H chain variable region is bound to a nucleic acid molecule encoding an H chain signal peptide and a nucleic acid molecule encoding an H chain constant region to produce the antibody of the present invention. A nucleic acid molecule encoding an L chain variable region is bound to a nucleic acid molecule encoding an L chain signal peptide and a nucleic

acid molecule encoding an L chain constant region to produce the antibody of the present invention.

[0229] These H chain gene and L chain gene are incorporated into a vector, for example, a cloning vector or an expression vector, suitable for expression in a selected host cell. In this case, the H chain gene and the L chain gene may be incorporated into one vector or separate vectors such that both genes can be expressed.

[0230] The vector into which the H chain gene and the L chain gene are incorporated is then introduced into the host cell. Examples of host cells include eukaryotic cells, such as mammalian cells, insect cells, yeast cells or plant cells, and bacterial cells. A method of introducing the genes into the host cell may be appropriately selected from a chemical method such as calcium phosphate process or a lipofection process, a physical method such as an electroporation process or a particle gun process, and a method based on infection with a virus or a phage. The host cell into which the H chain gene and L chain gene are introduced can be used in culturing without any selection, selectively condensing of recombinant cells into which the genes are introduced using properties of, for example drug resistance and auxotrophy, or culturing of recombinant clone cells constructed from a single host cell into which the genes are introduced.

[0231] The host cell into which the H chain gene and L chain gene are introduced is cultured under an optimum medium and culturing condition. In this process, the products of the H chain gene and the L chain gene expressed in the host cell are usually secreted into the medium as antibody proteins, and the produced antibody proteins can be recovered by collecting the medium. However, through combining of the genes and the host cell, the antibody proteins accumulated in the cell can be recovered by destruction of the host cell as needed, or the antibody proteins can be recovered from a periplasm fraction in the case of a prokaryotic cell. Examples of methods generally used for purifying an antibody from a sample such as a medium containing the recovered antibody proteins include salt precipitation; enrichment or solvent exchange by dialysis and ultrafiltration; and affinity chromatography using a carrier that contains, for example, immobilized protein A, protein G, or antigen. Also available are ion exchange chromatography, hydrophobic chromatography, mixed mode chromatography, and size exclusion chromatography. A variety of techniques used in these methods is well known to those skilled in the art.

[0232] In this connection, a person skilled in the art can produce various antibodies such as antibody chimeric proteins, low molecule antibodies, and scaffold antibodies using known techniques, e.g., by making a genetic modification to a gene encoding a heavy chain and/or a light chain of an immunoglobulin for introducing a desired trait, or by using structure information of variable regions or CDR regions of a heavy chain and/or a light chain of an immunoglobulin. In addition, in order to improve the performance of the antibody or avoiding side effects, it is possible to introduce a modification into the structure of a constant region of an antibody or to introduce glycosylation sites of an antibody, using techniques well-known to persons skilled in the art as appropriate.

[Drug Containing the Anti-IGF-1 Receptor Humanized Antibody]

[0233] The antibody of the present invention can be used as a therapeutic agent or a prophylactic agent or a diagnostic agents for conditions associated with IGF-1 or diseases caused by effects on IGF-1 receptors. The therapeutic agents, prophylactic agents, or diagnostic agents will be collectively referred to as "drugs" or "agents."

[0234] Specifically, conditions associated with IGF-1 or diseases that can be the target of therapy or prevention using the anti-IGF-1 receptor agonist antibody include, although not limited to: muscular atrophy disease (e.g., disuse muscle atrophy, sarcopenia and cachexia), dwarfism (e.g., Laron type dwarfism and growth hormone resistant dwarfism), hepatic cirrhosis, hepatic fibrosis, diabetic nephropathy, chronic renal failure, aging, intrauterine growth restriction (IUGR), neurological diseases, stroke, spinal cord injury, cardiovascular protection, diabetes, insulin resistant, metabolic syndrome, nephropathy, osteoporosis, cystic fibrosis, wound healing, myotonic dystrophy, AIDS-associated sarcopenia, HIV-associated fat redistribution syndrome, burns, Crohn's disease, Werner's syndrome, X-linked combined immunodeficiency disease, hearing loss, anorexia nervosa and retinopathy of prematurity, Turner's syndrome, Prader-Willi syndrome, Silver-Russell syndrome, idiopathic dwarfism, obesity, multiple sclerosis, ulcerous colitis, low muscle mass, myocardial ischemia, and decreased bone density.

[0235] The antibody of the invention may preferably be for use as a therapeutic or prophylactic agent for muscle atrophic disease (e.g., disuse muscular atrophy, sarcopenia, cathepsis, etc.) and/or dwarfism (e.g., Laron-type short stature, growth hormone-resistant short stature, etc.). The antibody of the present invention may also be superior in that it does not cause fluctuations in the blood glucose level upon administration. An antibody drug, antibody-drug conjugate, or diagnostic agent in which a part or all of the anti-IGF-1 receptor antibody as a component can be used for treating or preventing or diagnosing diseases including: neuroblastoma, rhabdomyosarcoma, bone cancer, pediatric cancer, acromegalia, ovary cancer, pancreas cancer, benign prostate hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, neck cancer, synoviosarcoma, urinary bladder cancer, stomach cancer, Wilms' tumor, diarrhea associated with metastatic carcinoid and vasoactive intestinal peptide secreting tumor, vipoma, Verner-Morrison syndrome, Beckwith-Wiedemann syndrome, kidney cancer, renal-cell cancer, transitional cell cancer, Ewing's sarcoma, leukemia, acute lymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatous brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, undifferentiated neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendrogloma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, systemic erythematoses, myasthenia gravis, autoimmune thyroiditis, Hashimoto's thyroiditis, thyroid ophthalmopathy, hyperthyroidism, and Behcet's disease.

[0236] A drug containing the antibody of the present invention may be formulated in the form of a pharmaceutical composition which contains, in addition to the antibody of the present invention, a pharmaceutically acceptable carrier and/or any other excipient. Drug formulation using a phar-

maceutically acceptable carrier and/or any other excipient can be carried out in accordance with, e.g., a method described in the University of the Sciences in Philadelphia, "Remington: The Science and Practice of Pharmacy, 20th EDITION", Lippincott Williams & Wilkins, 2000.

[0237] Such an agent may be provided as a liquid formulation prepared by dissolving, suspending, or emulsifying the ingredients into sterile aqueous medium or oily medium, or as a lyophilized formulation thereof. A medium or solvent for preparing such a formulation may be an aqueous medium, examples of which include distilled water for injection and physiological saline solution, which may optionally be used with addition of an osmoregulating agent (e.g., D-glucose, D-sorbitol, D-mannitol, and sodium chloride), and/or in combination with a suitable dissolving aid such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol or polyethylene glycol), or a nonionic surfactant (e.g., polysorbate 80 or polyoxyethylene hydrogenated castor oil 50). Such a formulation can also be prepared with an oily medium or solvent, examples of which include sesame oil and soybean oil, which can optionally be used in combination with a dissolving aid such as benzyl benzoate and benzyl alcohol. Such liquid drugs may often be prepared using appropriate additives such as buffering agents (e.g., phosphate buffering agents and acetate buffering agents), soothing agents (e.g., benzalkonium chloride and procaine hydrochloride), stabilizers (e.g., human serum albumin and polyethylene glycol), preservatives (e.g., ascorbic acid, erythorbic acid, and their salts), coloring agents (e.g., copper chlorophyll β-carotene, Red #2 and Blue #1), antiseptic agents (e.g., paraoxybenzoic acid esters, phenol, benzethonium chloride and benzalkonium chloride), thickeners (e.g., hydroxypropyl cellulose, carboxymethyl cellulose, and their salts), stabilizers (e.g., human serum albumin mannitol and sorbitol), and odor correctives (e.g., menthol and citrus aromas).

[0238] Other alternative forms include agents for application onto mucous membranes, such formulations often containing additives such as pressure-sensitive adhesives, pressure-sensitive enhancers, viscosity regulators, thickening agents and the like (e.g., mucin, agar, gelatin, pectin, carrageenan, sodium alginate, locust bean gum, xanthan gum, tragacanth gum, gum arabic, chitosan, pullulan, waxy starch, sucralfate, cellulose and its derivatives (such as hydroxypropyl methyl cellulose), polyglycerol fatty acid esters, acrylic acid-alkyl (meth)acrylate copolymers, or their salts and polyglycerol fatty acid esters), primarily for the purpose of imparting mucosal adsorption or retention properties. However, the form, solvent and additives for the therapeutic agent or prophylactic agent to be administered to the body are not limited to these, and appropriately selection may be made by a person skilled in the art.

[0239] A drug containing the antibody of the present invention may further contain, in addition to the antibody of the present invention, another known agent (active ingredient). It can also be fused or linked to other drugs such as antibody-drug conjugates or bispecific or multispecific antibodies. A drug containing the anti-IGF-1 receptor antibody of the present invention may be combined with another known agent in the form of a kit. Examples of active ingredients to be combined with the anti-IGF-1 receptor agonist antibody include: growth hormone or an analog thereof, insulin or an analog thereof, IGF-2 or an analog thereof, an anti-myostatin antibody, myostatin antagonist,

anti-activin type IIB receptor antibody, activin type IIB receptor antagonist, soluble activin type IIB receptor or an analog thereof, ghrelin or an analog thereof, follistatin or an analog thereof, a beta-2 agonist, and a selective androgen receptor modulator.

[0240] In the preparation of an antibody drug or antibody-drug conjugate containing the anti-IGF-1 receptor antibody of the present invention as a component, examples of active ingredients to be combined with the anti-IGF-1 receptor antibody or to be included with the anti-IGF-1 receptor antibody include: corticosteroid, antiemetic, ondansetron hydrochloride, granisetron hydrochloride, metoclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, cancer vaccine, GM-CSF inhibitor, GM-CSF DNA vaccine, cell-based vaccine, dendritic cell vaccine, recombinant virus vaccine, heat shock protein (HSP) vaccine, homologous tumor vaccine, autologous tumor vaccine, analgesic, ibuprofen, naproxen, choline magnesium trisalicylate, oxycodone hydrochloride, anti-angiogenic, antithrombotic, anti-PD-1 antibody, nivolumab, pembrolizumab, anti-PD-L1 antibody, atezolizumab, anti-CTLA4 antibody, ipilimumab, anti-CD20 antibody, rituximab, anti-HER2 antibody, trastuzumab, anti-CCR4 antibody, mogamulizumab, anti-VEGF antibody, bevacizumab, anti-VEGF receptor antibody, soluble VEGF receptor fragment, anti-TWEAK antibody, anti-TWEAK receptor antibody, soluble TWEAK receptor fragment, AMG 706, AMG 386, antiproliferative, farnesyl protein transferase inhibitor, alpha v beta 3 inhibitor, alpha v beta 5 inhibitor, p53 inhibitor, Kit receptor inhibitor, ret receptor inhibitor, PDGFR inhibitor, growth hormone secretion inhibitor, angiopoietin inhibitor, tumor-infiltrating macrophage inhibitor, c-fms inhibitor, anti-c-fms antibody, CSF-1 inhibitor, anti-CSF-1 antibody, soluble c-fms fragment, pegvisomant, gemcitabine, panitumumab, irinotecan, and SN-38. The dosage of the other agent used in combination with the antibody may be within a dosage used for normal therapy, but can be increased or decreased depending on the situation.

[0241] The agents according to the present invention can be parenterally administered for the purpose of improving symptoms. For parenteral administration, a transnasal agent may be prepared, and a liquid drug, suspension or solid formulation may be selected. An injection may be prepared as a different form of parenteral administration, the injection being selected as subcutaneous injection, intravenous injection, infusion, intramuscular injection, intracerebroventricular injection or intraperitoneal injection. Other formulations used for parenteral administration include suppositories, sublingual agents, percutaneous agents and transmucosal administration agents other than transnasal agents. In addition, intravascular local administration is possible by a mode of addition or coating onto a stent or intravascular obturator.

[0242] The dose for an agent for treatment or prevention according to the invention will differ depending on the patient age, gender, body weight and symptoms, the therapeutic effect, the method of administration, the treatment time, or the types of active ingredients in the medical composition, but normally it may be administered in the range of 0.1 mg to 1 g and preferably in the range of 0.5 mg to 100 mg of active compound per administration for adults, once every one to four weeks, or once every one to two months. However, since the administration dose and frequency will vary depending on a variety of conditions, lower

administration dose and fewer administration frequency than those mentioned above may be sufficient, or administration dose and frequency exceeding these ranges may be necessary.

EXAMPLES

[0243] The present invention will now be described in more detail by way of the following Examples. However, the present invention should not be construed to be limited to these Examples, but can be implemented in any form without departing from the spirit of the present invention.

[Example 1]Design of Humanized Antibodies Based on the Mouse Antibody IGF11-16

Selection of Human Frameworks

[0244] A mouse monoclonal antibody against the IGF-1 receptor, IGF11-16, was generated by the hybridoma method of Kohler et al (Nature, (1975), Vol. 256, pp. 495-497) (Patent Literature 1). From this antibody, the complementarity determining region (CDR) amino acids in the heavy chain variable region (VH) and light chain variable region (VL) were transferred into template human antibodies. As the template human antibodies, two different humanized antibody frameworks were prepared based on germlines of human antibodies having amino acid sequences highly homologous to the VH and VL amino acid sequences (SEQ ID NO: 39 and 41, respectively) of mouse antibody IGF11-16 (mouse parent antibody), by selecting VH-1-46 (SEQ ID NO: 95) and VH-1-e (SEQ ID NO: 96) as heavy chain sequences, JH4 (SEQ ID NO: 97) as a heavy chain J-segment, VK1-L5 (SEQ ID NO: 98) and VK1-A20 (SEQ ID NO: 99) as light chain sequences, and JK2 (SEQ ID NO: 100) as a light chain J-segment, and combining these sequences as shown in Table 1 below.

TABLE 1

Humanized antibody framework	Heavy chain	Heavy chain J-segment	Light chain	Light chain J-segment
FW1	VH-1-46	JH4	VK1-L5	JK2
FW2	VH-1-e	JH4	VK1-A20	JK2

Grafting of CDR Regions and Substitutions of FR Amino Acids

[0245] The essential amino acid sequences from the VH and VL of the mouse antibody IGF11-16 were transferred to the FRs of the template human antibodies above to thereby prepare humanized antibodies.

[0246] Specifically, the amino acid sequence of the VH sequence of the mouse antibody IGF11-16 was humanized by replacing the CDR amino acid sequences and several FR amino acids of the VH of the template human antibodies mentioned above with the corresponding amino acid sequences in the VH of the mouse antibody IGF11-16, and a DNA sequence encoding these amino acids was also designed.

[0247] The amino acid sequence of the VL sequence of the mouse antibody IGF11-16 was humanized by replacing the CDR amino acid sequence and several FR amino acids of the VL of the template human antibody mentioned above with the corresponding amino acid sequence in the VL of the mouse antibody IGF11-16, and a DNA sequence encoding these amino acids was also designed.

[0248] The constitutions of the designed heavy and light chains for humanized antibodies are shown in Table 2 below.

[0249] Incidentally, in the descriptions of the examples below and in the related figures, the name(s) of a humanized heavy chain variable region and/or a humanized light chain variable region designed herein may be used for referring to a humanized heavy chain composed of the designed humanized heavy chain variable region linked to a heavy chain constant region and/or a humanized light chain composed of the designed light chain variable region linked to a light chain constant region, as well as a complete humanized antibody by combining the humanized heavy chain and the humanized light chain. For example, “VL22/VH13_PS” in FIG. 1A refers to a humanized antibody designed by combining a light chain composed of VL22 as the light chain variable region and a human kappa chain constant region linked thereto, and a heavy chain composed of VH13_PS as the heavy chain variable region and an IgG4S228P heavy chain constant region linked thereto. Examples of nucleotide sequences corresponding to the amino acid sequences of SEQ ID NOS: 15, 17, 19, 21, 23, 25, and 27 are shown in SEQ ID NOS: 16, 18, 20, 22, 24, 26, and 28, respectively.

TABLE 2

Constitutions of the humanized antibodies as designed														
antibody	name	Light chain variable region				Heavy chain variable region								
		FW1	FW1	Amino acid substitution			FW1	Amino acid substitution						
				FR2		heavy		CDR2		FR3				
		chain*1		Y36	A43	K45	chain*2	N61	E62	K65	S66	V93		
FW1 var1	FW1_VL1 (SEQ ID NO: 21)	FW1_VL1 (SEQ ID NO: 21)	C	I	K	FW1_VH1 (SEQ ID NO: 15)	A	Q	Q	G	V			
FW1 var9	FW1_VL3 (SEQ ID NO: 23)	FW1_VL3 (SEQ ID NO: 23)	Y	A	K	FW1_VH1	A	Q	Q	G	V			
FW1_var10	FW1_VL3	FW1_VL3	Y	A	K	FW1_VH2 (SEQ ID NO: 17)	A	Q	Q	G	T			

TABLE 2-continued

Constitutions of the humanized antibodies as designed											
FW1_var14	FW1_VL4 (SEQ ID NO: 25)	Y	A	R	FW1_VH2	A	Q	Q	G	T	
FW2	FW2	Amino acid substitution		FW2	Amino acid substitution						
antibody	light	FR2		heavy	CDR2		FR3				
name	chain* ³	Y36	V43	K45	chain* ⁴	N61	E62	K65	S66	V93	
FW2_var2	FW2_VL2 (SEQ ID NO: 27)	Y	I	K	FW2_VH1 (SEQ ID NO: 19)	A	Q	Q	G	V	

*¹Amino acid substitutions introduced to FW1 light chains

Amino acid substitution to restore amino acids in the mouse parent antibody: Y36C, A43I

Amino acid substitutions to simulate the human germline sequence for reducing immunogenicity: K45R

*²Amino acid substitutions introduced to FW1 heavy chains

Amino acid substitutions to simulate the human germline sequence for reducing immunogenicity: N61A, E62Q, K65Q, and S66G

Amino acid substitutions to reduce immunogenicity: V93T

*³Amino acid substitutions introduced to FW2 light chain

Amino acid substitution to restore amino acids in the mouse parent antibody: V43I

*⁴Amino acid substitutions introduced to FW2 heavy chain

Amino acid substitutions to simulate the human germline sequence for reducing immunogenicity: N61A, E62Q, K65Q, and S66G

[Example 2] Preparation of Humanized Antibodies

[0250] DNAs were synthesized which encode each of the designed heavy chain variable regions for humanized antibodies linked to a heavy chain constant region of the human IgG4S228P mutant, which is a stabilized mutant of the human IgG4 subclass. The synthesized DNAs were integrated and linked into a pcDNA3.4 expression vector to prepare plasmids expressing the humanized antibody heavy chains.

[0251] DNAs were also synthesized which encode each of the designed light chain variable regions for humanized antibodies linked to a K-chain constant region, and the synthesized DNAs were incorporated into a pcDNA3.4 expression vector to prepare plasmids expressing the humanized antibody light chains.

[0252] These plasmids expressing the humanized antibody heavy chains and the humanized antibody light chains were mixed and introduced into cells using the ExpiCHO® Expression System (Thermo Fisher Scientific) for causing them to express various antibodies. In this connection, the humanized antibody expressed by a combination of the heavy chain expressing plasmid carrying FW1_VH1 and the light chain expressing plasmid carrying FW1_VL1 is referred to as the FW1_var1 antibody, and the humanized antibody expressed by combining the heavy chain expression plasmid carrying FW2_VH1 and the light chain expression plasmid carrying FW2_VL2 is referred to as the FW2_var2 antibody. The same procedure and nomenclature were used for FW1_var9, FW1_var10, and FW1_var14. Humanized antibodies were obtained from culture supernatant of cells transfected with the plasmids expressing the humanized antibody heavy chain and the humanized antibody light chain, via affinity purification using a Protein A column.

[0253] Subsequent preparation of humanized antibodies was also carried out according to the method described above.

[Example 3] IGF-1 Receptor Activation Effect Using PathHunter®

[0254] In order to detect the effect of activating the IGF-1 receptor by the designed humanized antibodies on, the PathHunter® IGF1R Functional Assay (DiscoverX) was used to detect the activation of IGF-1 receptor signaling by the following procedure.

[0255] Cells expressing the IGF-1 receptor were seeded in a poly-D-lysine-coated or collagen-I-coated 96-well plate (Black/clear or White/clear) at 90 µL/well (2×10^4 cells/well or 5×10^3 cells/well) and incubated at 37° C. with 5% CO₂. The next day, 10 µL/well of each concentration of the drug was added and incubated at 37° C. with 5% CO₂. On the following day, 30 µL of the culture supernatant was taken, 15 µL of substrate solution was added, and the reaction was allowed to continue for 60 minutes. The luminescence signal (RLU) was measured with a luminometer (Tristar, Berthold). The fluorescence intensity when 12.5 nM of the antibody was added was determined, from which the value with 0.1 nM of the antibody was subtracted as background, and the resulting value was used as the activity level. The activity level of the mouse parent antibody IGF11-16 was assumed as 1, and the relative value of the activity level of each humanized antibody was calculated.

[0256] The results are shown in Table 3. These results indicate that the IGF-1 receptor activation ability of the humanized antibodies (FW1_var1, var9, var10, var14, and FW2_var2) was attenuated by more than 20% compared to the mouse parent antibody IGF11-16.

TABLE 3

Measurement of IGF-1 receptor activation by humanized antibodies using PathHunter® system

	Fluorescence intensity (12.5 nM) (RLU)	Fluorescence intensity (0.1 nM) (RLU)	Activation intensity (RLU)	Ratio
IGF11-16	2734	557	2177	1.00
FW1_var1	2159	555	1604	0.74
FW1_var9	2044	591	1454	0.67
FW1_var10	1864	516	1348	0.62
FW1_var14	1903	558	1345	0.62
FW2_var2	1893	572	1321	0.61

[0257] Next, the humanized antibodies were modified at their CDR regions (antigen-binding regions), by replacing A61, Q62, Q65, and G66 in the heavy-chain CDR2 region, which are different from the corresponding residues of the mouse parent antibody, with N61, E62, K65, and S66, respectively, to make them identical to those of the mouse parent antibody. The resulting humanized antibodies with amino acid substitutions (FW1_var10_NEKS, FW1_var14_NEKS) were compared for their ability to activate the IGF-1 receptor by the same procedure as described above, using the mouse parent antibodies IGF11-16 and FW1_var1 as standard for comparison.

[0258] The results are shown in Table 4. These results indicate that no recovery of activity level was observed.

TABLE 4

Measurement of IGF-1 receptor activation by mouse CDR-substituted humanized antibodies by PathHunter® system

	Fluorescence intensity (12.5 nM) (RLU)	Fluorescence intensity (0.1 nM) (RLU)	Activation intensity (RLU)	Ratio
IGF11-16	3801	230	3572	1.00
FW1_var1	2477	209	2269	0.64
FW1_var10_NEKS	2186	223	1963	0.55
FW1_var14_NEKS	1965	221	1744	0.49

[0259] These results indicated that even when the amino acid sequences of the CDRs were changed back to the same as the CDRs of the mouse parent antibody IGF11-16, its activity level was not restored to the same level as that of the mouse parent antibody IGF11-16 (activity level ratio within $\pm 20\%$). Therefore, it was inferred that the FRs (framework regions), not the CDRs, were responsible for the decrease in the activity level.

[0260] Therefore, the humanized antibodies were modified by replacing their FR1, FR2, and FR3 with the corresponding FRs of the mouse antibody. The humanized antibodies modified via mouse FR substitutions are shown in Table 5. Activation of the IGF-1 receptor signaling by these modified antibodies was evaluated by the PathHunter® system as described above. A human chimeric IGF11-16 antibody (Chimera), which is a chimera of the variable regions of the mouse parent antibody IGF11-16 and the constant regions of human IgG4 (S228P), was used as a positive control, and the signal intensity at an antibody concentration of 16.7 nM was compared as described above. The results are shown in Table 5. Examples of nucleotide sequences corresponding to the amino acid sequences of

SEQ ID NOS: 29, 31, 33, 35, and 37 are shown in SEQ ID NOS: 30, 32, 34, 36, and 38, respectively.

TABLE 5

Humanized antibodies modified via mouse FR substitutions and their signal intensity ratio				Signal intensity (ratio to IGF11-16)
Anti-body name	Heavy chain variable region	Light chain variable region	Contents of substitutions	
Human IGF11-16	IGF11-16_VH	IGF11-16_VL		1.00
FW1_var9_mFR-H1	FW1_VH1_mH1 (SEQ ID NO: 29)	FW1_VL3	Heavy chain FR-H1 was replaced with FR-H1 of IGF11-16	1.08
FW1_var9_mFR-H2	FW1_VH1_mH2 (SEQ ID NO: 31)	FW1_VL3	Heavy chain FR-H2 was replaced with FR-H2 of IGF11-16	0.51
FW1_var9_mFR-H3	FW1_VH1_mH3 (SEQ ID NO: 33)	FW1_VL3	Heavy chain FR-H3 was replaced with FR-H3 of IGF11-16	0.70
FW1_var9_mFR-L1	FW1_VH1_mL1 (SEQ ID NO: 35)	FW1_VL3	Light chain FR-L1 was replaced with FR-L1 of IGF11-16	0.51
FW1_var9_mFR-L2 + L3	FW1_VH1_mL2 + L3 (SEQ ID NO: 37)	FW1_VL3	Light chain FR-L2 & L3 were replaced with FR-L2 & L3 of IGF11-16	0.50

[0261] These results indicate that the modified antibody whose signal intensity is equivalent (within $\pm 20\%$ of the value) to that of the human chimeric IGF11-16 antibody is FW1_var9_mFR-H1, suggesting that the mouse heavy chain FR1 is essential for maintaining the activity of the humanized antibodies.

[0262] The next step was to identify the amino acids essential for maintaining the activity in the mouse heavy chain FR1. Since there were seven amino acid differences in the heavy chain FR1 sequence between the mouse parent antibody IGF11-16 and the humanized antibodies, each of these amino acids was changed one at a time to the corresponding amino acid of the mouse parent antibody. The humanized antibodies modified via mouse FR1 amino acid substitutions are shown in Table 6. The signal intensity of IGF-1 receptor activation was measured for these humanized antibodies with mouse FR1 amino acid substitutions using the PathHunter® system, and the signal intensity at an antibody concentration of 16.7 nM was compared with that of the mouse parent antibody IGF11-16. As a result, only the humanized antibody in which serine at position 25 was replaced with proline had an equivalent level of activity (activity ratio within $\pm 20\%$) to that of the mouse parent antibody IGF11-16. The results are shown in Table 6.

TABLE 6

Signal intensities of humanized antibodies modified via mouse FR1 amino acid substitutions				
Antibody name	Heavy chain variable region	Heavy chain amino acid substitution relative to FW1_VH1	Light chain variable region	
IGF11-16	IGF11-16_VH	IGF11-16_VL	1.00	
FW1_var1	FW1_VH1	FW1_VL1	0.66	
FW1_var9	FW1_VH1	FR-H1: V2I	FW1_VL3	0.70
hH1a	hH1a			
FW1_var9	FW1_VH1	FR-H1: V5Q	FW1_VL3	0.54
hH2a	hH2a			
FW1_var9	FW1_VH1	FR-H1: S7P	FW1_VL3	0.60
hH3a	hH3a			
FW1_var9	FW1_VH1	FR-H1: V11L	FW1_VL3	0.65
hH4a	hH4a			
FW1_var9	FW1_VH1	FR-H1: K12V	FW1_VL3	0.56
hH5a	hH5a			
FW1_var9	FW1_VH1	FR-H1: V20L	FW1_VL3	0.55
hH6a	hH6a			
FW1_var9	FW1_VH1	FR-H1: S25P	FW1_VL3	1.09
hH7a	hH7a			

[0263] These results indicate that the proline at position 25 of the heavy chain FR1 region is critical for maintaining the activity. Therefore, all subsequent humanized antibodies used in the examples below included P (proline, Pro) substitution at position 25 of the heavy chain.

[Example 4] Identification of Amino Acids in the CDR Region that are Important for Maintaining Activity by Alanine Substitution

[0264] In order to identify the amino acids in the CDR region required to maintain the activity, each amino acid in the mouse parent antibody IGF11-16 was replaced one at a time with alanine, and the resulting substituted antibodies were compared for their signal activation ability in terms of the EC₅₀ and E_{max} values, and also evaluated for their binding activity by antigen ELISA. The activity of each antibody was evaluated in comparison with that of the mouse parent antibody IGF11-16, and antibodies having an EC₅₀ value within 2-fold and an E_{max} value within ±20% of that of the mouse parent antibody IGF11-16 are determined to have a similar level of activity.

[0265] The ability to activate IGF-1 receptor signaling was evaluated in the PathHunter® system described in Example 3. The EC₅₀ and E_{max} values were calculated using GraphPad Prism analysis software. The binding activity was measured by antigen ELISA using a recombinant IGF-1 receptor extracellular region as an antigen. Specifically, human recombinant IGF-1R (manufactured by R&D SYSTEMS) solution was prepared at 0.5 µg/mL in PBS (phosphate buffered saline). The prepared human recombinant IGF-1R solution was added to the solidified plate at 50 µL/well. The reaction was allowed to occur overnight at 4° C., the medium was replaced with 3% BSA/PBS (containing 0.02% sodium azide), and the solution was stored at 4° C. until used for ELISA. The test substance solution (antibody solution at a concentration of 5 nM) was added to the solidified plate at 50 µL/well. The reaction was allowed to run for 1 hour at room temperature, and then washed twice with washing solution (PBST; phosphate buffered saline

containing 0.05% Tween 20). An anti-mouse IgG antibody labelled with alkaline phosphatase (diluted 2000-fold in 3% BSA/PBS) was added at 50 µL/well. The reaction was allowed to run for 45 minutes at room temperature, washed three times with washing solution, and then the substrate (pNPP; para-nitrophenyl phosphate) was added to start the reaction. After 1 hour of reaction at room temperature, the absorbance was measured at 405 and 550 nm, and the difference between the absorbances at 405 nm and at 550 nm was calculated. This value was analyzed as the binding activity.

[0266] The CDR-substituted IGF11-16 antibodies produced and the results of signal activation and binding activity measurements are shown in Tables 7 and 8. These results indicate that five alanine substitutions made in the CDR region which reduced the binding activity by about 10 to 20%, i.e., tryptophan at position 32 of CDR-L1, tryptophan at position 33 of CDR-H1, glutamate at position 50 of CDR-H2, asparagine at position 52 of CDR-H2, and arginine at position 102 of CDR-H3, are crucial for maintaining the activity. In addition, histidine at position 35 of CDR-H1, serine at position 54 of CDR-H2, asparagine at position 55 of CDR-H2, serine at position 56 of CDR-H2, asparagine at position 59 of CDR-H2, and phenylalanine at position 64 of CDR-H2 are also deemed to contribute to the retention of the activity since their activity was decreased by Ala substitution.

[0267] On the other hand, among the 54 amino acid residues in the alanine-substituted CDR region, 44 residues showed a binding activity of 80% or more even after the alanine substitution.

TABLE 7

Evaluation results of signal activation of alanine substitutions in the light chain CDR region (Only the amino acid residue whose activity was reduced by the alanine substitution are shown.)					
Position	Alanine-substituted position	Signal activation		Binding	
		Amino acid	EC ₅₀ vs IGF11-16	EC ₅₀ @5 nM	E _{max} vs IGF11-16
CDR-L1	32*	W	9.5	1.5	14

*An amino acid residue whose binding activity is reduced to about 10-20% by alanine substitution.

TABLE 8

Evaluation results of signal activation of alanine substitutions in the heavy chain CDR region (Only the amino acid residues whose activity was reduced by the alanine substitution are shown.)					
Position	Alanine-substituted position	Signal activation		Binding	
		Amino acid	EC ₅₀ vs IGF11-16	EC ₅₀	E _{max} vs IGF11-16
CDR-H1	33*	W	0.5	0.0	9
	35	H	2.2	1.0	49
CDR-H2	50*	E	ND	ND	9
	52*	N	2.7	0.0	21
	54	S	2.5	1.0	97
	55	N	3.0	1.0	94
	56	S	2.9	1.1	108

TABLE 8-continued

Evaluation results of signal activation of alanine substitutions in the heavy chain CDR region (Only the amino acid residues whose activity was reduced by the alanine substitution are shown.)					
Alanine-substituted position		Signal activation		Binding	
Position	Amino acid	EC ₅₀	E _{max} vs IGF11-16	EC ₅₀	
CDR-H3	59	N	2.3	0.9	112
	64	F	2.4	0.9	84
	102*	R	54.4	4.8	9

*Amino acid residues whose binding activity are reduced to about 10-20% by alanine substitution.

[Example 5] Design of Humanized Heavy Chain Variable Regions

[0268] Since the results of Example 3 showed that the proline at position 25 of the heavy chain is important for maintaining the activity, humanized heavy chain variable regions having P at position 25 of the heavy chain were designed using FW1_VH1 and FW2_VH1 as basic frameworks. Since amino acid substitutions were examined using the FR1 of FW1_VH1 as the basic sequence, the FR1 region of FW2_VH1 was modified to be identical to FW1_FR1 by introducing S16A substitution. The introduction of amino acid substitutions for immunogenicity reduction was carried out based on the results of immunogenicity score analysis of Epibase® (Lonza). A list of designed heavy chain variable regions is shown in Table 9 below.

TABLE 9

Design of humanized heavy chain variable regions		
Humanized heavy chain variable region	Amino acid substitution	SEQ ID NO:
FW1_VH1	Basic framework	15
VH13_PN	S25P(FR-H1), V93T(FR-H3)	43
FW2_VH1	Basic framework	19
VH23_PN	S16A(FR-H1), S25P(FR-H1)	49
VH25_PN	S16A(FR-H1), S25P(FR-H1), K74T(FR-H3)	55

Note:
V93T and K74T are substitutions intended to reduce immunogenicity.

[Example 6] Design of Humanized Light Chain Variable Regions

[0269] Humanized light chain variable regions were designed using FW1_VL1 and FW2_VL2 as basic frameworks. The introduction of amino acid substitutions to reduce the immunogenicity score was carried out based on the results of Epibase® (Lonza) analysis. A list of designed light chain variable regions is shown in Table 10 below.

TABLE 10

Design of humanized light chain variable regions		
Humanized light chain variable region	Amino acid substitution	SEQ ID NO:
FW1_VL1	Basic framework	21
VL13	C36Y(FR-L2), I43A(FR-L2)	61
VL14	C36Y(FR-L2), I43A(FR-L2), K45R(FR-L2)	63

TABLE 10-continued

Design of humanized light chain variable regions		
Humanized light chain variable region	Amino acid substitution	SEQ ID NO:
FW2_VL2	Basic framework	27
VL22	Same as FW2_VL2	65
VL23	I43V(FR-L2)	67
VL24	I43V(FR-L2), L54R(CDR-L2)	69

Notes:
C36Y, I43A, and I43V are amino acid substitutions back to the human framework sequence intended to reduce immunogenicity; K45R is a human germline sequence amino acid substitution intended to reduce immunogenicity; L54R is an amino acid substitution intended to reduce immunogenicity.

[Example 7] Design of Humanized Antibodies Via Substitution of Amino Acids at Deamidation Risk

[0270] If deamidation occurs during the production of humanized antibodies, quality control will be difficult. It is therefore necessary to replace the amino acids at risk of deamidation with other amino acids that do not affect the activity in advance. Common sequences at risk for deamidation include NG, NT, NS, and NN. The NS sequence is present in the CDR-H2 region of the heavy chain of the present humanized antibodies. Hence, amino acid substitutions were made taking into account the risk of asparagine (N) at position 55 being deamidated and converted to aspartic acid (D). A list of substituted heavy chains is shown in Table 11. Examples of nucleotide sequences corresponding to the amino acid sequences of SEQ ID NOs: 45, 51, and 57 are shown in SEQ ID NOs: 46, 52, and 58, respectively.

TABLE 11

Substitutions of amino acids at deamidation risk in humanized heavy chains		
Humanized heavy chain variable region	Amino acid substitution	SEQ ID NO:
VH13_PN	Basic framework	43
VH13_PQ	N55Q(CDR-H2)	45
VH13_PS	N55S(CDR-H2)	47
VH23_PN	Basic framework	49
VH23_PQ	N55Q(CDR-H2)	51
VH23_PS	N55S(CDR-H2)	53
VH25_PN	Basic framework	55
VH25_PQ	N55Q(CDR-H2)	57
VH25_PS	N55S(CDR-H2)	59

[Example 8] Selection of Humanized Antibodies for Activation of IGF-1 Receptor Signaling

[0271] The humanized antibodies were evaluated based on their ability to activate the IGF-1 receptor, and humanized antibodies having activity equivalent to that of the mouse parent antibody IGF11-16 were selected.

[0272] In order to detect the activating effect of the anti-IGF-1 receptor agonist antibodies on the IGF-1 receptor, the activation of IGF-1 receptor signaling was measured using the PathHunter® IGF1R Functional Assay (DiscoverX).

[0273] Cells expressing the IGF-1 receptor were seeded in poly-D-lysine-coated or collagen-I-coated 96-well plates (Black/clear or White/clear) at 90 µL/well (2×10⁴ cells/well or 5×10³ cells/well) and incubated at 37° C. with 5% CO₂.

The next day, 10 µL/well of each concentration of the drug was added and incubated at 37° C. with 5% CO₂. The following day, 30 µL of culture supernatant was taken, 15 µL of substrate solution was added, and the reaction was allowed to run for 60 minutes, and the luminescence signal (RLU) was measured with a luminometer (Tristar, Berthold).

[0274] As a result of the measurement, the humanized antibodies whose activity was confirmed to be equivalent to that of the mouse parent antibody IGF11-16 (EC₅₀ value: within 2-fold and E_{max} value: within ±20% compared to the mouse parent antibody IGF11-16) are shown in Table 12.

TABLE 12

List of humanized antibodies that have been confirmed to be as active as the mouse parent antibody IGF11-16 by the PathHunter® system					
	Light chain				
	VL13	VL14	VL22	VL23	VL24
Heavy chain	VH13_PS (SEQ ID NO: 47)	VL13/ VH13_PS	VL14/ VH13_PS	VL22/ VH13_PS	VL23/ VH13_PS
	VH23_PS (SEQ ID NO: 53)	VL13/ VH23_PS	VL14/ VH23_PS	VL22/ VH23_PS	VL23/ VH23_PS
	VH25_PS (SEQ ID NO: 59)	VL13/ VH25_PS	VL14/ VH25_PS	VL22/ VH25_PS	VL23/ VH25_PS
	VH13_PN (SEQ ID NO: 43)	VL13/ VH13_PN	VL14/ VH13_PN	VL22/ VH13_PN	VL23/ VH13_PN
	VH23_PN (SEQ ID NO: 49)	VL13/ VH23_PN	VL14/ VH23_PN	VL22/ VH23_PN	VL23/ VH23_PN
	VH25_PN (SEQ ID NO: 55)	VL13/ VH25_PN	VL14/ VH25_PN	VL22/ VH25_PN	VL23/ VH25_PN
	VH13_PQ (SEQ ID NO: 45)	VL13/ VH13_PQ	VL14/ VH13_PQ	VL22/ VH13_PQ	VL23/ VH13_PQ
	VH23_PQ (SEQ ID NO: 51)	VL13/ VH23_PQ	VL14/ VH23_PQ	VL22/ VH23_PQ	VL23/ VH23_PQ
	VH25_PQ (SEQ ID NO: 57)	VL13/ VH25_PQ	VL14/ VH25_PQ	VL22/ VH25_PQ	VL23/ VH25_PQ

[Example 9] Selection of Humanized Antibodies by their Human Myoblast Proliferative Activity

[0275] The humanized antibodies were evaluated based on their human myoblast proliferative activity, whereby humanized antibodies with activity equivalent to that of the mouse parent antibody IGF11-16 were selected.

[0276] In order to examine the proliferative activity of the anti-IGF-1 receptor humanized antibodies against human myoblasts, the drug was added to human myoblasts, and the amount of ATP in the cells was measured after 4 days.

[0277] Normal human skeletal muscle myoblast cells (HSMM, Lonza) were seeded in 96-well plates (Collagen type I coated) using medium containing 1% BSA in SkBM-2 (Lonza, CC-3246) at 0.1 mL/well (2×10³ cells/well), and incubated at 37° C. with 5% CO₂. The day after cell seeding, various drugs were added at 25 µL/well and incubated for 4 days at 37° C. with 5% CO₂. As an indicator of cell proliferation, the amount of ATP in the cells was measured using the CellTiter-Glo (registered trademark) Luminescent Cell Viability Assay (Promega). After incubated for 4 days,

the supernatant was removed from each well so that the culture medium was 50 µL/well, and the 96-well plate was allowed to stand at room temperature for at least 30 minutes. 50 µL/well of CellTiter-Glo (registered trademark) reagent was added and allowed to react for at least 10 minutes before measuring the luminescence signal with a luminometer (Tristar, Berthold).

[0278] As a result, the humanized antibodies whose activity was confirmed to be equivalent to that of the mouse parent antibody IGF11-16 (EC₅₀ value: within 10-fold, E_{max}: 90% or more compared to the mouse parent antibody

IGF11-16) are shown in Table 13. The graphs of the measurement results are shown in FIGS. 1A to 1F.

TABLE 13

List of humanized antibodies that have been confirmed to be as active as the mouse parent antibody IGF11-16 by myoblast proliferation assay					
	Light chain				
		VL22	VL23	VL24	
Heavy chain	VH13_PS	VL22/ VH13_PS	VL23/ VH13_PS	VL24/ VH13_PS	
	VH23_PS	VL22/ VH23_PS	VL23/ VH23_PS	VL24/ VH23_PS	
	VH25_PS	VL22/ VH25_PS	VL23/ VH25_PS	VL24/ VH25_PS	
	VH13_PN	VL22/ VH13_PN	VL23/ VH13_PN	VL24/ VH13_PN	

TABLE 13-continued

List of humanized antibodies that have been confirmed to be as active as the mouse parent antibody IGF11-16 by myoblast proliferation assay

Light chain		
VL22	VL23	VL24
VH23_PN	VL23/ VH23_PN	
VH25_PN	VL23/ VH25_PN	

[Example 10] Evaluation of Immunogenicity

[0279] To analyze the immunogenicity of the humanized antibodies, Lonza's Epibase® in Silico was used to calculate immunogenicity scores. Lonza's Epibase® in Silico platform is an immunogenicity prediction method that utilizes the structural characteristics of the HLA class II receptor as well as the experimentally determined binding affinity between a 10-mer peptide and an HLA class II receptor to predict the potential peptide/HLA binding, which is a necessary condition for T cell activation, in an amino acid sequence contained in the antibody, and to calculate it as an immunogenicity score. Evaluation in 85 HLA class II allotypes (43 types of DRB1, 8 types of DRB3/4/5, 22 types of DQ, and 12 types of DP) can cover more than 99% of the entire population. Immunogenicity scores were determined by taking into account the frequency of occurrence as well as the binding affinity of the allotypes.

[0280] The results are shown in Tables 14 and 15. Compared to the immunogenicity scores of the mouse parent antibody IGF11-16 and the mouse-human chimeric antibody (an antibody with the variable region of the mouse parent antibody IGF11-16 and the constant region of human IgG4 (S228P)), which were evaluated in a similar manner, the immunogenicity of the humanized antibodies was found to be lower.

TABLE 14

Immunogenicity scores of humanized heavy and light chains and humanized antibodies

H chain	Name	Score	L chain					
			FW1_VL1	VL13	VL14	VL22	VL23	VL24
H	VH13_PN	296.2	851.6	857.8	811.1	895.3	857.8	804.6
	VH13_PQ	302.8	858.2	864.4	817.7	901.9	864.4	811.2
	VH13_PS	301.7	857.1	863.3	816.6	900.8	863.3	810.1
	VH23_PN	346.5	901.9	908.1	861.4	945.6	908.1	854.9
	VH23_PQ	353.1	908.5	914.7	868.0	952.2	914.7	861.5
	VH23_PS	352.0	907.4	913.6	866.9	951.1	913.6	860.4
	VH25_PN	311.9	867.3	873.5	826.8	911.0	873.5	820.3
	VH25_PQ	318.5	873.9	880.1	833.4	917.6	880.1	826.9
	VH25_PS	317.4	872.8	879.0	832.3	916.5	879.0	825.8

TABLE 15

Comparison of immunogenicity scores between humanized antibodies and mouse and chimeric antibodies

Name	Description	Immunogenicity score		
		Heavy chain	Light chain	Complete antibody
Mouse parent antibody	Mouse IgG1 antibody	2319.4	1089.1	3408.5
IGF11-16				
Chimeric antibody	Variable region: mouse IGF11-16 Constant region: human IgG4 (S228P)	791.1	665.4	1456.5
Humanized antibody	Variable region: VL23/VH13_PS Constant region: human IgG4(S228P)	301.7	561.6	863.3
hIGF13_PS				
Humanized antibody	Variable region: VL23/VH25_PS Constant region: human IgG4 (S228P)	317.4	561.6	879.0
hIGF25_PS				

[Example 11] Evaluation of Binding Activity to Mammalian IGF-1 Receptors

[0281] In order to investigate the binding activity of the anti-IGF-1 receptor agonist antibodies against the IGF-1 receptors of human (SEQ ID NO: 71), crab-eating macaque (SEQ ID NO: 73), rabbit (SEQ ID NO: 75), guinea pig (SEQ ID NO: 77), rat (SEQ ID NO: 79) and mouse (SEQ ID NO: 81), a cell-based ELISA was performed using cells expressing various IGF-1 receptors.

[0282] HEK293T cells were transfected by lipofection method with pEF1 expression vectors (Thermo Fisher) incorporated with the IGF-1 receptor genes of rabbit (SEQ ID NO: 76), guinea pig (SEQ ID NO: 78), rat (SEQ ID NO: 80) and mouse SEQ ID NO: 82). The transfected HEK293T cells were allowed to grow overnight or longer after the lipofection, and were then added to a 96-well plate (poly-D-lysine coated) at 4×10^4 cells/well. The cells were then fixed in 10% buffered formalin (Mildform® 10NM, Wako) and blocked with phosphate buffer containing 3% BSA before used for ELISA.

[0283] ELISA was carried out as follows. 100 μ L of each humanized antibody solution prepared at 5 nM in 1% BSA/1% FBS/PBS was added to each well, and reacted at 37° C. for about 1 hour. Anti-human IgG antibody HRP conjugate solution prepared at each concentration in 1% BSA/1% FBS/PBS was added to each well at 100 μ L, reacted at 37° C. for about 1 hour, and washed three times with washing solution. The reaction was initiated by adding 100 μ L of substrate (TMB) to each well. After about 30 minutes, 100 μ L of 1M sulfuric acid was added to each well, the absorbances at 450 and 650 nm were measured, and the difference between the absorbances at 450 nm and at 650 nm was calculated. The calculated difference was compared with the difference between the absorbances at 450 nm and at 650 nm for HEK293T cells without IGF-1 receptor gene (Mock) to analyze the binding activity.

[0284] FIG. 2 shows the results of reactivity to the IGF-R of each of the human, guinea pig, crab-eating macaque, and rabbit. As a result, the humanized antibodies hIGF13_PS and hIGF25_PS increased the binding activity of human, guinea pig, crab-eating macaque and rabbit IGF-1 receptor-expressing cells by about 2-fold compared to Mock cells, and the reactivity was comparable to that of the human mouse chimeric antibody IGF11-16. On the other hand, the binding activity to cells expressing rat and mouse IGF-1 receptors was comparable to that of Mock cells. These results indicate that the humanized antibodies hIGF13_PS and hIGF25_PS bind to human, guinea pig, crab-eating macaque, and rabbit IGF-1 receptors, but not to rat and mouse IGF-1 receptors.

[Example 12] Binding Affinity to IGF-1 Receptor by Surface Plasmon Resonance

[0285] In order to examine the binding properties (binding and dissociation rates) of the drug to the IGF-1 receptor, the binding was measured by surface plasmon resonance (SPR) method.

[0286] The BIACORE T200 system was used as the measurement system. Antihistidine-tagged monoclonal antibodies was fixed in all flow cells of a sensor chip CM3 (BR-1005-36, GE) with Amine Coupling Kit (BR-1000-50, GE) and His Capture Kit (28-9950-56, GE) at approximately 3000 RU before use. HBS-EP+ (BR-1006-69, GE) was used as the running buffer. A recombinant human IGF-1 receptor histidine tag (305-GR-050, R&D SYSTEMS, hereafter IGF-1R-His) was captured in the measurement and used as a ligand. Each concentration of the drug was used as an analyte. A flow cell without IGF-1R-His capture was used as a ligand negative control. PBS (PBS pH 7.4 (lx), #10010049, Gibco) was used as a drug negative control.

[0287] The measurement temperature of the measurement system was set at 40° C. The anti-histidine-tagged monoclonal antibodies in the flow cells (2 and 4) were reacted with IGF-1R-His (<2 \times 10 \times 8M) at less than 100 RU. The flow rate was set at 30 μ L/min, 10 nM of purified mouse IgG2a, kappa, isotype Ctrl, Clone: MG2a-53 (401502, BioLegend, hereafter ctrl IgG2a) was reacted for 1 min, and HBS-EP+ was passed for at least 10 min. The analyte was diluted in steps (0.5 to 8 \times 10 \times 10 \times M) with HBS-EP+ and reacted in all flow cells.

[0288] As measurement conditions, the single cycle kinetics method was used. Each concentration of the analyte was reacted for 600 seconds to obtain a binding curve, and then HBS-EP+ was reacted for 1200 seconds to obtain a disso-

ciation curve. After the reaction, regeneration buffer 1 (0.2% SDS), regeneration buffer 2 (100 mM Tris-HCl (pH 8.5), 1 M NaCl, 15 mM MgCl₂), and regeneration buffer 3 (10 mM glycine-HCl (pH 1.5)) were reacted for 1 minute each for removing IGF-1R-His from the measurement system and washing the measurement system. The dissociation rate constant (ka, 1/Ms), binding rate constant (kd, 1/s), and dissociation constant (KD, M) were calculated by using Biacore T200 Evaluation software (ver. 2.0) with 1:1 Binding model. The results are shown in Table 16.

TABLE 16

Binding affinity of the humanized antibodies and the mouse parent antibody IGF11-16				
Ligand	Analyte	Ka (1/Ms)	Kd (1/s)	KD (M)
IGF-1 receptor	IGF11-16	2.67E+06	7.72E-05	3.14E-11
IGF-1 receptor	hIGF13_PS	2.85E+06	1.58E-04	5.78E-11
IGF-1 receptor	hIGF25_PS	2.87E+06	1.35E-04	5.10E-11

[0289] The KD values of hIGF13_PS and hIGF25_PS against the human IGF-1 receptor were found to be less than E-10, meeting the most favorable criterion for anti-IGF-1 receptor agonist humanized antibodies.

[Example 13] In Vivo Hypoglycemic Effect (Hypoglycemic Effect in Guinea Pigs)

[0290] In order to confirm whether the anti-IGF-1 receptor agonist antibodies have a hypoglycemic effect in vivo, a single dose of hIGF13_PS or hIGF25_PS was administered to guinea pigs, and the blood glucose levels were measured over time for determining the presence or absence of a hypoglycemic effect. The hypoglycemic effect used herein refers to the effect of lowering the blood glucose level to 50 mg/dL or less or causing hypoglycemic symptoms.

[0291] The guinea pigs were fasted for 12 hours, and each of the humanized antibodies hIGF13_PS and hIGF25_PS was administered intravenously as a single dose at 10 mg/kg. Guinea pigs were fasted until 24 hours after administration. Blood samples were taken from the guinea pigs awake before (0 h), 1, 2, 4, 8, 24, 48, 72, and 144 h after the administration, and their blood glucose levels were measured using a Glutest sensor (Sanwa Kagaku Kenkyusho). The results are shown in FIGS. 3A and B.

[0292] Neither of the humanized antibodies showed any significant difference in the blood glucose levels compared to the solvent control group, which received only solvent, and the blood glucose levels after administration were all above 50 mg/dL. This indicates that each humanized antibody does not have a significant hypoglycemic effect like IGF-1, and does not affect blood glucose levels, indicating its potential as a drug to overcome hypoglycemia, which is a side effect of IGF-1.

[Example 14] Hemodynamics of the Humanized Antibodies in Guinea Pigs

[0293] Guinea pigs were fasted for 12 hours, and each of the humanized antibodies hIGF13_PS and hIGF25_PS or IGF11-16 (mouse parent antibody) was administered intravenously in a single doses at 1 or 10 mg/kg. Guinea pigs

were fasted until 24 hours after the administration, at which time they were re-fed. Blood samples were taken from the guinea pigs awake before (0 h), 2, 4, 8, 24, 48, 72, 96, 120, and 144 h after the administration, and the concentration of the humanized antibody in plasma was measured by ELISA. [0294] Specifically, recombinant IGF-1R (manufactured by R&D SYSTEMS) was used, and the measurement was made by antigen ELISA. A calibration curve for quantification of each antibody administered to guinea pigs was prepared by diluting the antibody of a known concentration serially with guinea pig plasma to form a series of standards. Both the standards and the plasma samples were diluted 10 to 1000 times to perform the measurement.

[0295] A PBS solution of 0.5 µg/mL of the recombinant IGF-1R was added to a 96-well plate (MaxiSorp (NUNC)) and fixed at 4° C. overnight. Further blocking with 3% BSA/PBS was performed to prepare a recombinant-IGF-1R fixed plate. On the other hand, plasma from a guinea pig to which no antibody was administered was used for diluting each administered antibody serially to prepare a series of standards. Each of the plasma samples and the standards was diluted 10-fold and added to the recombinant-IGF-1R fixed plate at 50 µL/well. The reaction was carried out for 1 hour and 30 minutes at room temperature, followed by washing operation with PBS-T (PBS, 0.025% Tween 20). Subsequently, a solution of alkaline phosphatase-conjugated anti-human IgG (H+L) polyclonal antibody (Southern Biotechnology Associates, Cat. #2087-04) diluted 2000-fold with 3% BSA/PBS was added at 50 µL/well. The cells were reacted for 1 hour at room temperature, after which washing was performed with PBS-T, and 100 µL/well of pNpp (Wako, Cat #149-02342) was added as a chromogenic substrate, and incubated for 1 hour at room temperature. After that, the absorbance was measured at 405 nm and at 550 nm using a plate reader, and the difference between the absorbances at 405 nm and at 550 nm was determined. A calibration curve was drawn over the concentration range of the antibody using the series of standards, and the antibody concentration in each plasma sample was calculated.

[0296] The results are shown in FIG. 4. The plasma concentration of each humanized antibody increased in a dose-dependent manner, and even in the low-dose group, the plasma concentration of the humanized antibody was maintained until 144 hours after the administration at more than 50% of that at 24 hours after the administration. These results indicate that the hemodynamics of the humanized antibodies were more persistent than that of the mouse parent antibody IGF11-16.

[Example 15] Effect of Increasing Muscle Mass in Normal Guinea Pigs by the Humanized Antibodies

[0297] A single intravenous dose of hIGF13_PS was administered to normal guinea pigs, and muscle mass was measured after 2 weeks, and compared with the muscle mass-increasing effect of continuous administration of IGF-1 and intravenous administration of the mouse parent antibody IGF11-16.

[0298] Either hIGF13_PS or the mouse parent antibody IGF11-16 was administered as a single dose at 0.1 mg/kg intravenously to normal guinea pigs. As a positive control, human IGF-1 (mecasermin) was implanted subcutaneously using an osmotic pump (Alzette) and administered continuously at 1 mg/kg/day. As a control, only solvent was administered intravenously. Two weeks after the drug

administration, each guinea pigs was anesthetized and bled to death, the extensor digitorum longus muscle was removed, and the muscle mass was measured.

[0299] The results are shown in FIG. 5. The group to which hIGF13_PS was administered intravenously at 0.1 mg/kg significantly increased the muscle mass compared to the control group treated only with solvent. The drug effect was comparable in intensity to that of the group treated with continuous administration of human IGF-1 at 1 mg/kg/day and that of the group treated with intravenous administration of the mouse parent antibody IGF11-16.

[0300] These results indicate that a single dose of hIGF13_PS can be expected to have a drug effect equivalent to that of 2-week continuous administration of human IGF-1.

[Example 16] Elongation Effect of Growth Plate Cartilage in Hypophysectomized Guinea Pigs by the Humanized Antibodies

[0301] In order to evaluate the proliferation effect of growth plate cartilage by hIGF13_PS, the epiphyseal line thickness of the proximal tibia was evaluated using a guinea pig hypophysectomized (HPX) model. The guinea pig hypophysectomized (HPX) model is in a low IGF-1 state since the production of growth hormone is suppressed due to removal of the pituitary gland.

[0302] A single subcutaneous dose of hIGF13_PS was administered at 0.3 mg/kg or 1.0 mg/kg to hypophysectomized guinea pigs, and the right lower limbs were collected 2 weeks later. Tissue specimens of the growth plate cartilage were prepared from the proximal part of the tibia, and the thickness of the growth plate cartilage (epiphyseal thickness) was measured with toluidine blue. As a positive control, IGF-1 (mecasermin) preparation was continuously administered subcutaneously at 1 mg/kg/day using osmotic pump, and GH (somatropin) preparation was subcutaneously administered once a day at 1 mg/kg/day.

[0303] The results are shown in FIG. 6. These results indicate that an increase in the epiphyseal thickness was observed in each of the IGF-1 and GH groups, which was caused presumably since the blood IGF-1 level reduced due to HPX was supplemented, or since GH lost due to HPX was supplemented. The hIGF13_PS antibody group was shown to increase the epiphyseal thickness in a dose-dependent manner without increasing the blood IGF-1 levels in hypophysectomized (HPX) individuals.

[0304] These results indicate that the hIGF13_PS antibody is able to restore the occlusion of the epiphyseal line caused by the decrease in the IGF-1 concentration due to hypophysectomizing (HPX) treatment via activation of the IGF-1R-mediated signaling.

[Example 17] Hypoglycemic Effect in Crab-Eating Macaques by the Humanized Antibodies

[0305] In order to confirm whether the anti-IGF-1 receptor agonist antibodies have a hypoglycemic effect on crab-eating macaques, a single dose of hIGF13_PS was administered to crab-eating macaques, the blood glucose levels were measured in succession, and the hypoglycemic effect was compared with that of a single dose of IGF-1 (1 mg/kg). The hypoglycemic effect herein refers to the effect of

lowering the blood glucose level to less than 50% compared to the solvent group or the effect of causing hypoglycemic symptoms.

[0306] Each humanized antibody was administered to crab-eating macaques at 10 mg/kg as a single intravenous or subcutaneous dose. Blood samples were taken before (0 hour), 5 and 30 minutes, and 1, 2, 4, 8, and 24 hours after the administration, and the blood glucose levels were measured using a Medisafe Fit (Terumo Corporation).

[0307] The results are shown in FIG. 7. Each humanized antibody showed no difference in the blood glucose levels compared to the solvent control group, which received only solvent, and all blood glucose levels after administration were at the same level as those of the solvent control group. On the other hand, the IGF-1 group became hypoglycemic after 2 hours and showed hypoglycemic symptoms, so glucose was administered to recover.

[Example 18] Blood Kinetics of the Humanized Antibodies in Crab-Eating Monkeys

[0308] The humanized antibody hIGF13_PS was administered intravenously or subcutaneously as a single dose to crab-eating macaques at 1 or 10 mg/kg. Blood samples were collected before (0 hours), 2, 4, 8, 24, 48, 72, and 144 hours after the administration, and the concentration of humanized antibody in plasma was measured by ELISA.

[0309] Specifically, the measurement was performed by antigen ELISA using recombinant IGF-1R (305-GR-050, R&D SYSTEMS). A calibration curve of each antibody administered to macaques was prepared by diluting a known concentration of the antibody stepwise to prepare a series of standard samples. Each of the standards and the plasma samples was diluted 10- to 1000-fold for measurement.

[0310] A 0.5 µg/mL solution of the recombinant IGF-1R in PBS was added to a 96-well plate (MaxiSorp (NUNC)) and fixed at 4° C. overnight. Further blocking with 3% BSA/PBS was performed to prepare a recombinant-IGF-1R fixed plate. Plasma taken from a macaque to which no antibody was administered was used for diluting the antibody stepwise to prepare a series of standard samples. Each of the plasma samples and the standard samples was diluted 10-fold and added to the recombinant-IGF-1R fixed plate at 50 µL/well. The reaction was carried out for 1 hour and 30 minutes at room temperature, followed by washing operation with PBS-T (PBS, 0.025% Tween 20). Subsequently, a solution of alkaline phosphatase-conjugated anti-human IgG (H+L) polyclonal antibody (Southern Biotechnology Associates, Cat. #2087-04) diluted 2000-fold in 3% BSA/PBS was added at 50 µL/well, and the reaction was allowed to run for 1 hour at room temperature. Subsequently, washing operation was performed with PBS-T, pNpp (Wako, Cat #149-02342) was added as a chromogenic substrate at 100 µL/well, followed by incubation for 1 hour at room temperature. After that, the absorbance was measured at 405 nm and 550 nm with a plate reader, and the difference between the absorbances at 405 nm and at 550 nm was calculated. A calibration curve was drawn over the concentration range of the antibody using the series of standards, and the antibody concentration in each plasma sample was calculated.

[0311] The results are shown in FIG. 8. These results indicate that hIGF13_PS has excellent blood kinetics in crab-eating macaques.

[Example 19] Effect of Increasing the Muscle Mass in Crab-Eating Macaques by the Humanized Antibodies

[0312] Two crab-eating macaques received intravenous administration of mg/kg of hIGF13_PS. The muscle mass was measured by DXA (Dual Energy X-ray Absorptiometry) before and 3-4 weeks after the administration.

[0313] Specifically, the macaques were subjected to general anesthesia by intramuscular administration (buttocks) of ketamine hydrochloride (Arevipharma GmbH, 50 mg/mL, 0.2 mL/kg) and medetomidine hydrochloride solution (Domitor, Orion Corporation, 1 mg/mL, 0.08 mL/kg). A dual-energy X-ray absorptiometry system (Discovery-A, HOLOGIC) was used to measure the fat mass (g), lean body mass (Lean) (g), and bone mineral content (BMC) (g), and the lean body mass was analyzed as the muscle mass. BMC (bone mineral content) and Lean+BMC (g) of the right and left arms (upper limbs) were measured, and the muscle mass (g) was calculated and compared to that before administration.

[0314] As a result, both animals showed an increase in the muscle mass compared to the measurement before administration, and the muscle gain rate of the upper limbs was 7.4% and 10.9%, respectively, compared to the values before administration. These results confirm the muscle gaining effect of hIGF13_PS.

[0315] In addition, hIGF13_PS was subcutaneously administered to two crab-eating macaques at 10 mg/kg. Muscle mass was measured by DXA (Dual Energy X-ray Absorptiometry) before and 3 to 4 weeks after the administration.

[0316] Specifically, the macaques were subjected to general anesthesia by intramuscular administration (buttocks) of ketamine hydrochloride (Arevipharma GmbH, 50 mg/mL, 0.2 mL/kg) and medetomidine hydrochloride solution (Domitor, Orion Corporation, 1 mg/mL, 0.08 mL/kg). A dual-energy X-ray absorptiometry system (Discovery-A, HOLOGIC) was used to measure the fat mass (g), lean body mass (Lean) (g), and bone mineral content (BMC) (g), and the lean body mass was analyzed as the muscle mass. BMC (bone mineral content) and Lean+BMC (g) of the right and left lower limbs were measured, and the muscle mass (g) was calculated and compared to that before administration.

[0317] As a result, both animals showed an increase in the muscle mass compared to the measurement before administration, and the muscle gain rate of the lower limbs was 3.3% and 12.7%, respectively, compared to the values before administration. These results confirm the muscle gaining effect of hIGF13_PS.

[Example 20] Effect of IGF11-16 on HepG2 Cell Proliferation

[0318] The concentration-dependent effect of the mouse parent antibody IGF11-16 on HepG2 cell proliferation was evaluated by cell survival assay.

[0319] HepG2 cell line was suspended in DMEM (Gibco, 11995) with 1% FBS and seeded in a collagen-I coated 96-well plate (Corning, 356650) at 0.25×10^4 cells/well. The next day, each of BSA/PBS, IGF-1 (mecasermine), control mouse IgG1 antibody (mIgG1), IGF11-16 antibody, and cixutumumab (IGF-1 receptor antagonist antibody) diluted from 50 nM at a constant ratio of $1/10$ was added to the plate. After 2 days, the amount of ATP in the cells was determined

as an indicator of cell proliferation by measuring the luminescence signal with a multi-detection mode microplate reader (SPARK, TECAN) by CellTiter-Glo® Luminescent Cell Viability Assay (Promega, G7571). The measurement obtained for the control mouse IgG1 antibody (mIgG1) at each concentration point was set at 100%, and each measurement obtained for the other samples at each concentration point was calculated in the unit of % of Control, and plotted on a graph (FIG. 9).

[0320] The results indicated that the mouse parent antibody IGF11-16 has an inhibitory effect on HepG2 cell proliferation, suggesting that IGF11-16 has an antagonist effect on at least some types of cancer cells.

[Example 21] Effect of IGF11-16 on the Proliferative Activity of Human Breast Cancer Cell Line (MCF7) Induced by IGF-1

[0321] In order to evaluate the effect of IGF11-16 on the proliferative activity of human breast cancer cell line (MCF7) induced by IGF-1, the concentration-dependent proliferative activity of hIGF-1 (Mecacervin) in the presence of 50 nM IGF11-16 was measured based on the amount of ATP in the cells 2 days after the addition.

[0322] Human breast cancer cell line (MCF7) was cultured in DMEM/F12 medium containing 10% FBS. The next day, the cells were seeded at 0.1 mL/well (2.5×10^4 cells/well) in 96-well plates (Collagen-type I coated) using DMEM/F12 medium containing 10% FBS, and incubated at 37°C with 5% CO₂. The day after cell seeding, the medium was changed to DMEM/F12 medium containing 1% BSA, and the culture was incubated at 37°C and 5% CO₂ for about 8 hours. Subsequently, 50 nM of 0.1% BSA/PBS or the IGF11-16 antibody was added, and a series of IGF-1 diluted sequentially from 50 nM at a common ratio of 1/10 was added, and the culture was incubated for 2 days at 37°C with 5% CO₂. The amount of intracellular ATP was

measured as an indicator of cell proliferation by using the CellTiter-Glo (registered trademark) Luminescent Cell Viability Assay (Promega, G7571), and detecting the luminescence signal with a multi-detection mode microplate reader (SPARK, TECAN). For each concentration of IGF-1, the mean value of the group with 0.1% BSA/PBS was set as 100%, and the change in the group with 50 nM IGF11-16 was expressed by calculating the % of Control. The results are shown in Table 17.

TABLE 17

	IGF-1 alone	with 50 nM IGF11-16
0.5 nM IGF-1	100%	67%
5 nM IGF-1	100%	67%
50 nM IGF-1	100%	74%

[0323] The results indicated that the mouse parental antibody IGF11-16 had an inhibitory effect on reducing the maximum activity of IGF-1 on human breast cancer cell line (MCF7). These results suggest that IGF11-16 has an allosteric antagonist effect.

INDUSTRIAL APPLICABILITY

[0324] The present invention can provide anti-IGF-1 receptor humanized antibodies that specifically bind to vertebrate IGF-1 receptors and increase the muscle mass via the IGF-1 receptors without decreasing the blood glucose levels, and thus can be used in the treatment, prevention, or diagnosis of IGF-1 receptor-related disorders. The present invention can also be used in the treatment, prevention, or diagnosis of diseases related to abnormal cell proliferation or activation by suppressing excessive signaling of IGF-1 receptors. Therefore, the present invention has extremely high industrial value.

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR-L3

<400> SEQUENCE: 13

Leu Gln Gly Gln Ser Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 14
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR-L3

<400> SEQUENCE: 14

ctccaaaggcc agtccctaccc ttacaca

27

-continued

```

<210> SEQ ID NO 15
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH1

<400> SEQUENCE: 15

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65          70          75          80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100         105         110

Val Thr Val Ser Ser
115

```

```

<210> SEQ ID NO 16
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH1

<400> SEQUENCE: 16

caagttcagc tggtgccagtc cggcgctgag gtgaagaagc cccgcgcctc cgtgaaggtg      60
tcttgtaagg cctccggcta caccttcacc tcctactggaa tgcactgggt gaggcaagct      120
cccggtcaag gtttagatgt gatggggcag accaaccctt ccaactccgt gaccaactac      180
gcccagaagt tccaaggctcg tgcacttta accgtggaca cctccacccctc caccgcctac      240
atggagctgt cctcttaag gtccgaggac accgcccgtgt actactgtac catcggtcgt      300
ggccggggct ttgcttattg gggacaaggt acttttagtga ccgtgacgac c      351

```

```

<210> SEQ ID NO 17
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH2

<400> SEQUENCE: 17

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

```

-continued

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 18
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH2

<400> SEQUENCE: 18

caagttcagc tgggtgcagtc cggcgctgag gtgaagaagc cccggcgccctc cgtgaaggtg	60
tcttgttaagg cctccggcta caccttcacc tcctactgga tgcactgggt gaggcaagct	120
cccggtcaag gtttagatgt gatggggcag accaaccctt ccaactccgt gaccaactac	180
gcccagaagt tccaaggctcg tgtgacttta accgtggaca cctccacctc caccgcctac	240
atggagctgt ccttttaag gtccgaggac accgccaccc actactgtac catcggtcgt	300
ggccggggct ttgcttattt gggacaaggt acttttagtga ccgtgagcag c	351

<210> SEQ ID NO 19
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW2_VH1

<400> SEQUENCE: 19

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 20
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW2_VH1

-continued

<400> SEQUENCE: 20

```
caagttcagc tggtgcagtc cggcgctgag gtgaagaagc cggcgtccctc cgtgaaggtg      60
tcttgtttaagg cctccggctta caccttcacc tcctactgga tgcactgggt gaggcaagct     120
cccggtcaag gtttagagtg gatggggcag accaaccctt ccaactccgt gaccaactac     180
gcccagaagt tccaaggctcg tgtgacttta accgtggaca agtccacctc caccgcctac     240
atggagctgt cctctttaag gtccgaggac accggcgtgt actactgtac catcggtcgt     300
ggccggggct ttgcttattt gggacaaggt actttagtga ccgtgagcag c             351
```

<210> SEQ_ID NO 21
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VL1

<400> SEQUENCE: 21

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1															15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asn	Ile	Asn	Phe	Trp
															30
Leu	Ser	Trp	Cys	Gln	Gln	Lys	Pro	Gly	Lys	Ile	Pro	Lys	Leu	Ile	
Tyr	Lys	Ala	Ser	Asn	Leu	His	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
															60
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
															80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Gly	Gln	Ser	Tyr	Pro	Tyr
															95
Thr	Phe	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
100															

<210> SEQ_ID NO 22
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VL1

<400> SEQUENCE: 22

```
gacatccaga tgacacagtc ccccaagtcgtcc gtgtccgctta gcgtgggaga cgggggtgacc      60
attacttgtc gggcctccca gaacatcaac ttctgggtca gctgggtcgtca gcagaaggccc     120
ggcaagatcc ccaagttatt aatctacaag gccagcaatt tacacaccgg agtgccttct     180
cggttctccg gcagcggcag cgaaaccgac ttcaactttaa ccatctccctc tttacagccc     240
gaggacttcg ccacctaacta ttgtttacaa ggtcagtcgt atccctacac cttcggccgc     300
ggaaccaagt tagaaatcaa g                         321
```

<210> SEQ_ID NO 23
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VL3

-continued

<400> SEQUENCE: 23

```

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

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

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

Tyr Lys Ala Ser Asn Leu His Thr 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 Leu Gln Gly Gln Ser Tyr Pro Tyr
85          90          95

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

```

<210> SEQ ID NO 24

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL3

<400> SEQUENCE: 24

```

gacatccaga tgactcagag cccttcctcc gtcagcgctt ccgtgggaga tagggtgact      60
atcaacttgta gggcctccca gaacatcaac ttctggctga gctggtatca gcagaagccc     120
ggcaaagccc ctaagctgct gatctacaag gctagcaatc tgcacactgg cgtcccttcc     180
agattcagcg gtcggcag cgccactgac ttcaactctca caatcagctc tctgcagcca     240
gaggacttcg ctacatacta ctgcctccaa ggccagtct atccttacac attcggaggc     300
ggcacaaaagc tggagatcaa g                                         321

```

<210> SEQ ID NO 25

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL4

<400> SEQUENCE: 25

```

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

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

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

Tyr Lys Ala Ser Asn Leu His Thr 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 Leu Gln Gly Gln Ser Tyr Pro Tyr
85          90          95

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

```

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<210> SEQ ID NO 26
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VL4

<400> SEQUENCE: 26

gacatccaga tgactcagag cccttcctcc gtcagcgctt ccgtggaga tagggtgact      60
atcaacttgta gggcctccca gaacatcaac ttctggctga gctggtatca gcagaagccc     120
ggcaaagccc ctaggctgct gatctacaag gctagcaatc tgcacactgg cgtcccttcc     180
agattcagcg gtcggcggcag cggcactgac ttcaactctca caatcagctc tctgcagcca     240
gaggacttcg ctacatacta ctgcctccaa ggccagtcct atccttacac attcggaggc     300
ggcacaaaagc tggagatcaa g                                         321

<210> SEQ ID NO 27
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW2_VL2

<400> SEQUENCE: 27

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 Asn Ile Asn Phe Trp
20          25          30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ile Pro Lys Leu Leu Ile
35          40          45
Tyr Lys Ala Ser Asn Leu His Thr 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 Val Ala Thr Tyr Tyr Cys Leu Gln Gly Gln Ser Tyr Pro Tyr
85          90          95
Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
100         105

<210> SEQ ID NO 28
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW2_VL2

<400> SEQUENCE: 28

gatatccaga tgactcagag cccaaatctt ctgagcgta gcgtggaga tagggtcaca      60
atcaacttgta gggcctccca gaacatcaac ttctggctca gctggatcca gcagaaaccc     120
ggcaagatcc ctaagctgct gatctacaag gccagcaacc tccacactgg agtcccatct     180
aggtttagcg gatccggcag cggaaactgac ttcaactctca caatcagctc tctgcagcca     240
gaggacgtgg ctacatacta ctgcctccaa ggccagtcctt acccttacac attcggggc     300
ggcacaaaac tggagatcaa g                                         321

```

-continued

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<210> SEQ ID NO 29
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH1_mH1

<400> SEQUENCE: 29

Gln Ile Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1           5          10          15

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65          70          75          80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100         105         110

Val Thr Val Ser Ser
115

```

```

<210> SEQ ID NO 30
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH1_mH1

<400> SEQUENCE: 30

cagattcagc tgcagcagcc cggcgctgaa ctgggtgaaac cggcgccctc cgtgaaaactc      60
agctgttaagg ccccccggcta cactttcaca tcctactggaa tgcactgggt gagacaagcc      120
cccgcccaag gactggagtg gatggggcag acaaacccta gcaactccgt cactaactac      180
gcccaagaat tccaaggaag ggtgactctc acagtggaca ctagcacatc cacagcctac      240
atggaactgt ccagcctcag atccgaggac actgctgtgt actactgcac aatcgccaga      300
ggaaggggat tcgcttactg gggccaaggc acactcgtga ctgtcagctc c      351

```

```

<210> SEQ ID NO 31
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FW1_VH1_mH2

<400> SEQUENCE: 31

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

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

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35          40          45

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

```

-continued

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 32

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VH1_mH2

<400> SEQUENCE: 32

caagtgcagc tcgtccaaag cggcgctgaa gtgaagaaac ccggcgccag cgtgaaggc	60
agctgcaaag cctccggcta cacattcaca tcctactgga tgcactgggt caagcagagg	120
cccgccaag gactggagt gatcgccgaa acaaaccctt ccaacagcgt cactaactac	180
gcccagaagt ttcaaggaag ggtgacactg actgtcgaca cttagcactag cactgcctat	240
atggagctga gctctctgag gagcgaggac actgccgtt attactgcac tatcggaagg	300
ggcagaggat tcgcctactg gggccaaggc actctcgta cagtcagcag c	351

<210> SEQ ID NO 33

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VH1_mH3

<400> SEQUENCE: 33

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> SEQ ID NO 34

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VH1_mH3

-continued

<400> SEQUENCE: 34

```
caagtgaac tggcgtcagtc cggcgccgag gtgaagaagc cggcgccag cgtgaaggtg      60
agctgttaag ccagcgcccta cacattcaca tcctactgga tgcactgggt gagacaagcc     120
cccgccaaag gactggagtg gatggggcga actaacccctt ccaacagcgt cacaatttat     180
gttcagaaat tccagggaaag ggtgacactg acagtcgaca aaagcagcag cacagccat     240
atgcagctga gctctctgac tagcggggac tccggcgtgt actactgcac aatttggaaagg    300
ggcagaggat tcgcctactg gggacaaggc actctggtga cagtcagcgc c             351
```

<210> SEQ ID NO 35

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL3_mL1

<400> SEQUENCE: 35

```
Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1           5           10          15

Asp Thr Ile Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asn Phe Trp
20          25          30

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

Tyr Lys Ala Ser Asn Leu His Thr 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 Leu Gln Gly Gln Ser Tyr Pro Tyr
85          90          95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100         105
```

<210> SEQ ID NO 36

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL3_mL1

<400> SEQUENCE: 36

```
gacatccaga tgaatcagag cccttcctcc ctctccgttt ctctggcgaa cacaatcaca     60
atcaacttgta gggcccgcca gaacatcaac ttctggctga gctggtagcc gcaaaagccc    120
ggcaaaagccc ctaagctgct gatttacaag gcctccaacc tccacactgg agtgcctagc    180
agattctccg gcagcggcag cgaaacagac ttcaactctca caatcagctc tctgcagcca    240
gaggacttcg ctacatacta ctgcctccaa ggccagtcct atccttacac attcggccgc    300
ggcactaaggc tggagatcaa g                           321
```

<210> SEQ ID NO 37

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL3_mL2+L3

-continued

<400> SEQUENCE: 37

```

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

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

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

Tyr Lys Ala Ser Asn Leu His Thr 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 Ile Ala Thr Tyr Tyr Cys Leu Gln Gly Gln Ser Tyr Pro Tyr
85          90          95

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

```

<210> SEQ ID NO 38

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FW1_VL3_mL2+L3

<400> SEQUENCE: 38

```

gacattcaga tgacacagtc cccaaagctcc gtgtccgcta gcgtcgagaa cagagtgaca      60
atcacatgta gggcttagcca gaacatcaac ttctggctga gctggtagcc gcagaaggccc    120
ggcaacatcc ctaagctgct gatctacaag gcctccaatc tgcacactgg cgtgccttagc    180
agattcagcg gatccggctc cggaactgac ttcaactctca caatcagctc tctgcagcc     240
gaggacatcg ctacatacta ctgcctccaa ggccagagct atccttacac attcggaggc     300
ggcacaaaagc tggagatcaa g                                         321

```

<210> SEQ ID NO 39

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: IGF11-16_VH

<400> SEQUENCE: 39

```

Gln Ile Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1           5           10          15

```

```

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

```

```

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35          40          45

```

```

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Asn Glu Lys Phe
50          55          60

```

```

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

```

```

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

```

```

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100         105         110

```

-continued

Val Thr Val Ser Ala
115

<210> SEQ ID NO 40
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGF11-16_VH

<400> SEQUENCE: 40

cagatccaggc	tgcagcagcc	cggtgcttag	ctggtaagc	ccgggtccag	cgtaaagt	60
tctttaagg	ccccgggta	cacttcaca	agctactgg	tgcactgggt	caagcagaga	120
cccggtcaag	gtttagaatg	gatcggcgaa	acaaatcctt	ccaacagcgt	gacaaactat	180
aacgagaagt	tcaagagcaa	ggctactctg	actgtggaca	agagcagcag	cactgcctat	240
atgcagctgt	cctctttaac	aagcgaggac	agcgccgtgt	actactgtac	aatcggtcgt	300
ggtcgtggat	ttgcctactg	gggacaaggt	acactggta	cagtgtccgc	c	351

<210> SEQ ID NO 41
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGF11-16_VL

<400> SEQUENCE: 41

Asp	Ile	Gln	Met	Asn	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Leu	Gly
1							5		10					15	
Asp	Thr	Ile	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asn	Ile	Asn	Phe	Trp
							20		25					30	
Leu	Ser	Trp	Cys	Gln	Gln	Lys	Pro	Gly	Asn	Ile	Pro	Lys	Leu	Leu	Ile
						35		40				45			
Tyr	Lys	Ala	Ser	Asn	Leu	His	Thr	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	Ile	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Gly	Gln	Ser	Tyr	Pro	Tyr
					85		90						95		
Thr	Phe	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
					100		105								

<210> SEQ ID NO 42
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGF11-16_VL

<400> SEQUENCE: 42

gacatccaga	tgaatcagag	ccctagctct	ttaagcgcct	ctttaggaga	cactatcact	60
atcacttgta	ggcccgccca	gaacatcaac	ttctggctga	gctggtgccca	gcagaagccc	120
ggtaaacatcc	caaagctgct	gatctacaaa	gccagcaatt	tacacactgg	tgtccctct	180
cgttttagcg	gctccggcag	cggcacagac	ttcactctga	caatctccctc	tttacagcca	240
gaggacatcg	ccacttacta	ctgtttacaa	ggtcagagct	acccttacac	ttttggccgc	300

-continued

ggcactaac tggagatcaa g 321

```

<210> SEQ ID NO 43
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH13_PN

<400> SEQUENCE: 43

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

```

```
<210> SEQ ID NO 44
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH13_PN

<400> SEQUENCE: 44

caagtgcagc tgggcccgaa gtaaaaaagc cggccgcctc cgtcaaagtc 60
agctgcaagg cccctggcta cacccacc tcctactgga tgcactgggt gaggcaagct 120
cccggtcaag gtttagatgt gatggggcag accaaccctt ccaactccgt gaccaactac 180
gcccaagaat tccaaggctcg tgtgacttta accgtggaca cttccaccc taccggctac 240
atggagatgt cctctttaag gtccgaggac accggccacct actactgtac catcggtcg 300
ggccggggact ttgtttatgt gggtacaaaggat acttttgtaa ccgtggccggc 351
```

```

<210> SEQ ID NO 45
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH13_PQ

<400> SEQUENCE: 45

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

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

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

```

-continued

Gly Glu Thr Asn Pro Ser Gln Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 46

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH13_PQ

<400> SEQUENCE: 46

```
caagtgcagc tggtccagag cggagccgaa gtaaaaaggc cggcgccctc cgtcaaagtc      60
agctgcaagg cccctggcta caccttacc tcctactggta tgcaactgggt gaggcaagct     120
cccggtcaag gtttagatgt gatgggcgag accaaccctt cccagtcgtt gaccaactac     180
gcccgagaat tccaaggctcg tttttttttt accgtggaca cttccaccc tcaccgttac     240
atggagctgt cttttttttttt gtcggaggac accggccacctt actactgttcatcggttgt    300
ggccgggggtt ttgtttttttt gggacaaggat acatgttgc cccgttgcacacacacacac   351
```

<210> SEQ ID NO 47

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH13_PS

<400> SEQUENCE: 47

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

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

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

Gly Glu Thr Asn Pro Ser Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 48

<211> LENGTH: 351

<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH13_PS

<400> SEQUENCE: 48

```
caagtccaac tggtccagtc cggagccgaa gtgaagaaac ccggcgctag cgtcaaggc       60
agctgttaagg ccccccggcta cacattcaact agctactggaa tgcaactgggt gaggcaagcc   120
cccgcccaag gactggagtg gatggggcga acaaacccaa gcagctccgt cactaactac     180
gcccagaagt ttcaaggaag ggtgactctc acagtggaca catccacaag cactgcctat     240
atggagctca gtccttcag aagcgaggat acagccactt actactgcac tatcggaagg     300
ggaaggggat tcgcttactg gggccaaggc acactggtca cagtcagctc c               351
```

<210> SEQ ID NO 49

<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH23_PN

<400> SEQUENCE: 49

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50           55           60

Gln Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65           70           75           80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100          105          110

Val Thr Val Ser Ser
115
```

<210> SEQ ID NO 50

<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH23_PN

<400> SEQUENCE: 50

```
caagtgcagc tggtccagag cggagccgaa gtaaaaaaagc ccggcgccctc cgtcaaagtc       60
agctgcaagg cccctggcta cacattcacc tcctactggaa tgcaactgggt gaggcaagct    120
cccggtcaag gtttagagtg gatggggcag accaaccctt ccaactccgt gaccaactac     180
gcccagaagt tccaaaggctc tggacttta accgtggaca agtccacctc caccgcctac     240
atggagctgt cctctttaag gtccgaggac accggccgtgt actactgtac catcggtcgt    300
ggccggggct ttgcttattt gggacaaggat acttttagtga ccgtgagcag c               351
```

<210> SEQ ID NO 51

-continued

```

<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH23_PQ

<400> SEQUENCE: 51

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

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

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

Gly Glu Thr Asn Pro Ser Gln Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

Gln Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65          70          75          80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100         105         110

Val Thr Val Ser Ser
115

```

```

<210> SEQ ID NO 52
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH23_PQ

<400> SEQUENCE: 52

caagtgcagc tggtcacagcg cggagccgaa gtgaaaaaagc ccggcgccctc cgtcaaagtc       60
agctgcaagg cccctggcta caccttacc tcctactggta tgcactgggt gaggcaagct      120
cccggtcaag gtttagagtgc gatgggcgag accaaccctt cccagtcgtt gaccaactac      180
gcccagaagt tccaagggtcg tggacttta accgtggaca agtccacccctc caccgcctac      240
atggagctgt cctcttaag gtccgaggac accggccgtgt actactgtac catcggtcg      300
ggccggggct ttgcttattt gggacaaggat actttagtgc ccgtgagcagc      351

```

```

<210> SEQ ID NO 53
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH23_PS

<400> SEQUENCE: 53

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

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

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

Gly Glu Thr Asn Pro Ser Ser Val Thr Asn Tyr Ala Gln Lys Phe
50          55          60

```

-continued

Gln Gly Arg Val Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 54

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH23_PS

<400> SEQUENCE: 54

caagtccaaac tggtccagtc cggagccgaa gtgaagaaac cccgcgttag cgtcaaggtc	60
agctgttaagg ccccccggcta cacattcaact agctactggaa tgcactgggt gaggcaagcc	120
cccgcccaag gactggagtg gatgggcgaa acaaacccaa gcagctcgt cactaactac	180
gccccagaagt ttcaaggaag ggtgactctc acagtggaca agtccacaag cactgcctat	240
atggagctca gtccttcag aagcgaggat acagccgtgt actactgcac tatcggaagg	300
ggaaggggat tcgcttactg gggccaaggc acactggtca cagtcagctc c	351

<210> SEQ ID NO 55

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH25_PN

<400> SEQUENCE: 55

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

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

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

Gly Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 56

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH25_PN

-continued

<400> SEQUENCE: 56

```
caagtgcagc tggccagag cggagccgaa gtaaaaaagc cggcgccctc cgtcaaagtc      60
agctgcaagg cccctggcta cacccacc tacactggta tgcactgggt gaggcaagct      120
ccccgtcaag gtttagagtg gatgggcag accaaccctt ccaactccgt gaccaactac      180
ccccagaagt tccaaggctcg tgcactttt accgtggaca cctccaccc caccgcctac      240
atggagctgt ctccttaag gtccgaggac accgcgtgt actactgtac catcggtcgt      300
ggccggggct ttgcttattt gggacaaggacttttagtga ccgtgagcag c            351
```

<210> SEQ ID NO 57

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH25_PQ

<400> SEQUENCE: 57

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1															

5	10	15
---	----	----

Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Pro	Gly	Tyr	Thr	Phe	Ser	Tyr
20														

25	30
----	----

Trp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
35															

35	40	45
----	----	----

Gly	Glu	Thr	Asn	Pro	Ser	Gln	Ser	Val	Thr	Asn	Tyr	Ala	Gln	Lys	Phe
50															

50	55	60
----	----	----

Gln	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
65															

65	70	75	80
----	----	----	----

Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
85															

85	90	95
----	----	----

Thr	Ile	Gly	Arg	Gly	Arg	Gly	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu
100															

100	105	110
-----	-----	-----

Val	Thr	Val	Ser	Ser

115

<210> SEQ ID NO 58

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH25_PQ

<400> SEQUENCE: 58

```
caagtgcagc tggccagag cggagccgaa gtaaaaaagc cggcgccctc cgtcaaagtc      60
agctgcaagg cccctggcta cacccacc tacactggta tgcactgggt gaggcaagct      120
ccccgtcaag gtttagagtg gatgggcag accaaccctt ccaactccgt gaccaactac      180
ccccagaagt tccaaggctcg tgcactttt accgtggaca cctccaccc caccgcctac      240
atggagctgt ctccttaag gtccgaggac accgcgtgt actactgtac catcggtcgt      300
ggccggggct ttgcttattt gggacaaggacttttagtga ccgtgagcag c            351
```

<210> SEQ ID NO 59

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: VH25_PS

<400> SEQUENCE: 59

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

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

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

Gly Glu Thr Asn Pro Ser Ser Ser Val Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Val Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 60

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH25_PS

<400> SEQUENCE: 60

caagtccaaac tggtccagtc cggagccgaa gtgaagaaac ccggcgctag cgtcaaggc 60
agctgttaagg ccccccggcta cacattcaact agctactggaa tgcactgggt gaggcaagcc 120
cccgccaaag gactggagtg gatggggcgaa acaaacccaa gcagctccgt cactaactac 180
gcccaagaat ttcaaggaag ggtgactctc acagtggaca catccacaag cactgcctat 240
atggagctca gtccttcag aagegaggat acagccgtgt actactgcac tatcgaaagg 300
ggaaggggat tcgcttactg gggccaaggc acactggtca cagtcagctc c 351

<210> SEQ ID NO 61

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VL13

<400> SEQUENCE: 61

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

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

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

Tyr Lys Ala Ser Asn Leu His Thr 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 Leu Gln Gly Gln Ser Tyr Pro Tyr

-continued

85

90

95

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

<210> SEQ ID NO 62
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL13

<400> SEQUENCE: 62

gacatccaga tgactcagag cccttcctcc gtcagcgctt ccgtgggaga tagggtgact	60
atcaacttgta gggcctccca gaacatcaac ttctggctga gctggtatca gcagaaggccc	120
ggcaaagccc ctaagctgct gatctacaag gctagcaatc tgcacactgg cgtcccttcc	180
agattcagcg gtcccggcag cgccactgac ttcaactctca caatcagctc tctgcagcca	240
gaggacttcg ctacatacta ctgcctccaa ggccagtctt atccttacac attcggaggc	300
ggcacaaagc tggagatcaa g	321

<210> SEQ ID NO 63
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL14

<400> SEQUENCE: 63

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

<210> SEQ ID NO 64
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL14

<400> SEQUENCE: 64

gacatccaga tgactcagag cccttcctcc gtcagcgctt ccgtgggaga tagggtgact	60
atcaacttgta gggcctccca gaacatcaac ttctggctga gctggtatca gcagaaggccc	120
ggcaaagccc ctaggctgct gatctacaag gctagcaatc tgcacactgg cgtcccttcc	180
agattcagcg gtcccggcag cgccactgac ttcaactctca caatcagctc tctgcagcca	240

-continued

```
gaggacttcg ctacatacta ctgcctccaa ggccagtcct atccttacac attcgaggc      300
ggcacaaaagc tggagatcaa g                                         321
```

```
<210> SEQ ID NO 65
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL22
```

```
<400> SEQUENCE: 65
```

```
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 Asn Ile Asn Phe Trp
20          25          30
```

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

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

```
Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
100         105
```

```
<210> SEQ ID NO 66
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL22
```

```
<400> SEQUENCE: 66
```

```
gatatccaga tgactcagag cccaaagtct ctgagcgcta gcgtcgaaaa tagggtcaca      60
atcaacttgc gggcctccaa gaacatcaac ttctggctca gctggtagca gcagaaaaacc      120
ggcaagatcc ctaagctgct gatctacaag gccagcaacc tccacactgg agtcccatct      180
aggtttagcg gatccggcag cggaactgac ttcactctca caatcagctc tctgcagcca      240
gaggacgtgg ctacatacta ctgcctccaa ggccagtcct acccttacac attcgccggc      300
ggcacaaaac tggagatcaa g                                         321
```

```
<210> SEQ ID NO 67
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VL23
```

```
<400> SEQUENCE: 67
```

```
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 Asn Ile Asn Phe Trp
20          25          30
```

```
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35          40          45
```

-continued

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

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

<210> SEQ ID NO 68

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VL23

<400> SEQUENCE: 68

gatatccaga tgactcagag cccaaagctct ctgagcgcta gcgtcgaaaa tagggtcaca	60
atcaacttgcata gggcctccca gaacatcaac ttctggctca gctggatcca gcagaaaccc	120
ggcaagggtcc ctaagctgct gatctacaag gccagcaacc tccacactgg agtccccatct	180
agggttagcg gatccggcag cggaactgac ttcaactctca caatcagctc tctgcagcca	240
gaggacgtgg ctacatacta ctgcctccaa ggccagtcct acccttacac attcggccgc	300
ggcacaaaac tggagatcaa g	321

<210> SEQ ID NO 69

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VL24

<400> SEQUENCE: 69

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 Asn Ile Asn Phe Trp
20 25 30

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

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

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

<210> SEQ ID NO 70

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VL24

<400> SEQUENCE: 70

gatatccaga tgactcagag cccaaagctct ctgagcgcta gcgtcgaaaa tagggtcaca	60
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- continued

atcaacttgtta	gggcctccca	gaacatcaac	ttctggctca	gctggatcca	gcagaaaacc	120
ggcaagggtcc	ctaaagtgtc	gatctacaag	gccagcaaca	ggcacactgg	agtcccattct	180
aggttttagcg	gatccggcag	cggaaactgac	ttcactctca	caatcagtc	tctgcagcca	240
gaggacgtgg	ctacatacta	ctgcctccaa	ggccagtcct	acccttacac	attcggcgcc	300
ggcacaaaac	tggagatcaa	g				321

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<210> SEQ ID NO 71
<211> LENGTH: 1367
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(1367)
<223> OTHER INFORMATION: Homo sapiens IGF-I receptor
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<400> SEQUENCE: 71

Met Lys Ser Gly Ser Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu
1 5 10 15

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile
20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
 35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
50 55 60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
65 70 75 80

Ile	Thr	Glu	Tyr	Leu	Leu	Leu	Phe	Arg	Val	Ala	Gly	Leu	Glu	Ser	Leu
				85					90				95		

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
100 105 110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile
 115 120 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu
130 135 140

Lys	Asn	Ala	Asp	Leu	Cys	Tyr	Leu	Ser	Thr	Val	Asp	Trp	Ser	Leu	Ile
145					150					155					160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
165 170 175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys
180 185 190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
195 200 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys
310 315 320

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser
 225 226 227 228 229 230 231 232 233 234 235 236 237 238

Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr

Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala

275 280 285

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Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met
 290 295 300
 Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr
 305 310 315 320
 Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Lys
 325 330 335
 Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly
 340 345 350
 Cys Thr Ile Phe Lys Gly Asn Leu Ile Asn Ile Arg Arg Gly Asn
 355 360 365
 Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val
 370 375 380
 Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser
 385 390 395 400
 Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly
 405 410 415
 Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp
 420 425 430
 Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe
 435 440 445
 Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu
 450 455 460
 Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
 465 470 475 480
 Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
 485 490 495
 Ser Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
 500 505 510
 Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
 515 520 525
 Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
 530 535 540
 Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
 545 550 555 560
 Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
 565 570 575
 Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
 580 585 590
 His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
 595 600 605
 Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
 610 615 620
 Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
 625 630 635 640
 Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
 645 650 655
 Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
 660 665 670
 Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
 675 680 685

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Thr	Glu	Val	Cys	Gly	Gly	Glu	Lys	Gly	Pro	Cys	Cys	Ala	Cys	Pro	Lys
690				695			700								
Thr	Glu	Ala	Glu	Lys	Gln	Ala	Glu	Lys	Glu	Ala	Glu	Tyr	Arg	Lys	
705				710			715								720
Val	Phe	Glu	Asn	Phe	Leu	His	Asn	Ser	Ile	Phe	Val	Pro	Arg	Pro	Glu
	725						730								735
Arg	Lys	Arg	Arg	Asp	Val	Met	Gln	Val	Ala	Asn	Thr	Thr	Met	Ser	Ser
	740						745								750
Arg	Ser	Arg	Asn	Thr	Thr	Ala	Ala	Asp	Thr	Tyr	Asn	Ile	Thr	Asp	Pro
	755						760								765
Glu	Glu	Leu	Glu	Thr	Glu	Tyr	Pro	Phe	Phe	Glu	Ser	Arg	Val	Asp	Asn
	770						775								780
Lys	Glu	Arg	Thr	Val	Ile	Ser	Asn	Leu	Arg	Pro	Phe	Thr	Leu	Tyr	Arg
	785						790								800
Ile	Asp	Ile	His	Ser	Cys	Asn	His	Glu	Ala	Glu	Lys	Leu	Gly	Cys	Ser
	805							810							815
Ala	Ser	Asn	Phe	Val	Phe	Ala	Arg	Thr	Met	Pro	Ala	Glu	Gly	Ala	Asp
	820						825								830
Asp	Ile	Pro	Gly	Pro	Val	Thr	Trp	Glu	Pro	Arg	Pro	Glu	Asn	Ser	Ile
	835						840								845
Phe	Leu	Lys	Trp	Pro	Glu	Pro	Glu	Asn	Pro	Asn	Gly	Leu	Ile	Leu	Met
	850						855								860
Tyr	Glu	Ile	Lys	Tyr	Gly	Ser	Gln	Val	Glu	Asp	Gln	Arg	Glu	Cys	Val
	865						870								880
Ser	Arg	Gln	Glu	Tyr	Arg	Lys	Tyr	Gly	Gly	Ala	Lys	Leu	Asn	Arg	Leu
	885						890								895
Asn	Pro	Gly	Asn	Tyr	Thr	Ala	Arg	Ile	Gln	Ala	Thr	Ser	Leu	Ser	Gly
	900						905								910
Asn	Gly	Ser	Trp	Thr	Asp	Pro	Val	Phe	Phe	Tyr	Val	Gln	Ala	Lys	Thr
	915						920								925
Gly	Tyr	Glu	Asn	Phe	Ile	His	Leu	Ile	Ile	Ala	Leu	Pro	Val	Ala	Val
	930						935								940
Leu	Leu	Ile	Val	Gly	Gly	Leu	Val	Ile	Met	Leu	Tyr	Val	Phe	His	Arg
	945						950								960
Lys	Arg	Asn	Asn	Ser	Arg	Leu	Gly	Asn	Gly	Val	Leu	Tyr	Ala	Ser	Val
	965						970								975
Asn	Pro	Glu	Tyr	Phe	Ser	Ala	Ala	Asp	Val	Tyr	Val	Pro	Asp	Glu	Trp
	980						985								990
Glu	Val	Ala	Arg	Glu	Lys	Ile	Thr	Met	Ser	Arg	Glu	Leu	Gly	Gln	Gly
	995						1000								1005
Ser	Phe	Gly	Met	Val	Tyr	Glu	Gly	Val	Ala	Lys	Gly	Val	Val	Lys	
	1010						1015								1020
Asp	Glu	Pro	Glu	Thr	Arg	Val	Ala	Ile	Lys	Thr	Val	Asn	Glu	Ala	
	1025						1030								1035
Ala	Ser	Met	Arg	Glu	Arg	Ile	Glu	Phe	Leu	Asn	Glu	Ala	Ser	Val	
	1040						1045								1050
Met	Lys	Glu	Phe	Asn	Cys	His	His	Val	Val	Arg	Leu	Leu	Gly	Val	
	1055						1060								1065
Val	Ser	Gln	Gly	Gln	Pro	Thr	Leu	Val	Ile	Met	Glu	Leu	Met	Thr	
	1070						1075								1080
Arg	Gly	Asp	Leu	Lys	Ser	Tyr	Leu	Arg	Ser	Leu	Arg	Pro	Glu	Met	

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1085	1090	1095
Glu Asn Asn Pro Val Leu Ala Pro Pro Ser Leu Ser Lys Met Ile		
1100	1105	1110
Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala		
1115	1120	1125
Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val		
1130	1135	1140
Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg		
1145	1150	1155
Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu		
1160	1165	1170
Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp Gly Val		
1175	1180	1185
Phe Thr Thr Tyr Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp		
1190	1195	1200
Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn		
1205	1210	1215
Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu Asp Lys		
1220	1225	1230
Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg Met Cys		
1235	1240	1245
Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu Ile Ile		
1250	1255	1260
Ser Ser Ile Lys Glu Glu Met Glu Pro Gly Phe Arg Glu Val Ser		
1265	1270	1275
Phe Tyr Tyr Ser Glu Glu Asn Lys Leu Pro Glu Pro Glu Glu Leu		
1280	1285	1290
Asp Leu Glu Pro Glu Asn Met Glu Ser Val Pro Leu Asp Pro Ser		
1295	1300	1305
Ala Ser Ser Ser Ser Leu Pro Leu Pro Asp Arg His Ser Gly His		
1310	1315	1320
Lys Ala Glu Asn Gly Pro Gly Pro Gly Val Leu Val Leu Arg Ala		
1325	1330	1335
Ser Phe Asp Glu Arg Gln Pro Tyr Ala His Met Asn Gly Gly Arg		
1340	1345	1350
Lys Asn Glu Arg Ala Leu Pro Leu Pro Gln Ser Ser Thr Cys		
1355	1360	1365

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<210> SEQ ID NO 72
<211> LENGTH: 4101
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4101)
<223> OTHER INFORMATION: Homo sapiens IGF-I receptor

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<400> SEQUENCE: 72

atgaagtctg gctccggagg agggtccccg acctcgctgt gggggctctt ctcc	60
gccgcgtct cgcgtggcc gacgagtgaa gaaatctgca ggccaggcat cgacatccgc	120
aacgactatac agcagctgaa gcgccctggag aactgcacgg tgatcgaggg ctacctccac	180
atcctgtctca tctccaaggc cgaggactac cgcaagctacc gttccccaa gtcacggc	240

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attaccgagt	acttgcgtct	gttccgagtg	gctggcctcg	agagcctcg	agacatcttc	300
cccaacctca	cggcatccg	cggctggaaa	ctcttctaca	actacgcct	ggcatcttc	360
gagatgacca	atctcaagga	tattgggctt	tacaacctga	ggaacattac	tcggggggcc	420
atcaggattg	agaaaaatgc	tgacctctgt	tacctctcca	ctgtggactg	gtccctgatc	480
ctggatgcgg	tgtccaataa	ctacattgt	ggaataagc	ccccaaagga	atgtggggac	540
ctgtgtccag	ggaccatgga	ggagaagccg	atgtgtgaga	agaccacca	caacaatgag	600
tacaactacc	gctgctggac	cacaaaccgc	tgccagaaaa	tgtgccaag	cacgtgtggg	660
aagcgggcgt	gcacccgagaa	caatgagtgc	tgccaccccg	agtgcctggg	cagctgcagc	720
gcccctgaca	acgacacggc	ctgtgttagt	tgccgccact	actactatgc	cggtgtctgt	780
gtgcctgcct	gccccccaa	cacctacagg	tttgagggt	ggcgctgtgt	ggaccgtgac	840
ttctgcgcca	acatccctag	cggcggagago	agcgactccg	aggggtttgt	gatccacgac	900
ggcgagtgca	tgcaggagt	ccccctgggc	ttcatccgca	acggcagcca	gagcatgtac	960
tgcacatccct	gtgaagggtc	ttgccccaa	gtctgtgagg	aagaaaagaa	aacaaagacc	1020
attgattctg	ttacttctgc	tcagatgctc	caaggatgca	ccatcttcaa	ggcaatttgc	1080
ctcattaaca	tccgacgggg	gaataacatt	gcttcagagc	tggagaactt	catggggctc	1140
atcgagggtgg	tgacgggcta	cgtgaagato	cggcattctc	atgccttgg	ctccttgc	1200
ttccctaaaa	accttcgcct	catecttagga	gaggagcgc	tagaaggggaa	ttactccctc	1260
taacgtcctcg	acaaccagaa	cttgcagcaa	ctgtggact	gggaccaccc	caacctgacc	1320
atcaaaggcg	ggaaaatgt	cttgttttc	aatcccaa	tatgtgtttc	cgaaatttac	1380
cgcacatggagg	aagtgacggg	gactaaaggg	cggccaaagca	aaggggacat	aaacaccagg	1440
aacaacgggg	agagagcctc	ctgtgaaagt	gacgtctgc	atttcacctc	caccaccacg	1500
tcaagaatac	gcatcatcat	aacctggcac	cggttaccggc	cccctgacta	cagggatctc	1560
atcagcttca	cggtttacta	caaggaagca	ccctttaaga	atgtcacaga	gtatgtggg	1620
caggatgcct	cgggctccaa	cagctggaa	atggtggacg	tggacctccc	gcccaacaag	1680
gacgtggagg	cggcatctt	actacatggg	ctgaagccct	ggactcagta	cggcgtttac	1740
gtcaaggctg	tgaccctcac	catggtggag	aacgaccata	tccgtggggc	caagagttag	1800
atcttgcata	ttcgcaccaa	tgcttcagtt	ccttccattc	ccttggacgt	tcttcagca	1860
tcgaactcct	cttctcagtt	aatcgtgaag	tggaaccctc	cctctctgac	caacggcaac	1920
ctgagttact	acattgtgc	ctggcagcgg	cagcctcagg	acggctacct	ttacggcac	1980
aattactgct	ccaaagacaa	aatcccatc	aggaagtatg	ccgacggcac	catcgacatt	2040
gaggagggtca	cagagaaccc	caagactgag	gtgtgtgggt	gggagaaagg	gccttgctgc	2100
gcctgccccca	aaactgaagc	cgagaagcg	gccgagaagg	aggaggctga	ataccgcaaa	2160
gtctttgaga	atttcctgca	caactccatc	ttcgtgccc	gacctgaaag	gaagcggaga	2220
gatgtcatgc	aaatggccaa	caccatcg	tccagccgaa	gcaggaacac	cacggccgca	2280
gacacccata	acatcaccga	cccgaaagag	ctggagacag	agtaccctt	ctttgagac	2340
agagtggata	acaaggagag	aactgtcatt	tctaaccctt	ggcctttcac	attgtaccgc	2400
atcgatatacc	acagctgca	ccacgaggct	gagaagctgg	gctgcagcgc	ctccaaacttc	2460
gtctttgcaa	ggactatgcc	cgcagaagga	gcagatgaca	ttcctggggcc	agtgcac	2520

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gagccaaggc	ctgaaaactc	cattttta	aagtggccgg	aacctgagaa	tcccaatgg	2580
ttgattctaa	tgtatgaaat	aaaatacgg	tcacaagttg	aggatcagcg	agaatgttg	2640
tccagacagg	aatacaggaa	gtatggaggg	gccaagctaa	accggctaaa	cccgaaaaac	2700
tacacagccc	ggattcaggc	cacatctctc	tctggaaatg	ggtcgtggac	agatcctgtg	2760
ttcttctatg	tccaggccaa	aacaggatat	gaaaacttca	tccatctgtat	catcgctctg	2820
cccgctcgctg	tcctgttgc	cgtggggaggg	tttgtgatta	tgctgtacgt	tttccataga	2880
aagagaaata	acagcaggct	gggaaatgg	gtgctgtatg	cctctgtgaa	cccgaggatc	2940
ttcagcgtcg	ctgatgtgt	cgttctgtat	gagtgggagg	tggctcggg	gaagatcacc	3000
atgagccggg	aacttggca	ggggtcgttt	gggatggct	atgaaggagt	tgccaagggt	3060
gtgggtgaaag	atgaacctga	aaccagagtg	gccattaaaa	cagtgaacga	ggccgcaagc	3120
atgcgtgaga	ggatttgagtt	tctcaacgaa	gcttctgtg	tgaaggagtt	caattgtcac	3180
catgtggtgc	gattgttgg	tgtgggtgtc	caaggccagc	caacactggt	catcatggaa	3240
ctgtatgac	ggggcgatct	caaaaat	ctccggtctc	tgagggcaga	aatggagaat	3300
aatccagtc	tagcacctcc	aagectgago	aagatgatc	agatggccgg	agagattgca	3360
gacggcatgg	catacctcaa	cgccaaataag	tccgtccaca	gagaccttgc	tgcccgaaat	3420
tgcgtatgg	ccgaagattt	cacagtcaaa	atcgagatt	tttgtatgac	gcgagatatc	3480
tatgagacag	actattaccg	gaaaggaggg	aaagggtgc	tgccctgtcg	ctggatgtct	3540
cctgagtc	tcaaggatgg	agtcttcacc	acttactcg	acgtctggc	cttcggggc	3600
gtcctctgg	agatcgccac	actggccag	cagccctacc	agggcttgc	caacgagcaa	3660
gtccttegct	tcgtcatgga	ggggggcctt	ctggacaagc	cagacaactg	tcctgacatg	3720
ctgtttga	tgtatgecat	gtgctggcag	tataacccca	agatggggcc	ttccttcctg	3780
gagatcatca	gcagcatcaa	agaggagatg	gagcctggct	tccgggaggt	tccttc tac	3840
tacagcgagg	agaacaagct	gccegagccg	gaggagctgg	acctggagcc	agagaacatg	3900
gagagcgtcc	ccctggaccc	ctcgccctcc	tcgtccccc	tgccactgcc	cgacagacac	3960
tcaggacaca	aggccgagaa	cgccccggc	cctgggggtgc	tggctctccg	cgccagatcc	4020
gacgagagac	gccttacgc	ccacatgaac	ggggccgca	agaacgagcg	ggccttgcg	4080
ctgccccagt	cttcgac	c				4101

<210> SEQ ID NO 73
<211> LENGTH: 1367
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(1367)
<223> OTHER INFORMATION: Macaca fascicularis IGF-I receptor

<400> SEQUENCE: 73

Met Lys Ser Gly Ser Gly Glu Ser Pro Thr Ser Leu Trp Gly Leu
1 5 10 15

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile
20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile

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50	55	60
Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val		
65	70	75
Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu		
85	90	95
Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe		
100	105	110
Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile		
115	120	125
Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu		
130	135	140
Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile		
145	150	155
Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys		
165	170	175
Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys		
180	185	190
Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr		
195	200	205
Asn Arg Cys Gln Lys Met Cys Pro Ser Ala Cys Gly Lys Arg Ala Cys		
210	215	220
Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser		
225	230	235
Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr		
245	250	255
Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu		
260	265	270
Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala		
275	280	285
Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met		
290	295	300
Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr		
305	310	315
Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Lys		
325	330	335
Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly		
340	345	350
Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn		
355	360	365
Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val		
370	375	380
Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser		
385	390	395
Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly		
405	410	415
Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp		
420	425	430
Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe		
435	440	445
Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu		
450	455	460

-continued

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
465 470 475 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
485 490 495

Ser Thr Thr Trp Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
500 505 510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
515 520 525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
530 535 540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
545 550 555 560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
565 570 575

Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
580 585 590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
595 600 605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
610 615 620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
625 630 635 640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
645 650 655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
660 665 670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
675 680 685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
690 695 700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Ala Glu Tyr Arg Lys
705 710 715 720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
725 730 735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser
740 745 750

Arg Ser Arg Asn Thr Thr Val Ala Asp Thr Tyr Asn Ile Thr Asp Leu
755 760 765

Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
770 775 780

Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
785 790 795 800

Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
805 810 815

Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
820 825 830

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile
835 840 845

Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met
850 855 860

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Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val
865 870 875 880

Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu
885 890 895

Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly
900 905 910

Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr
915 920 925

Gly Tyr Glu Asn Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val
930 935 940

Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg
945 950 955 960

Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val
965 970 975

Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp
980 985 990

Glu Val Ala Arg Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly
995 1000 1005

Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys
1010 1015 1020

Asp Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala
1025 1030 1035

Ala Ser Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val
1040 1045 1050

Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly Val
1055 1060 1065

Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr
1070 1075 1080

Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Met
1085 1090 1095

Glu Asn Asn Pro Val Leu Ala Pro Pro Ser Leu Ser Lys Met Ile
1100 1105 1110

Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala
1115 1120 1125

Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val
1130 1135 1140

Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg
1145 1150 1155

Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu
1160 1165 1170

Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp Gly Val
1175 1180 1185

Phe Thr Thr Tyr Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp
1190 1195 1200

Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn
1205 1210 1215

Glu Gln Val Leu Arg Phe Val Met Glu Gly Leu Leu Asp Lys
1220 1225 1230

Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg Met Cys
1235 1240 1245

Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu Ile Ile

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1250	1255	1260
Ser Ser Ile Lys Asp Glu Met	Glu Pro Gly Phe Arg	Glu Val Ser
1265	1270	1275
Phe Tyr Tyr Ser Glu Glu Asn	Lys Leu Pro Glu Pro	Glu Glu Leu
1280	1285	1290
Asp Leu Glu Pro Glu Asn Met	Glu Ser Val Pro Leu	Asp Pro Ser
1295	1300	1305
Ala Ser Ser Ser Ser Leu Pro	Leu Pro Asp Arg His	Ser Gly His
1310	1315	1320
Lys Ala Glu Asn Gly Pro	Pro Gly Val Leu Val	Leu Arg Ala
1325	1330	1335
Ser Phe Asp Glu Arg Gln Pro	Tyr Ala His Met Asn	Gly Gly Arg
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Lys Asn Glu Arg Ala Leu Pro	Leu Pro Gln Ser Ser	Thr Cys
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<210> SEQ ID NO 74
<211> LENGTH: 4104
<212> TYPE: DNA
<213> ORGANISM: Macaca fascicularis
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4104)
<223> OTHER INFORMATION: Macaca fascicularis IGF-I receptor

<400> SEQUENCE: 74

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aacgactatc agcagctgaa gcgcctggag aactgcacgg tgatcgaggg ctacctccac      180
atcctgctca tctccaaggc cgaggactac cgcaagctacc gtttccccaa gtcacggtc      240
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gagatgacca atctcaagga tattgggtt tacaacctga ggaacattac tcggggggcc      420
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ctgtgtccgg ggaccatgga ggagaagccg atgtgcgaga agaccaccaat caacaatgag      600
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ggcgagtgca tgcaggagtg cccctcaggc ttcatccgca acggcagcga gagcatgtac      960
tgcatccctt gtgaagggtcc ttgccccaa gtcgtgtgagg aagaaaagaa aacaaagacc      1020
attgattctg ttacttctgc tcagatgctt caaggatgca ccatcttcaa gggcaatttg      1080
ctcatattaaca tccgacgggg gaataacatt gcttcagaac tggagaactt catggggctc      1140
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tcgaactctt cttctcagtt aatctgtgaaat tggaaacccttc cttctctgcc caacggcaac	1920
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<210> SEQ ID NO 75
<211> LENGTH: 1425
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(1425)
<223> OTHER INFORMATION: Oryctolagus cuniculus IGF-I receptor

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<400> SEQUENCE: 75

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Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Phe Gln Gln Leu Lys Arg
35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Phe Leu His Ile Leu Leu Ile
50 55 60

Ser Lys Ala Glu Asp Tyr Arg Asn Tyr Arg Phe Pro Lys Leu Thr Val
65 70 75 80

Ile Thr Glu Tyr Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu
85 90 95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
100 105 110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile
115 120 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu
130 135 140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile
145 150 155 160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Ser Pro Lys
165 170 175

Glu Cys Gly Asp Met Cys Pro Gly Thr Leu Glu Glu Lys Pro Leu Cys
180 185 190

Glu Lys Thr Ala Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
195 200 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Ala Cys Gly Lys Arg Ala Cys
210 215 220

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys His

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225	230	235	240
Ala Pro Asp Asp Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Phe			
245	250	255	
Ser Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu			
260	265	270	
Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Pro Asn Ala			
275	280	285	
Asp Gly Gly Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met			
290	295	300	
Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Phe			
305	310	315	320
Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Asp Lys			
325	330	335	
Lys Thr Lys Thr Ile Asp Ser Val Asn Ser Ala Gln Met Leu Gln Gly			
340	345	350	
Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn			
355	360	365	
Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val			
370	375	380	
Thr Gly Tyr Val Lys Ile Ser His Ser His Ala Leu Val Ser Leu Ser			
385	390	395	400
Phe Leu Lys Asn Leu Arg Gln Ile Leu Gly Glu Glu Gln Leu Glu Gly			
405	410	415	
Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp			
420	425	430	
Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe			
435	440	445	
Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Asp			
450	455	460	
Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg			
465	470	475	480
Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Ile Leu His Phe Thr			
485	490	495	
Ser Thr Asn Thr Trp Lys Asn Arg Ile Ile Leu Thr Trp His Arg Tyr			
500	505	510	
Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys			
515	520	525	
Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys			
530	535	540	
Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys			
545	550	555	560
Asp Leu Glu Pro Gly Ile Leu Leu Gln Gly Leu Lys Pro Trp Thr Gln			
565	570	575	
Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp			
580	585	590	
His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala			
595	600	605	
Ser Val Pro Ser Ile Pro Leu Asp Ile Leu Ser Ala Ser Asn Ser Ser			
610	615	620	
Ser Gln Leu Ile Val Lys Trp Ser Pro Pro Ser Leu Pro Asn Gly Asn			
625	630	635	640

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Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
 645 650 655
 Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
 660 665 670
 Tyr Ala Asp Gly Thr Ile Asp Val Glu Glu Val Thr Glu Asn Pro Lys
 675 680 685
 Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
 690 695 700
 Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Ala Glu Tyr Arg Lys
 705 710 715 720
 Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
 725 730 735
 Arg Lys Arg Arg Asp Val Ala Gln Val Ala Asn Thr Thr Leu Ser Gly
 740 745 750
 Arg Gly Arg Asn Gly Thr Ala Val Asp Met Tyr Asn Ser Thr Asp Leu
 755 760 765
 Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Thr Arg Val Asp Lys
 770 775 780
 Glu Ile Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Ser Tyr Arg Ile
 785 790 795 800
 Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser Ala
 805 810 815
 Ser Asn Phe Val Phe Ala Arg Thr Lys Pro Ala Glu Gly Ala Asp Asp
 820 825 830
 Ile Pro Gly Pro Val Thr Trp Glu Ala Arg Pro Glu Asn Ser Ile Phe
 835 840 845
 Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met Tyr
 850 855 860
 Glu Ile Lys Tyr Gly Ser Gln Ile Glu Asp Gln Arg Glu Cys Val Ser
 865 870 875 880
 Arg Gln Gln Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu Asn
 885 890 895
 Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly Asn
 900 905 910
 Gly Ser Trp Thr Glu Pro Val Phe Phe Tyr Val Pro Ala Lys Ala Thr
 915 920 925
 Tyr Glu Ser Phe Met His Leu Ile Ile Ala Leu Pro Val Ala Ile Leu
 930 935 940
 Leu Ile Val Gly Gly Leu Leu Ile Val Leu Tyr Val Phe His Arg Lys
 945 950 955 960
 Arg Ser Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val Asn
 965 970 975
 Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp Glu
 980 985 990
 Val Ala Arg Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly Ser
 995 1000 1005
 Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys Asp
 1010 1015 1020
 Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala Ala
 1025 1030 1035

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Ser	Met	Arg	Glu	Arg	Ile	Glu	Phe	Leu	Asn	Glu	Ala	Ser	Val	Met
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Lys	Glu	Phe	Asn	Cys	His	His	Val	Val	Arg	Leu	Leu	Gly	Val	Val
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Ser	Gln	Gly	Gln	Pro	Thr	Leu	Val	Ile	Met	Glu	Leu	Met	Thr	Arg
1070					1075					1080				
Gly	Asp	Leu	Lys	Ser	Tyr	Leu	Arg	Ser	Leu	Arg	Pro	Glu	Val	Glu
1085					1090					1095				
Ala	Glu	Leu	Gln	Arg	Glu	Arg	Gln	Arg	Gln	Asn	Phe	Ile		
1100					1105				1110					
Arg	Arg	Phe	Ala	Pro	Arg	Met	Ala	Ala	Thr	Ala	Arg	Ala	Gly	Pro
1115					1120				1125					
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1130					1135				1140					
Val	Gln	Gly	Pro	Lys	Asp	Leu	Gly	His	Leu	Pro	Leu	Pro	Ser	Gln
1145					1150				1155					
Asn	Arg	Ala	Pro	Ala	Pro	Pro	Ser	Leu	Ser	Lys	Met	Ile	Gln	Met
1160					1165				1170					
Ala	Gly	Glu	Ile	Ala	Asp	Gly	Met	Ala	Tyr	Leu	Asn	Ala	Asn	Lys
1175					1180				1185					
Phe	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met	Val	Ala	Glu
1190					1195				1200					
Asp	Phe	Thr	Val	Lys	Ile	Gly	Asp	Phe	Gly	Met	Thr	Arg	Asp	Ile
1205					1210				1215					
Tyr	Glu	Thr	Asp	Tyr	Tyr	Arg	Lys	Gly	Gly	Lys	Gly	Leu	Leu	Pro
1220					1225				1230					
Val	Arg	Trp	Met	Ser	Pro	Glu	Ser	Leu	Lys	Asp	Gly	Val	Phe	Thr
1235					1240				1245					
Thr	His	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Val	Leu	Trp	Glu	Ile
1250					1255				1260					
Ala	Thr	Leu	Ala	Glu	Gln	Pro	Tyr	Gln	Gly	Phe	Ser	Asn	Glu	Gln
1265					1270				1275					
Val	Leu	Arg	Phe	Val	Met	Glu	Gly	Gly	Leu	Leu	Asp	Lys	Pro	Asp
1280					1285				1290					
Asn	Cys	Pro	Asp	Met	Leu	Phe	Glu	Leu	Met	Arg	Met	Cys	Trp	Gln
1295					1300				1305					
Tyr	Asn	Pro	Lys	Met	Arg	Pro	Ser	Phe	Leu	Glu	Ile	Ile	Gly	Ser
1310					1315				1320					
Val	Arg	Asp	Glu	Met	Glu	Pro	Gly	Phe	Arg	Glu	Val	Ser	Phe	Tyr
1325					1330				1335					
Tyr	Ser	Glu	Glu	Asn	Lys	Pro	Pro	Glu	Ala	Glu	Glu	Leu	Asp	Leu
1340					1345				1350					
Glu	Pro	Glu	Asn	Met	Glu	Ser	Val	Pro	Leu	Asp	Pro	Ser	Ala	Asn
1355					1360				1365					
Ala	Ala	Ala	Ala	Val	Ala	Ala	Leu	Gln	Pro	Asp	Arg	His	Lys	Ala
1370					1375				1380					
Glu	Asn	Gly	Pro	Ser	Ala	Gly	Ala	Met	Val	Leu	Arg	Ala	Ser	Phe
1385					1390				1395					
Asp	Glu	Arg	Arg	Pro	Tyr	Ala	His	Met	Asn	Gly	Gly	Arg	Thr	Asp
1400					1405				1410					
Glu	Arg	Ala	Leu	Pro	Leu	Pro	Gln	Ser	Ser	Thr	Cys			

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1415

1420

1425

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<210> SEQ ID NO 76
<211> LENGTH: 4278
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4278)
<223> OTHER INFORMATION: Oryctolagus cuniculus IGF-I receptor

<400> SEQUENCE: 76

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gacccatggcctt ctgggtattctt actgcacggg ctgaaggccctt ggactcagta cggccgttgc 1740
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atcttgcata ttccgcacccaa cgcctcaggattt cttccatcc cttggacat cctctcgca 1860

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aactactgt ccaaagacaa aattccatc aggaagtatg cggacggcac catcgacgt	2040
gaggaggtga cggagaaccc caagacggag gtctgtggcg gagagaaggg gccttgcgtc	2100
gcgtgccccca agaccgaagc cgagaagcg gctgagaagg aggaggcgga gtaccgcaag	2160
gtgttcgaga acttcctgca caactccatc ttctgtccca gacccgagag gaagcgagaa	2220
gatgtcgccc aggtggccaa caccacgctg tccggcccgag gcaggaacgg cacggcggt	2280
gacatgtaca acagcacgga cctggaggag ctggagacag aataccctt ctggagacc	2340
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<210> SEQ ID NO 77
<211> LENGTH: 1367
<212> TYPE: PRT
<213> ORGANISM: Cavia porcellus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(1367)
<223> OTHER INFORMATION: Cavia porcellus IGF-I receptor

<400> SEQUENCE: 77

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Leu	Phe	Leu	Ser	Ala	Ala	Leu	Ser	Leu	Trp	Pro	Thr	Ser	Gly	Glu	Ile
															4260
Cys	Gly	Pro	Gly	Ile	Asp	Ile	Arg	Asn	Asp	Tyr	Gln	Gln	Leu	Lys	Arg
															4278
Leu	Glu	Asn	Cys	Thr	Val	Ile	Glu	Gly	Tyr	Leu	His	Ile	Leu	Leu	Ile
Ser	Lys	Ala	Glu	Asp	Tyr	Arg	Ser	Tyr	Arg	Phe	Pro	Lys	Leu	Thr	Val
															400
Ile	Thr	Glu	Tyr	Leu	Leu	Phe	Arg	Val	Ala	Gly	Leu	Glu	Ser	Leu	
															400
Gly	Asp	Leu	Phe	Pro	Asn	Leu	Thr	Val	Ile	Arg	Gly	Trp	Lys	Leu	Phe
															400
Tyr	Asn	Tyr	Ala	Leu	Val	Ile	Phe	Met	Thr	Asn	Leu	Lys	Asp	Ile	
															400
Gly	Leu	Tyr	Asn	Leu	Arg	Asn	Ile	Thr	Arg	Gly	Ala	Ile	Arg	Ile	Glu
															400
Lys	Asn	Ala	Asp	Leu	Cys	Tyr	Leu	Ser	Thr	Val	Asp	Trp	Ser	Leu	Ile
															400
Leu	Asp	Ala	Val	Ser	Asn	Asn	Tyr	Ile	Val	Gly	Asn	Lys	Ser	Pro	Lys
															400
Glu	Cys	Gly	Asp	Leu	Cys	Pro	Gly	Thr	Met	Glu	Glu	Lys	Pro	Leu	Cys
															400
Glu	Lys	Thr	Thr	Ile	Asn	Asn	Glu	Tyr	Asn	Tyr	Arg	Cys	Trp	Thr	Thr
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Asn	Arg	Cys	Gln	Lys	Met	Cys	Pro	Ser	Ala	Cys	Gly	Lys	Arg	Ala	Cys
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Thr	Glu	Tyr	Gln	Glu	Cys	Cys	His	Pro	Glu	Cys	Leu	Gly	Ser	Cys	His
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Ala	Pro	Asp	Asp	Asp	Thr	Ala	Cys	Val	Ala	Cys	Arg	His	Phe	Tyr	Tyr
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Ala	Gly	Ile	Cys	Val	Pro	Ala	Cys	Pro	Pro	Gly	Thr	Tyr	Arg	Phe	Glu
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Gly	Trp	Arg	Cys	Val	His	Arg	Asp	Phe	Cys	Ala	Asn	Ile	Pro	Asn	Ala
															400
Glu	Ser	Ser	Asp	Ser	Glu	Gly	Phe	Val	Ile	His	Asp	Gly	Glu	Cys	Met
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Gln	Glu	Cys	Pro	Ser	Gly	Phe	Ile	Arg	Asn	Gly	Ser	Gln	Ser	Met	Tyr

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305	310	315	320
Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys			
325	330	335	
Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly			
340	345	350	
Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn			
355	360	365	
Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val			
370	375	380	
Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser			
385	390	395	400
Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly			
405	410	415	
Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp			
420	425	430	
Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ser Gly Lys Met Tyr Phe			
435	440	445	
Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu			
450	455	460	
Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg			
465	470	475	480
Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu Arg Phe Thr			
485	490	495	
Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr			
500	505	510	
Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys			
515	520	525	
Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys			
530	535	540	
Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys			
545	550	555	560
Asp Ala Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln			
565	570	575	
Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp			
580	585	590	
His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala			
595	600	605	
Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser			
610	615	620	
Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn			
625	630	635	640
Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Ser Tyr			
645	650	655	
Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys			
660	665	670	
Tyr Ala Asp Gly Thr Ile Asp Val Glu Glu Val Thr Glu Asn Pro Lys			
675	680	685	
Thr Glu Val Cys Gly Gly Lys Gly Pro Cys Cys Ala Cys Pro Lys			
690	695	700	
Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Ala Glu Tyr Arg Lys			
705	710	715	720

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Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
 725 730 735
 Arg Arg Arg Asp Val Ala Gln Met Ala Asn Thr Thr Met Ser Ser
 740 745 750
 Arg Ser Arg Asn Thr Thr Val Ala Asp Thr Tyr Asn Ala Thr Asp Pro
 755 760 765
 Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
 770 775 780
 Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
 785 790 795 800
 Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
 805 810 815
 Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
 820 825 830
 Asp Ile Pro Gly Pro Val Thr Trp Glu Ala Arg Pro Glu Asn Ser Ile
 835 840 845
 Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met
 850 855 860
 Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val
 865 870 875 880
 Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Ser Arg Leu
 885 890 895
 Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly
 900 905 910
 Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Pro Ala Lys Thr
 915 920 925
 Thr Tyr Glu Asn Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Ile
 930 935 940
 Leu Leu Ile Val Ala Gly Leu Ala Ile Met Leu Tyr Val Phe His Arg
 945 950 955 960
 Lys Arg Asn Ser Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val
 965 970 975
 Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp
 980 985 990
 Glu Val Ala Arg Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly
 995 1000 1005
 Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys
 1010 1015 1020
 Asp Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala
 1025 1030 1035
 Ala Ser Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val
 1040 1045 1050
 Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly Val
 1055 1060 1065
 Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr
 1070 1075 1080
 Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Val
 1085 1090 1095
 Glu Asn Ser Pro Ile Leu Ala Pro Pro Ser Leu Ser Lys Met Ile
 1100 1105 1110

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Gln	Met	Ala	Gly	Glu	Ile	Ala	Asp	Gly	Met	Ala	Tyr	Leu	Asn	Ala
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Asn	Lys	Phe	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met	Val
1130				1135			1140							
Ala	Glu	Asp	Phe	Thr	Val	Lys	Ile	Gly	Asp	Phe	Gly	Met	Thr	Arg
1145				1150			1155							
Asp	Ile	Tyr	Glu	Thr	Asp	Tyr	Tyr	Arg	Lys	Gly	Gly	Lys	Gly	Leu
1160				1165			1170							
Leu	Pro	Val	Arg	Trp	Met	Ser	Pro	Glu	Ser	Leu	Lys	Asp	Gly	Val
1175				1180			1185							
Phe	Thr	Thr	His	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Val	Leu	Trp
1190				1195			1200							
Glu	Ile	Ala	Thr	Leu	Ala	Glu	Gln	Pro	Tyr	Gln	Gly	Leu	Ser	Asn
1205				1210			1215							
Glu	Gln	Val	Leu	Arg	Phe	Val	Met	Glu	Gly	Gly	Leu	Leu	Asp	Lys
1220				1225			1230							
Pro	Asp	Asn	Cys	Pro	Asp	Met	Leu	Phe	Glu	Leu	Met	Arg	Met	Cys
1235				1240			1245							
Trp	Gln	Tyr	Asn	Pro	Lys	Met	Arg	Pro	Ser	Phe	Leu	Glu	Ile	Ile
1250				1255			1260							
Ser	Ser	Val	Lys	Asp	Glu	Leu	Glu	Ala	Gly	Phe	Arg	Glu	Val	Ser
1265				1270			1275							
Phe	Tyr	Tyr	Ser	Glu	Glu	Asn	Lys	Pro	Pro	Glu	Pro	Glu	Glu	Leu
1280				1285			1290							
Asp	Leu	Glu	Pro	Glu	Asn	Met	Glu	Ser	Val	Pro	Leu	Asp	Pro	Ser
1295				1300			1305							
Ala	Ser	Ser	Ser	Ser	Leu	Pro	Pro	Pro	Asp	Arg	His	Ser	Gly	His
1310				1315			1320							
Lys	Gly	Glu	Asn	Gly	Pro	Gly	Pro	Gly	Val	Leu	Val	Leu	Arg	Ala
1325				1330			1335							
Ser	Phe	Asp	Glu	Arg	Gln	Pro	Tyr	Ala	His	Met	Asn	Gly	Gly	Arg
1340				1345			1350							
Thr	Asn	Glu	Arg	Ala	Leu	Pro	Leu	Pro	Gln	Ser	Ser	Thr	Cys	
1355				1360			1365							

<210> SEQ ID NO 78
<211> LENGTH: 4104
<212> TYPE: DNA
<213> ORGANISM: Cavia porcellus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4104)
<223> OTHER INFORMATION: Cavia porcellus IGF-I receptor

<400> SEQUENCE: 78

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aatgactatac	agcagctaaa	acgcctggag	aactgcacgg	tgatcgaggg	ctacccac	180
atccctgtca	tctccaaggc	cgaggactac	cgcagctacc	gtttccccaa	gctcacccgtc	240
atcaccgagt	atctgtgtct	gttccgggtc	gctggctcg	agagcctcg	agaccccttc	300
ccgaacctca	ccgtcatccg	cggctggaaa	ctcttctata	actacgcct	ggtcatcttc	360
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gagatcatca	gcagcgtcaa	agacgagctg	gaggccggct	tccgggaggt	ctccttc tac	3840
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tcaggacaca	agggcgagaa	cggcccgccc	ccggcgtgc	tggtgtccg	cgccagatcc	4020
gacgagagac	agccttacgc	gcacatgaac	ggaggccgca	cgaacgagag	ggccttgcgc	4080
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<210> SEQ ID NO 79
<211> LENGTH: 1371
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(1371)
<223> OTHER INFORMATION: Rattus norvegicus IGF-I receptor

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<400> SEQUENCE: 79

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Val	Phe	Leu	Ser	Ala	Ala	Leu	Ser	Leu	Trp	Pro	Thr	Ser	Gly	Glu	Ile
				20			25			30					

Cys	Gly	Pro	Gly	Ile	Asp	Ile	Arg	Asn	Asp	Tyr	Gln	Gln	Leu	Lys	Arg
				35			40			45					

Leu	Glu	Asn	Cys	Thr	Val	Ile	Glu	Gly	Phe	Leu	His	Ile	Leu	Leu	Ile
	50				55			60							

Ser	Lys	Ala	Glu	Asp	Tyr	Arg	Ser	Tyr	Arg	Phe	Pro	Lys	Leu	Thr	Val
	65			70			75			80					

-continued

Ile	Thr	Glu	Tyr	Leu	Leu	Leu	Phe	Arg	Val	Ala	Gly	Leu	Glu	Ser	Leu
85															95
Gly	Asp	Leu	Phe	Pro	Asn	Leu	Thr	Val	Ile	Arg	Gly	Trp	Lys	Leu	Phe
100															110
Tyr	Asn	Tyr	Ala	Leu	Val	Ile	Phe	Glu	Met	Thr	Asn	Leu	Lys	Asp	Ile
115															125
Gly	Leu	Tyr	Asn	Leu	Arg	Asn	Ile	Thr	Arg	Gly	Ala	Ile	Arg	Ile	Glu
130															140
Lys	Asn	Ala	Asp	Leu	Cys	Tyr	Leu	Ser	Thr	Ile	Asp	Trp	Ser	Leu	Ile
145															160
Leu	Asp	Ala	Val	Ser	Asn	Asn	Tyr	Ile	Val	Gly	Asn	Lys	Pro	Pro	Lys
165															175
Glu	Cys	Gly	Asp	Leu	Cys	Pro	Gly	Thr	Leu	Glu	Glu	Lys	Pro	Met	Cys
180															190
Glu	Lys	Thr	Thr	Ile	Asn	Asn	Glu	Tyr	Asn	Tyr	Arg	Cys	Trp	Thr	Thr
195															205
Asn	Arg	Cys	Gln	Lys	Met	Cys	Pro	Ser	Val	Cys	Gly	Lys	Arg	Ala	Cys
210															220
Thr	Glu	Asn	Asn	Glu	Cys	Cys	His	Pro	Glu	Cys	Leu	Gly	Ser	Cys	His
225															240
Thr	Pro	Asp	Asp	Asn	Thr	Thr	Cys	Val	Ala	Cys	Arg	His	Tyr	Tyr	Tyr
245															255
Lys	Gly	Val	Cys	Val	Pro	Ala	Cys	Pro	Pro	Gly	Thr	Tyr	Arg	Phe	Glu
260															270
Gly	Trp	Arg	Cys	Val	Asp	Arg	Asp	Phe	Cys	Ala	Asn	Ile	Pro	Asn	Ala
275															285
Glu	Ser	Ser	Asp	Ser	Asp	Gly	Phe	Val	Ile	His	Asp	Gly	Glu	Cys	Met
290															300
Gln	Glu	Cys	Pro	Ser	Gly	Phe	Ile	Arg	Asn	Ser	Thr	Gln	Ser	Met	Tyr
305															320
Cys	Ile	Pro	Cys	Glu	Gly	Pro	Cys	Pro	Lys	Val	Cys	Gly	Asp	Glu	Glu
325															335
Lys	Lys	Thr	Lys	Thr	Ile	Asp	Ser	Val	Thr	Ser	Ala	Gln	Met	Leu	Gln
340															350
Gly	Cys	Thr	Ile	Leu	Lys	Gly	Asn	Leu	Leu	Ile	Asn	Ile	Arg	Arg	Gly
355															365
Asn	Asn	Ile	Ala	Ser	Glu	Leu	Glu	Asn	Phe	Met	Gly	Ile	Glu	Val	
370															380
Val	Thr	Gly	Tyr	Val	Lys	Ile	Arg	His	Ser	His	Ala	Leu	Val	Ser	Leu
385															400
Ser	Phe	Leu	Lys	Asn	Leu	Arg	Leu	Ile	Leu	Gly	Glu	Glu	Gln	Leu	Glu
405															415
Gly	Asn	Tyr	Ser	Phe	Tyr	Val	Leu	Asp	Asn	Gln	Asn	Leu	Gln	Gln	Leu
420															430
Trp	Asp	Trp	Asn	His	Arg	Asn	Leu	Thr	Val	Arg	Ser	Gly	Lys	Met	Tyr
435															445
Phe	Ala	Phe	Asn	Pro	Lys	Leu	Cys	Val	Ser	Glu	Ile	Tyr	Arg	Met	Glu
450															460
Glu	Val	Thr	Gly	Thr	Lys	Gly	Arg	Gln	Ser	Lys	Gly	Asp	Ile	Asn	Thr
465															480
Arg	Asn	Asn	Gly	Glu	Arg	Ala	Ser	Cys	Glu	Ser	Asp	Val	Leu	Arg	Phe

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485	490	495
Thr Ser Thr Thr Trp Lys Asn Arg Ile Ile Ile	Thr Trp His Arg	
500	505	510
Tyr Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe	Thr Val Tyr Tyr	
515	520	525
Lys Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp	Gly Gln Asp Ala	
530	535	540
Cys Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp	Leu Pro Pro Asn	
545	550	555
560		
Lys Glu Gly Glu Pro Gly Ile Leu Leu His Gly Leu	Lys Pro Trp Thr	
565	570	575
Gln Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr	Met Val Glu Asn	
580	585	590
Asp His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr	Ile Arg Thr Asn	
595	600	605
Ala Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser	Ala Ser Asn Ser	
610	615	620
Ser Ser Gln Leu Ile Val Lys Trp Asn Pro Pro	Thr Leu Pro Asn Gly	
625	630	635
640		
Asn Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln	Pro Gln Asp Gly	
645	650	655
Tyr Leu Phe Arg His Asn Tyr Cys Ser Lys Asp Lys	Ile Pro Ile Arg	
660	665	670
Lys Tyr Ala Asp Gly Thr Ile Asp Val Glu Glu Val	Thr Glu Asn Pro	
675	680	685
Lys Thr Glu Val Cys Gly Asp Lys Gly Pro Cys	Cys Ala Cys Pro	
690	695	700
Lys Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Ala	Glu Tyr Arg	
705	710	715
720		
Lys Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe	Val Pro Arg Pro	
725	730	735
Glu Arg Arg Arg Asp Val Leu Gln Val Ala Asn Thr	Thr Met Ser	
740	745	750
Ser Arg Ser Arg Asn Thr Thr Val Ala Asp Thr Tyr	Asn Ile Thr Asp	
755	760	765
Pro Glu Glu Phe Glu Thr Glu Tyr Pro Phe Phe Glu	Ser Arg Val Asp	
770	775	780
Asn Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro	Phe Thr Leu Tyr	
785	790	795
800		
Arg Ile Asp Ile His Ser Cys Asn His Glu Ala Glu	Lys Leu Gly Cys	
805	810	815
Ser Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro	Ala Glu Gly Ala	
820	825	830
Asp Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg	Pro Glu Asn Ser	
835	840	845
Ile Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn	Gly Leu Ile Leu	
850	855	860
Met Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp	Gln Arg Glu Cys	
865	870	875
880		
Val Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala	Lys Leu Asn Arg	
885	890	895

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Leu Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser
 900 905 910
 Gly Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Pro Ala Lys
 915 920 925
 Thr Thr Tyr Glu Asn Phe Met His Leu Ile Ile Ala Leu Pro Val Ala
 930 935 940
 Ile Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His
 945 950 955 960
 Arg Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser
 965 970 975
 Val Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu
 980 985 990
 Trp Glu Val Ala Arg Glu Lys Ile Thr Met Asn Arg Glu Leu Gly Gln
 995 1000 1005
 Gly Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val
 1010 1015 1020
 Lys Asp Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu
 1025 1030 1035
 Ala Ala Ser Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser
 1040 1045 1050
 Val Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly
 1055 1060 1065
 Val Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met
 1070 1075 1080
 Thr Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu
 1085 1090 1095
 Val Glu Gln Asn Asn Leu Val Leu Ile Pro Pro Ser Leu Ser Lys
 1100 1105 1110
 Met Ile Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu
 1115 1120 1125
 Asn Ala Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys
 1130 1135 1140
 Met Val Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met
 1145 1150 1155
 Thr Arg Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys
 1160 1165 1170
 Gly Leu Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp
 1175 1180 1185
 Gly Val Phe Thr Thr His Ser Asp Val Trp Ser Phe Gly Val Val
 1190 1195 1200
 Leu Trp Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu
 1205 1210 1215
 Ser Asn Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu
 1220 1225 1230
 Asp Lys Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg
 1235 1240 1245
 Met Cys Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu
 1250 1255 1260
 Ile Ile Gly Ser Ile Lys Asp Glu Met Glu Pro Ser Phe Gln Glu
 1265 1270 1275

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Val	Ser	Phe	Tyr	Tyr	Ser	Glu	Glu	Asn	Lys	Pro	Pro	Glu	Pro	Glu
1280					1285					1290				

Glu	Leu	Glu	Met	Glu	Leu	Glu	Leu	Glu	Pro	Glu	Asn	Met	Glu	Ser
1295					1300					1305				

Val	Pro	Leu	Asp	Pro	Ser	Ala	Ser	Ser	Ala	Ser	Leu	Pro	Leu	Pro
1310					1315					1320				

Glu	Arg	His	Ser	Gly	His	Lys	Ala	Glu	Asn	Gly	Pro	Gly	Val	Leu
	1325					1330					1335			

Val	Leu	Arg	Ala	Ser	Phe	Asp	Glu	Arg	Gln	Pro	Tyr	Ala	His	Met
1340					1345					1350				

Asn	Gly	Gly	Arg	Ala	Asn	Glu	Arg	Ala	Leu	Pro	Leu	Pro	Gln	Ser
	1355				1360					1365				

Ser	Thr	Cys												
		1370												

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<210> SEQ ID NO 80
<211> LENGTH: 4116
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4116)
<223> OTHER INFORMATION: Rattus norvegicus IGF-I receptor

<400> SEQUENCE: 80

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gccgcgtct ctgcgtggcc gacgagtgaa gaaatttgtg ggcccgccat tgacatccgc      120
aacgactatc agcagctgaa gcgcctggaa aactgcacgg tgatcgaggg cttccctcac      180
atccgtctca tctccaaggc cgaggactac cgaagctacc gtttccccaa gtcacagtc      240
atcaccgagt acttgcgtct gtttgcgtgt gccggcctcg agagcctggg agacctttc      300
ccgaacctca cagtcatccg tggctggaaa ctcttctaca attacgcact ggtcatttc      360
gagatgacca atctcaagga tattgggctt tataatctga ggaacattac tcggggggcc      420
atcaggattt agaaaaacgc tgacctctgt tacctctcca ccatagactg gtctctcatc      480
ttggatgcgg tgtccaataa ctacattgtg gggacaacgc ccccaaagga atgtggggac      540
ctgtgtccag ggaccttgga ggagaagccc atgtgtgaga agaccaccaat caacaatgag      600
tacaactacc gctgctggac cacaatcg tgcacggaaaa tgcgtccaaag tgcgtgtggg      660
aagcgagccct gcaccgagaa caatgagtgc tgcacccgg agtgcctagg cagctgcccc      720
acaccggacg acaacacaaac ctgcgtggcc tgcgcacact actactacaa aggctgtgc      780
gtgcctgcct gcccgcctgg cacctacagg ttgcagggtt ggcgcgtgtt ggacgggat      840
ttctgcgccta acatccccaa cggcgagago agtgactcaat gatggcttgcgtt catccacat      900
ggcgagtgca tgcaggaggta tccatcgagg ttcatccgca acagcaccca gagcatgtac      960
tgtatccccct gtgaaggccc ctgccttcaag gtctgcggcg atgaagaaaa gaaaacgaaa     1020
accatcgatt ctgtgcgttc tgccttcaat gatggcttgcgtt catccacat      1080
ctgcatttata acatccggcg aggcaataac attgcctgg aattggagaa cttcatgggg     1140
ctcatcgagg tggtgactgg ctacgtgaag atccgcattt cccatgcctt ggtctccctt     1200
tccttcctga agaaccttcg tctcatctta ggagaggagc agctagaagg aaactactcc     1260
ttctatgtcc tggacaacca gaacttgcag cagctgtggg actggAACCA ccggAACCTG     1320

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accgtcaggt caggaaaaat gtacttcgtt ttcaatccca agctgtgtgt ctctgaaatt	1380
taccgaatgg aggaggtgac aggaacaaag ggacggcaga gcaaaggaga cataaacacc	1440
aggaacaacg gagagcgcgc ttcctgtgaa agtgatgttc tccgtttcac ctccaccacc	1500
acctggaaga accgcatacat cataacgtgg cacccgtacc ggccgecgga ctaccggat	1560
ctcatcagtt tcacagtcta ctacaaggag gcaccctta aaaacgtcac ggaatacgac	1620
gggcaggatg cctgtggctc caacagctgg aacatggtgg acgtggacact gcctccgaac	1680
aaggaggggg agcctggcat tttgtgtcat gggctgaagc cctggaccga gtatgcagtc	1740
tatgtcaagg ctgtgaccct caccatggtg gaaaacgacc acatccgtgg ggccaaaagt	1800
gaaatcttgt acattcgac caacgcttca gttccttcca ttcccttaga tgtccctcgt	1860
gcatcaaact ctcctctca gctgatcgtg aagtggAACccccaaactct gcccaatgg	1920
aactttagttt actacattgtt gaggtggcag cggcagccgc aggtggcata tctgtccgg	1980
cacaactact gctccaaaga caaaaatacc atcagaaaatc acgcccgtgg taccatcgat	2040
gtggaggagg tgacagaaaa tcccaagaca gaagtgtgcg gtgggtataa agggccgtgc	2100
tgtgcctgtc ctaaaaccga agctgagaag caggctgaga aggaggaggc tgagtaccgt	2160
aaaagtctttg agaatttccct tcacaactcc atctttgtgc ccagacctga gaggaggcgg	2220
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gctgacacccat acaatatcac agacccggaa gagttcgaga cagaataccc ttctttgag	2340
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gtgtccagac aggagtacag gaagtatggg gggccaaac ttaaccgtct aaacccaggg	2700
aactataccg cccggattca ggctacccctt ctctctggaa atgggtcggt gacagatcct	2760
gtgttcttct atgtcccaacg caaaaacaacg tatgagaattt tcatgcacatc gatcatgt	2820
ctgcccgttg ccattctgtt gattgtgggg ggcctggtaa tcatgtgtta tgtctccat	2880
agaaagagga ataacagcag attggcaac ggggtgtgt acgcctctgt gaaccccgag	2940
tatttcagcg cagctgtatgt gtacgtgcctt gatgaatggg aggtagctcg ggagaagatc	3000
accatgaacc gggagctcg acaagggtcc ttccggatgg tctatgaagg agtggccaa	3060
ggcgtggta aggacgagcc tgaaaccaga gtggccatca agacagtggaa tgaggctca	3120
agtatgcgtg agagaattga gtttctcaac gaggcctcag tcatgtggaa gttcaactgt	3180
caccatgtgg tccgggtgtt ggggtgttagta tcccaaggcc agccacccctt ggtcatcat	3240
gaactaatga cacgtggcga tctcaaaatgt tatctccgtt ctctaaaggcc agaggtggag	3300
cagaataatc tagtccctgtat tccctccgago ttaagcaaga tcatgtggatgg ggctggagag	3360
attgcagatg gcatggccta cctcaatgcc aacaagttcg tccacagaga cctggctgt	3420
cggaactgca tggtagctga agatttcaca gtcaaaaattt gggatggatgg tatgacacga	3480
gacatctacg agacggacta ctaccggaaa ggccggaaagg gcttgcgtcc tggcgtgg	3540
atgtctcccg agtccctcaa ggtatggcgtc ttccaccatc attccgtatgt ctggccctt	3600

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ggggtcgtcc	tctggagat	cggcactctg	gctgagcagc	cgtaccaggg	cctgtccaa	3660
gagcaagttc	ttcgttcgt	catggagggc	ggccttctgg	acaagccgga	taactgc	3720
gatatgtgt	ttgaacttat	gchgatgtgc	tggcagtaca	acccaaga	gcccgttcc	3780
ttcctggaga	tcatcggaag	catcaaggat	gagatggagc	ccagttcca	ggagggttcc	3840
ttctactaca	gcgaggagaa	caagcctcca	gagccggagg	agctggagat	ggagctggag	3900
ctggagcccg	agaacatgg	gagcgtcccg	ctggaccct	cgccctcc	agcctcc	3960
cctctgcctg	aaagacactc	aggacacaag	gctgagaacg	gccctggcgt	gctggttc	4020
cgtgccagtt	ttgatgagag	acagccttac	gctcacatg	atgggggac	cgccaaacg	4080
agggccttgc	ctctgcccc	gtcctcaacc	tgctga			4116

<210> SEQ ID NO 81

<211> LENGTH: 1373

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF-I receptor

<222> LOCATION: (1)..(1373)

<223> OTHER INFORMATION: Mus musculus IGF-I receptor

<400> SEQUENCE: 81

Met	Lys	Ser	Gly	Ser	Gly	Gly	Ser	Pro	Thr	Ser	Leu	Trp	Gly	Leu
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Val	Phe	Leu	Ser	Ala	Ala	Leu	Ser	Leu	Trp	Pro	Thr	Ser	Gly	Glu	Ile
							20		25			30			

Cys	Gly	Pro	Gly	Ile	Asp	Ile	Arg	Asn	Asp	Tyr	Gln	Gln	Leu	Lys	Arg
							35		40			45			

Leu	Glu	Asn	Cys	Thr	Val	Ile	Glu	Gly	Phe	Leu	His	Ile	Leu	Leu	Ile
						50		55			60				

Ser	Lys	Ala	Glu	Asp	Tyr	Arg	Ser	Tyr	Arg	Phe	Pro	Lys	Leu	Thr	Val
						65		70			75			80	

Ile	Thr	Glu	Tyr	Leu	Leu	Phe	Arg	Val	Ala	Gly	Leu	Glu	Ser	Leu
						85		90			95			

Gly	Asp	Leu	Phe	Pro	Asn	Leu	Thr	Val	Ile	Arg	Gly	Trp	Lys	Leu	Phe
						100		105			110				

Tyr	Asn	Tyr	Ala	Leu	Val	Ile	Phe	Met	Thr	Asn	Leu	Lys	Asp	Ile
						115		120			125			

Gly	Leu	Tyr	Asn	Leu	Arg	Asn	Ile	Thr	Arg	Gly	Ala	Ile	Arg	Ile	Glu
						130		135			140				

Lys	Asn	Ala	Asp	Leu	Cys	Tyr	Leu	Ser	Thr	Ile	Asp	Trp	Ser	Leu	Ile
						145		150			155			160	

Leu	Asp	Ala	Val	Ser	Asn	Asn	Tyr	Ile	Val	Gly	Asn	Lys	Pro	Pro	Lys
						165		170			175				

Glu	Cys	Gly	Asp	Leu	Cys	Pro	Gly	Thr	Leu	Glu	Glu	Lys	Pro	Met	Cys
						180		185			190				

Glu	Lys	Thr	Thr	Ile	Asn	Asn	Glu	Tyr	Asn	Tyr	Arg	Cys	Trp	Thr	Thr
						195		200			205				

Asn	Arg	Cys	Gln	Lys	Met	Cys	Pro	Ser	Val	Cys	Gly	Lys	Arg	Ala	Cys
						210		215			220				

Thr	Glu	Asn	Asn	Glu	Cys	Cys	His	Pro	Glu	Cys	Leu	Gly	Ser	Cys	His
						225		230			235			240	

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Thr	Pro	Asp	Asp	Asn	Thr	Thr	Cys	Val	Ala	Cys	Arg	His	Tyr	Tyr	Tyr
245								250					255		
Lys	Gly	Val	Cys	Val	Pro	Ala	Cys	Pro	Pro	Gly	Thr	Tyr	Arg	Phe	Glu
260								265					270		
Gly	Trp	Arg	Cys	Val	Asp	Arg	Asp	Phe	Cys	Ala	Asn	Ile	Pro	Asn	Ala
275								280					285		
Glu	Ser	Ser	Asp	Ser	Asp	Gly	Phe	Val	Ile	His	Asp	Asp	Glu	Cys	Met
290								295					300		
Gln	Glu	Cys	Pro	Ser	Gly	Phe	Ile	Arg	Asn	Ser	Thr	Gln	Ser	Met	Tyr
305							310					315			320
Cys	Ile	Pro	Cys	Glu	Gly	Pro	Cys	Pro	Lys	Val	Cys	Gly	Asp	Glu	Glu
325							330						335		
Lys	Lys	Thr	Lys	Thr	Ile	Asp	Ser	Val	Thr	Ser	Ala	Gln	Met	Leu	Gln
340							345						350		
Gly	Cys	Thr	Ile	Leu	Lys	Gly	Asn	Leu	Leu	Ile	Asn	Ile	Arg	Arg	Gly
355							360						365		
Asn	Asn	Ile	Ala	Ser	Glu	Leu	Glu	Asn	Phe	Met	Gly	Leu	Ile	Glu	Val
370							375						380		
Val	Thr	Gly	Tyr	Val	Lys	Ile	Arg	His	Ser	His	Ala	Leu	Val	Ser	Leu
385						390					395			400	
Ser	Phe	Leu	Lys	Asn	Leu	Arg	Leu	Ile	Leu	Gly	Glu	Glu	Gln	Leu	Glu
405						410					415				
Gly	Asn	Tyr	Ser	Phe	Tyr	Val	Leu	Asp	Asn	Gln	Asn	Leu	Gln	Gln	Leu
420						425						430			
Trp	Asp	Trp	Asn	His	Arg	Asn	Leu	Thr	Val	Arg	Ser	Gly	Lys	Met	Tyr
435						440						445			
Phe	Ala	Phe	Asn	Pro	Lys	Leu	Cys	Val	Ser	Glu	Ile	Tyr	Arg	Met	Glu
450						455					460				
Glu	Val	Thr	Gly	Thr	Lys	Gly	Arg	Gln	Ser	Lys	Gly	Asp	Ile	Asn	Thr
465						470					475			480	
Arg	Asn	Asn	Gly	Glu	Arg	Ala	Ser	Cys	Glu	Ser	Asp	Val	Leu	Arg	Phe
485						490					495				
Thr	Ser	Thr	Thr	Trp	Lys	Asn	Arg	Ile	Ile	Ile	Thr	Trp	His	Arg	
500						505						510			
Tyr	Arg	Pro	Pro	Asp	Tyr	Arg	Asp	Leu	Ile	Ser	Phe	Thr	Val	Tyr	Tyr
515						520						525			
Lys	Glu	Ala	Pro	Phe	Lys	Asn	Val	Thr	Glu	Tyr	Asp	Gly	Gln	Asp	Ala
530						535					540				
Cys	Gly	Ser	Asn	Ser	Trp	Asn	Met	Val	Asp	Val	Asp	Leu	Pro	Pro	Asn
545						550					555			560	
Lys	Glu	Gly	Pro	Gly	Ile	Leu	Leu	His	Gly	Leu	Lys	Pro	Trp	Thr	
565						570					575			575	
Gln	Tyr	Ala	Val	Tyr	Val	Lys	Ala	Val	Thr	Leu	Thr	Met	Val	Glu	Asn
580						585					590				
Asp	His	Ile	Arg	Gly	Ala	Lys	Ser	Glu	Ile	Leu	Tyr	Ile	Arg	Thr	Asn
595						600					605				
Ala	Ser	Val	Pro	Ser	Ile	Pro	Leu	Asp	Val	Leu	Ser	Ala	Ser	Asn	Ser
610						615					620				
Ser	Ser	Gln	Leu	Ile	Val	Lys	Trp	Asn	Pro	Pro	Thr	Leu	Pro	Asn	Gly
625						630					635			640	
Asn	Leu	Ser	Tyr	Tyr	Ile	Val	Arg	Trp	Gln	Arg	Gln	Pro	Gln	Asp	Gly

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645	650	655
Tyr Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg		
660	665	670
Lys Tyr Ala Asp Gly Thr Ile Asp Val Glu Glu Val Thr Glu Asn Pro		
675	680	685
Lys Thr Glu Val Cys Gly Gly Asp Lys Gly Pro Cys Cys Ala Cys Pro		
690	695	700
Lys Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Ala Glu Tyr Arg		
705	710	715
Lys Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro		
725	730	735
Glu Arg Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser		
740	745	750
Ser Arg Ser Arg Asn Thr Thr Val Ala Asp Thr Tyr Asn Ile Thr Asp		
755	760	765
Pro Glu Glu Phe Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp		
770	775	780
Asn Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr		
785	790	795
Arg Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys		
805	810	815
Ser Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala		
820	825	830
Asp Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser		
835	840	845
Ile Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu		
850	855	860
Met Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys		
865	870	875
Val Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg		
885	890	895
Leu Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser		
900	905	910
Gly Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Pro Ala Lys		
915	920	925
Thr Thr Tyr Glu Asn Phe Met His Leu Ile Ile Ala Leu Pro Val Ala		
930	935	940
Ile Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His		
945	950	955
Arg Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser		
965	970	975
Val Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu		
980	985	990
Trp Glu Val Ala Arg Glu Lys Ile Thr Met Asn Arg Glu Leu Gly Gln		
995	1000	1005
Gly Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val		
1010	1015	1020
Lys Asp Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu		
1025	1030	1035
Ala Ala Ser Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser		
1040	1045	1050

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Val Met Lys Glu Phe Asn Cys His His Val Val Arg Leu Leu Gly
1055 1060 1065

Val Val Ser Gln Gly Gln Pro Thr Leu Val Ile Met Glu Leu Met
1070 1075 1080

Thr Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu
1085 1090 1095

Val Glu Gln Asn Asn Leu Val Leu Ile Pro Pro Ser Leu Ser Lys
1100 1105 1110

Met Ile Gln Met Ala Gly Glu Ile Ala Asp Gly Met Ala Tyr Leu
1115 1120 1125

Asn Ala Asn Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys
1130 1135 1140

Met Val Ala Glu Asp Phe Thr Val Lys Ile Gly Asp Phe Gly Met
1145 1150 1155

Thr Arg Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys
1160 1165 1170

Gly Leu Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu Lys Asp
1175 1180 1185

Gly Val Phe Thr Thr His Ser Asp Val Trp Ser Phe Gly Val Val
1190 1195 1200

Leu Trp Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu
1205 1210 1215

Ser Asn Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu
1220 1225 1230

Asp Lys Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg
1235 1240 1245

Met Cys Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu
1250 1255 1260

Ile Ile Gly Ser Ile Lys Asp Glu Met Glu Pro Ser Phe Gln Glu
1265 1270 1275

Val Ser Phe Tyr Tyr Ser Glu Glu Asn Lys Pro Pro Glu Pro Glu
1280 1285 1290

Glu Leu Glu Met Glu Leu Glu Met Glu Pro Glu Asn Met Glu Ser
1295 1300 1305

Val Pro Leu Asp Pro Ser Ala Ser Ser Ala Ser Leu Pro Leu Pro
1310 1315 1320

Glu Arg His Ser Gly His Lys Ala Glu Asn Gly Pro Gly Pro Gly
1325 1330 1335

Val Leu Val Leu Arg Ala Ser Phe Asp Glu Arg Gln Pro Tyr Ala
1340 1345 1350

His Met Asn Gly Gly Arg Ala Asn Glu Arg Ala Leu Pro Leu Pro
1355 1360 1365

Gln Ser Ser Thr Cys
1370

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<210> SEQ ID NO 82
<211> LENGTH: 4119
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: IGF-I receptor
<222> LOCATION: (1)..(4119)
<223> OTHER INFORMATION: Mus musculus IGF-I receptor

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<400> SEQUENCE: 82

atgaagtctg	gctccggagg	agggtccccg	acctcgctgt	gggggctcgt	gtttctctcc	60
gcccgcgtct	ctctctggcc	gacgagtggaa	gaaatctgtg	ggcccgccat	tgacatccgc	120
aacgactatac	acgagctgaa	gcgcctggaa	aactgcacgg	tgatcgaggg	cttcctccac	180
atcctgtca	tctccaaggc	cgaggactac	cgaagctacc	gttccccaa	gctcaccgtc	240
atcaactgagt	acttgtgct	cttccgagtc	gctggcctcg	agagcctggg	agaccttttc	300
cccaacctca	cagtcatccg	tggctggaaa	ctttctaca	actacgact	ggtcattttc	360
gagatgacca	atctcaagga	tattgggctt	tataatctga	ggaacattac	tcggggggcc	420
atcaggattg	agaagaacgc	cgacctctgt	tacctctcca	ccatagact	gtctctcatc	480
ttggatgcgg	tgtccaataa	ctacattgtg	gggaacaaggc	ccccgaagga	atgtggggac	540
ctgtgtccag	ggacatttggaa	ggagaagccc	atgtgtgaga	agaccacca	caacaatgag	600
tacaactacc	gctgctggac	cacaaatcg	tgccagaaaa	tgtgcccag	tgtgtgcggg	660
aagcgagcc	gcacccgagaa	caacgagtgc	tgccacccgg	agtgcctggg	cagctgccac	720
acacccggacg	acaacacaac	ctgcgtggcc	tgcagacact	actactacaa	aggcgtgtgt	780
gtgcctgcct	gccccctgg	cacctacagg	ttcgaggggct	ggcgctgtgt	ggatcgcgat	840
ttctgcgc	acatccccaa	cgctgagago	agtgactcg	atggcttgc	tatccacgac	900
gatgagtgc	tgcaggagtg	tccctcaggo	ttcatccgca	acagcaccca	gagcatgtac	960
tgtatcccc	gcgaaggccc	ctgccccaaa	gtctgcggcg	atgaagagaa	gaaaacgaaa	1020
accatcgatt	cggtgacttc	tgctcaa	ctccaaggat	gcaccatcct	gaaggggcaat	1080
ctgttatta	acatccggag	aggcaataac	attgcctcg	agttggagaa	cttcatgggg	1140
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tccttcctga	agaaccc	tctcatctta	ggagaggagc	agctggaaagg	gaactactcc	1260
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accgtcagg	ccggaaagat	gtactttgt	ttaatccca	agctgtgtgt	ctccgaaatt	1380
taccgcatt	aggaagtgc	cggaaccaag	ggacgcccaga	gaaaggggg	cataaacacc	1440
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ctcatcgat	tcacagttt	ctacaaggag	gcaccattt	aaaacgttac	ggaatatgac	1620
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gaaatctgt	acattcgac	caatgctca	gtcccttcca	ttccccat	tgtctctca	1860
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aacttggat	actacattgt	gaggtggc	cgccagcccc	aggatggtta	cctgtaccgg	1980
cacaactact	gctccaaaga	caaaataccc	atcagaa	acgccc	gtatgtgt	2040
gtggaggagg	tgacggaaaa	tcccaagaca	gaagtgtgt	gtgggtataa	aggccatgc	2100
tgccgttgcc	ctaaaactga	agctgagaag	caggctgaga	aggaggagc	tgagtaccgt	2160
aaagtcttg	agaatttcc	tcacaattcc	atcttgc	ccaggcccg	aaggaggcg	2220

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agagacgtca tgcaagtggc caacacgacc atgtccagcc gaagcaggaa caccacgta	2280
gctgacacct acaatatcac agacccggag gagttcgaga cagagtaccc tttctttag	2340
agcagactgg ataacaagga gaggactgtc atctccaacc tccggectt cactctgtac	2400
cgcatacgata tccacagctg caaccacgag gctgagaagc tgggctgcag cgccctccaa	2460
ttcgtctttg cgagaaccat gccagcagaa ggagcagatg atatccctgg tccggtgacc	2520
tgggagccaa gacccgaaaa ctccatctt ttaaagtggc cagaacccga gaaccccaac	2580
ggattgtatcc taatgtatga aattaaatac ggttcgcaag tcgaggatca gcggaaatgt	2640
gtgtccagac aggagtacag gaagtacgga gggccaaac tcaaccgtct aaacccagg	2700
aactatacag cccggattca ggctacccctc ctctctggg atgggtcatg gacagatcct	2760
gtgttcttct atgtccccgc caaaaacgacg tatgagaact tcatgcatct gatcattgct	2820
ctgcccggttt ccacatctgct gategttggg gggctggta tcatgctgta tgtctccat	2880
agaaagagaaa ataacagcag gttgggcaat ggagtgttgt atgcttctgt gaaccccgag	2940
tatttcagcg cagctgtatgt gtacgtgcct gatgaatggg aggtagctcg agagaagatc	3000
accatgaacc gggagctcg acaagggtcc tttgggatgg tctatgaagg agtggccaag	3060
ggtgtgttca aggtgaacc cgaaaccaga gtggccatca agacggtaaa cgaggctgca	3120
agtatgcgtg aaagaatcga gtttctcaac gaggcctcg tgatgaagga gttcaattgt	3180
caccatgtgg tccgggtgct ggggtgtggta tcccaaggcc agcccaccct ggtcatcatg	3240
gaactaatga cacgcgggtga tctcaaaagt tatctcccgat ctctgaggcc agaagtggag	3300
cagaataatc tagtccatcat tcctccgago ttaagcaaga tgatccagat ggctggagag	3360
attgcagatg gcatggccta cctcaatgcc aacaagttcg tccacagaga ctttgctgct	3420
aggaactgcg tggtagccga agattcaca gtcaaaaattg gagattcgg tatgacacga	3480
gacatctacg agacggacta ctacggaaa ggccggaaagg ggttgctgcc tggcgctgg	3540
atgtctcccg agtccctcaa ggtatggtgct ttcaactactc attctgtatgt ctggcccttc	3600
ggggtegtcc tctggagat cgccacgctg gctgagcagc cttaccagg ctgtccaaac	3660
gagcaagttc ttcgttcgt catggagggt ggcccttctgg acaagccgga caactgcct	3720
gatatgtgt ttgaacttat ggcgtgtc tggcagtata accccaagat gcccgcctcc	3780
ttccctggaga tcatcggcag catcaaggat gagatggagc ccagcttcca ggaggctcc	3840
ttctactaca gcgaggagaa caagectccc gagccagagg agctggagat ggagctggag	3900
atggagcctg agaacatggc gagegtccca ctggaccctt cggccctccctc agcctccctg	3960
cctctgcctg aaagacactc aggacacaag gctgagaatg gcccggccccc tggcgtgctc	4020
gttctcccgcg ccagtttga tgagagacag cttacgctc acatgaacgg gggacgcgc	4080
aacgagaggg cttgccttcc gcccagtc tcgacactc	4119

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<210> SEQ ID NO 83
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: IGF-I
<222> LOCATION: (1)..(70)
<223> OTHER INFORMATION: IGF-I

<400> SEQUENCE: 83

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Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

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

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
50 55 60

Lys Pro Ala Lys Ser Ala
65 70

<210> SEQ ID NO 84

<211> LENGTH: 210

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: IGF-I

<222> LOCATION: (1)..(210)

<223> OTHER INFORMATION: IGF-I

<400> SEQUENCE: 84

ggaccggaga cgctctgcgg ggctgagctg gtggatgctc ttcaaggctgt gtgtggagac	60
agggggcttt atttcaacaa gcccacaggg tatggctcca gcagtcggag ggcgcctcag	120
acaggcatcg tggatgagtg ctgcttccgg agctgtgatc taaggaggct ggagatgtat	180
tgcgcacccc tcaagcctgc caagtcagct	210

<210> SEQ ID NO 85

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-H1

<222> LOCATION: (1)..(5)

<223> OTHER INFORMATION: IGF11-16 CDR-H1

<400> SEQUENCE: 85

Ser Tyr Trp Met His	
1	5

<210> SEQ ID NO 86

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-H2

<222> LOCATION: (1)..(17)

<223> OTHER INFORMATION: IGF11-16 CDR-H2

<400> SEQUENCE: 86

Glu Thr Asn Pro Ser Asn Ser Val Thr Asn Tyr Asn Glu Lys Phe Lys	
1	5
	10
	15

Ser

<210> SEQ ID NO 87

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-H3

<222> LOCATION: (1)..(8)

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<223> OTHER INFORMATION: IGF11-16 CDR-H3

<400> SEQUENCE: 87

Gly Arg Gly Arg Gly Phe Ala Tyr
1 5

<210> SEQ ID NO 88

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-L1

<222> LOCATION: (1)..(11)

<223> OTHER INFORMATION: IGF11-16 CDR-L1

<400> SEQUENCE: 88

Arg Ala Ser Gln Asn Ile Asn Phe Trp Leu Ser
1 5 10

<210> SEQ ID NO 89

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-L2

<222> LOCATION: (1)..(7)

<223> OTHER INFORMATION: IGF11-16 CDR-L2

<400> SEQUENCE: 89

Lys Ala Ser Asn Leu His Thr
1 5

<210> SEQ ID NO 90

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 CDR-L3

<222> LOCATION: (1)..(9)

<223> OTHER INFORMATION: IGF11-16 CDR-L3

<400> SEQUENCE: 90

Leu Gln Gly Gln Ser Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 91

<211> LENGTH: 234

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<220> FEATURE:

<221> NAME/KEY: IGF11-16 Light chain

<222> LOCATION: (1)..(234)

<223> OTHER INFORMATION: IGF11-16 Light chain

<400> SEQUENCE: 91

Met Lys Leu Leu Ala Glu Leu Leu Gly Leu Leu Leu Phe Cys Phe Leu
1 5 10 15

Gly Val Arg Cys Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser
20 25 30

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

Ile Asn Phe Trp Leu Ser Trp Cys Gln Gln Lys Pro Gly Asn Ile Pro
50 55 60

-continued

Lys	Leu	Leu	Ile	Tyr	Lys	Ala	Ser	Asn	Leu	His	Thr	Gly	Val	Pro	Ser
65					70				75					80	
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	85					90						95			
Ser	Leu	Gln	Pro	Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Gly	Gln
	100					105					110				
Ser	Tyr	Pro	Tyr	Thr	Phe	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	
	115				120					125					
Ala	Asp	Ala	Ala	Pro	Thr	Val	Ser	Ile	Phe	Pro	Pro	Ser	Ser	Glu	Gln
	130				135				140						
Leu	Thr	Ser	Gly	Gly	Ala	Ser	Val	Val	Cys	Phe	Leu	Asn	Asn	Phe	Tyr
145					150				155			160			
Pro	Lys	Asp	Ile	Asn	Val	Lys	Trp	Lys	Ile	Asp	Gly	Ser	Glu	Arg	Gln
	165					170				175					
Asn	Gly	Val	Leu	Asn	Ser	Trp	Thr	Asp	Gln	Asp	Ser	Lys	Asp	Ser	Thr
	180					185				190					
Tyr	Ser	Met	Ser	Ser	Thr	Leu	Thr	Leu	Thr	Lys	Asp	Glu	Tyr	Glu	Arg
	195					200				205					
His	Asn	Ser	Tyr	Thr	Cys	Glu	Ala	Thr	His	Lys	Thr	Ser	Thr	Ser	Pro
	210				215				220						
Ile	Val	Lys	Ser	Phe	Asn	Arg	Asn	Glu	Cys						
	225				230										

<210> SEQ ID NO 92
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: IGF11-16 Light chain
<222> LOCATION: (1)..(705)
<223> OTHER INFORMATION: IGF11-16 Light chain

<400> SEQUENCE: 92

atgaaaactcc	ttgctgagct	cctggggctg	ctgctgttct	gctttttagg	tgtgagatgt	60
gacatccaga	tgaaccagtc	tccatccagt	ctgtctgcat	ccctcgagaa	cacaattacc	120
atcaacttgcc	gtgccagtca	gaacattaat	ttttggtaa	gctgggtgcca	gcagaaacca	180
ggaaatattc	ctaaactatt	gatctataag	gcttccaact	tgcacacagg	cgtcccatca	240
aggttttagtgc	gcagtggatc	tggAACAGAT	ttcacattaa	ccatcagcag	tctgcagcct	300
gaagacattg	ccacttacta	ctgtctacag	ggtcaaagtt	atccgtacac	gttcggaggg	360
gggaccaagc	tggaaataaa	acgggctgtat	gctgcaccaa	ctgttatccat	cttcccacca	420
tccagtggc	agttaacatc	tggaggtgccc	tcaagtgtgt	gcttcttggaa	caacttctac	480
cccaaagaca	tcaatgtcaa	gtgaaagatt	gatggcagtg	aacgacaaaa	tggcgtcctg	540
aacagttgaa	ctgatcagga	cagcaaagac	agcacctaca	gcatgagcag	caccctcact	600
ttgaccaagg	acgagttatgt	acgacataac	agctataccat	gtgaggccac	tcacaagaca	660
tcaacttcac	ccattgtcaa	gagcttcaac	aggaatgagt	gttag		705

<210> SEQ ID NO 93
<211> LENGTH: 460
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: IGF11-16 Heavy chain

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<222> LOCATION: (1) .. (460)

<223> OTHER INFORMATION: IGF11-16 Heavy chain

<400> SEQUENCE: 93

Met Gly Trp Ser Tyr Ile Ile Leu Phe Leu Val Ala Thr Val Thr Asp
1 5 10 15

Val His Ser Gln Ile Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys
20 25 30

Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Pro Gly Tyr Thr Phe
35 40 45

Thr Ser Tyr Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
50 55 60

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

Glu Lys Phe Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

Tyr Tyr Cys Thr Ile Gly Arg Gly Arg Gly Phe Ala Tyr Trp Gly Gln
115 120 125

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

Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr
145 150 155 160

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr
165 170 175

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
180 185 190

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser
195 200 205

Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala
210 215 220

Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys
225 230 235 240

Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
245 250 255

Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
260 265 270

Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe
275 280 285

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro
290 295 300

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

Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val
325 330 335

Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
340 345 350

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

Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp
370 375 380

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Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Ala Gln Pro
385 390 395 400

Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
405 410 415

Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala
420 425 430

Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His
435 440 445

His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> SEQ ID NO 94
<211> LENGTH: 1383
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: IGF11-16 Heavy chain
<222> LOCATION: (1)..(1383)
<223> OTHER INFORMATION: IGF11-16 Heavy chain

<400> SEQUENCE: 94

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tgcaaggctc cgggctacac ctaccaccgc tattggatc actgggtgaa gcagaggcct	180
ggacaaggcc ttgagtggat tggagagact aatcctagca atagtgttac taactacaat	240
gagaagttca agagcaaggc cacactgact gtagacaaaat cttccagcac agcctacatg	300
caactcagca gctgacate tgaggacttgc gcggtctatt actgtacaat agggaggggta	360
cggggatttg cttactgggg ccaaggact ctggctactg tctctgcagc caaaacgaca	420
cccccatctg tctatccact ggcccctggta tctgctgecc aaactaactc catggtgacc	480
ctgggatgcc tggcaaggg ctatccc gagccagtgta cagtgacccctg gaactctggaa	540
tccctgtcca gctgtgtgca cacttccca gctgtctgc agtctgaccccttacactctg	600
agcagctcg tgaactgtccc ctccagcac tggccagcg agaccgtcac ctgcaacgtt	660
gcccacccgg ccagcagcac caaggtggac aagaaaattg tgcccaggta ttgtggtgt	720
aaggccttgca tatgtacatg cccagaagta tcatctgtct tcatacttccc cccaaaggccc	780
aaggatgtgc tcaccattac tctgacttcc aaggtcacgt gtgttgtggta agacatcagc	840
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cagacgcaac cccgggaggaa gcagttcaac agcacattcc gctcagtcag tgaacttccc	960
atcatgcacc aggactggct caatggcaag gagttcaaatttgcaggggtcaa cagtgacgt	1020
ttccctgccc ccatcgagaa aaccatctcc aaaacccaaag gcagaccgaa ggctccacag	1080
gtgtacacca ttccacacttcc caaggagcag atggccaagg ataaagtcaatg tctgacccctgc	1140
atgataacacacttcc tgaagacatt actgtggagtttgcaggggtggaa tgccgcagcca	1200
gcggagaact acaagaacac tcagccatc atggacacag atggctcta ctgcgtctac	1260
agcaagtcataatgtcgagaa gagcaactgg gaggcaggaa atacttccatctgtctgt	1320
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tga	1383

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<210> SEQ ID NO 95
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1)..(98)
<223> OTHER INFORMATION: VH-1-46

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<400> SEQUENCE: 95

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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
															30

Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
															45

Gly	Ile	Ile	Asn	Pro	Ser	Gly	Gly	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe
50															60

Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
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Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
															95

Ala Arg

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<210> SEQ ID NO 96
<211> LENGTH: 98
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<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<223> OTHER INFORMATION: VH-1-e

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<400> SEQUENCE: 96

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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
															30

Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
															45

Gly	Gly	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe
50															60

Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
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Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
															95

Ala Arg

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<210> SEQ ID NO 97
<211> LENGTH: 15
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<220> FEATURE:

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<222> LOCATION: (1)..(15)

<223> OTHER INFORMATION: JH4

<400> SEQUENCE: 97

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<210> SEQ ID NO 98

<211> LENGTH: 95

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

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<222> LOCATION: (1)..(95)

<223> OTHER INFORMATION: VK1-L5

<400> SEQUENCE: 98

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

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	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	Ala	Asn	Ser	Phe	Pro
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<210> SEQ ID NO 99

<211> LENGTH: 95

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<221> NAME/KEY: VK1-A20

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<223> OTHER INFORMATION: VK1-A20

<400> SEQUENCE: 99

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

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

Tyr	Ala	Ala	Ser	Thr	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	Val	Ala	Thr	Tyr	Tyr	Cys	Gln	Lys	Tyr	Asn	Ser	Ala	Pro
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<210> SEQ ID NO 100
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1)..(12)
<223> OTHER INFORMATION: JK2

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<400> SEQUENCE: 100
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Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1           5           10
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1. An anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof comprising:
heavy-chain and light-chain complementarity determining regions (CDRs) each derived from mouse parent antibody IGF11-16; and
heavy-chain and light-chain framework regions (FRs) each derived from a human antibody,
wherein at least one of the CDRs contains a substitution of at least one amino acid residue relative to the corresponding CDR of the mouse parent antibody IGF11-16.
2. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, wherein the amino acid residue at the 25th position in Framework Region 1 of the heavy chain variable region (FR-H1) is a proline residue.
3. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, comprising:
as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), amino acid sequence defined in SEQ ID NO:1, or an amino acid sequence derived from SEQ ID NO:1 via substitution of any one amino acid residue thereof,
as a sequence of CDR-2 of the heavy chain variable region (CDR-H2), SEQ ID NO:3 or amino acid sequence defined in SEQ ID NO:5, or amino acid sequence derived from SEQ ID NO:3 or SEQ ID NO:5 via substitution of any one, two, or three amino acid residues thereof,
as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), amino acid sequence defined in SEQ ID NO:7, or an amino acid sequence derived from SEQ ID NO:7 via substitution of any one or two amino acid residues thereof,
as a sequence of CDR-1 of the light chain variable region (CDR-L1), amino acid sequence defined in SEQ ID NO:9, or an amino acid sequence derived from SEQ ID NO:9 via substitution of any one or two amino acid residues thereof,
as a sequence of CDR-2 of the light chain variable region (CDR-L2), amino acid sequence defined in SEQ ID NO:11, or an amino acid sequence derived from SEQ ID NO:11 via substitution of any one amino acid residue thereof,
as a sequence of CDR-3 of the light chain variable region (CDR-L3), amino acid sequence defined in SEQ ID

NO:13, or an amino acid sequence derived from SEQ ID NO:13 via substitution of any one or two amino acid residues thereof.

4. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, comprising:

as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), an amino acid sequence having a homology of 80% or more to SEQ ID NO:1,
as a sequence of CDR-2 of the heavy chain variable region (CDR-H2), an amino acid sequence having a homology of 82% or more to SEQ ID NO:3 or SEQ ID NO:5,
as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), an amino acid sequence having a homology of 75% or more to SEQ ID NO:7,
as a sequence of CDR-1 of the light chain variable region (CDR-L1), an amino acid sequence having a homology of 81% or more to SEQ ID NO:9,
as a sequence of CDR-2 of the light chain variable region (CDR-L2), an amino acid sequence having a homology of 85% or more to SEQ ID NO:11, and
as a sequence of CDR-3 of the light chain variable region (CDR-L3), an amino acid sequence having a homology of 77% or more to SEQ ID NO:13.

5. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, comprising:

as a sequence of CDR-1 of the heavy chain variable region (CDR-H1), an amino acid sequence derived from SEQ ID NO:1 in which Trp at the 3rd position of SEQ ID NO:1 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one amino acid residue other than the amino acid residue at the 3rd position or having a homology of 80% or more to SEQ ID NO:1,
as a sequence of CDR-2 of the heavy chain variable region (CDR-H2),
an amino acid sequence derived from SEQ ID NO:3 in which Glu at the 1st position and Asn at the 3rd position of SEQ ID NO:3 are each retained or substituted with a similar amino acid residue and Asn at the 6th position is retained or substituted with Ser or Gln, the amino acid sequence further including substitution of any one, two, or three amino acid residues other than the amino acid residues at the 1st

position, the 3rd position, and the 6th position or having a homology of 82% or more to SEQ ID NO:3, or

an amino acid sequence derived from SEQ ID NO:5 in which Glu at the 1st position and Asn at the 3rd position of SEQ ID NO:5 are each retained or substituted with a similar amino acid residue and Ser at the 6th position of SEQ ID NO:5 is retained or substituted with Asn or Gln, the amino acid sequence further including substitution of any one, two, or three amino acid residues other than the amino acid residues at the 1st position, the 3rd position, and the 6th position or having a homology of 82% or more to SEQ ID NO:5,

as a sequence of CDR-3 of the heavy chain variable region (CDR-H3), an amino acid sequence derived from SEQ ID NO:7 in which Arg at the 4th position of SEQ ID NO:7 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one or two amino acid residues other than the amino acid residue at the 4th position of SEQ ID NO:7 or having a homology of 75% or more to SEQ ID NO:7,

as a sequence of CDR-1 of the light chain variable region (CDR-L1), an amino acid sequence derived from SEQ ID NO:9 in which Trp at the 9th position of SEQ ID NO:9 is retained or substituted with a similar amino acid residue, the amino acid sequence further including substitution of any one or two amino acid residues other than the amino acid residue at the 9th position of SEQ ID NO:9 or having a homology of 81% or more to SEQ ID NO:9,

as a sequence of CDR-2 of the light chain variable region (CDR-L2), an amino acid sequence derived from SEQ ID NO:11 substitution of any one amino acid residue or having a homology of 85% or more to SEQ ID NO:11, as a sequence of CDR-3 of the light chain variable region (CDR-L3), an amino acid sequence derived from SEQ ID NO:13 substitution of any one or two amino acid residues or having a homology of 77% or more to SEQ ID NO:13.

6. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which binds specifically to an extracellular domain of human IGF-1 receptor having the amino acid sequence defined in SEQ ID NO:71.

7. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, comprising:

as a heavy chain variable region, an amino acid sequence defined in SEQ ID NO:43, 47, 49, 53, 55, or 59, an amino acid sequence derived from SEQ ID NO:43, 47, 49, 53, 55, or 59 via substitution, deletion, or addition of one or several amino acid residues, or an amino acid sequence having a homology of 90% or more to SEQ ID NO:43, 47, 49, 53, 55, or 59, and

as a light chain variable region, an amino acid sequence defined in SEQ ID NO:65, 67, or 69, an amino acid sequence derived from SEQ ID NO:65, 67, or 69 via substitution, deletion, or addition of one or several amino acid residues, or an amino acid sequence having a homology of 90% or more to SEQ ID NO:65, 67, or 69.

8. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, comprising as a constant region of heavy and/or light chains, a constant region of heavy and/or light chains of any class of human immunoglobulin.

9. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, wherein the heavy chain constant region is the heavy chain constant region of human IgG4 or a region derived therefrom via substitution of 1 to 10 amino acids.

10. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, wherein the heavy chain constant region is the heavy chain constant region of human IgG1 or a region derived therefrom via substitution of 1 to 10 amino acids.

11. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which binds to an IGF-1 receptor with an affinity represented by an equilibrium dissociation constant (KD) of 1×10^{-7} M or less.

12. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an ability to activate IGF-1 receptor signaling.

13. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which exhibits a proliferative activity in a myoblast proliferation assay.

14. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which exhibits a binding affinity equivalent to or higher than that of the mouse parent antibody IGF11-16 in a BIACORE binding assay to recombinant soluble IGF-1 receptor.

15. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an ability to induce muscle mass gain effect without inducing hypoglycemic symptoms in a normal mammal.

16. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an ability to induce growth plate cartilage elongation effect without inducing hypoglycemic symptoms in a hypophysectomized model animal.

17. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which, when administered to a vertebrate animal at a dose which induces an increase in muscle mass and/or body length, does not reduce the blood glucose level of the vertebrate animal.

18. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which, even at a blood exposure level 10 times higher than an effective dose sufficient to induce an increase in muscle mass and/or body length, does not reduce the blood glucose level of a vertebrate animal.

19. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an ability to inhibit the activation of IGF-1 receptor signaling.

20. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which inhibits the proliferative activity of at least one ligand of IGF-1, IGF-2 and insulin, which ligand can activate the IGF-1 receptor in a myoblast proliferation assay.

21. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an activity to inhibit cell proliferation in a cancer cell proliferation assay.

22. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has at least one characteristic selected from:

- (1) inhibiting the proliferation of vertebrate-derived cells induced by an IGF-1 receptor activating ligand;
- (2) inhibiting the proliferation of cells in a vertebrate animal induced by an IGF-1 receptor activating ligand in a cell proliferative disorder;
- (3) not affecting glucose uptake by differentiated muscle cells at a dose sufficient to inhibit the proliferation of vertebrate-derived cells induced by an IGF-1 receptor activating ligand; and
- (4) not affecting the blood glucose level in a vertebrate animal even at a dose sufficient to inhibit cell proliferation in a vertebrate cell proliferative disorder caused by IGF-1 receptor activating ligand.

23. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1, which has an ability to induce an inhibitory effect on cancer cell proliferation without affecting the blood glucose level in a cancer-bearing model animal.

24. The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 23, which, even at a blood exposure level 10 times higher than an effective dose sufficient to induce an inhibitory effect on cancer cell proliferation in a cancer-bearing model animal, does not affect the blood glucose level of the model animal.

25. A nucleic acid molecule comprising a polynucleotide sequence encoding an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1.

26. A cloning vector or expression vector comprising at least one nucleic acid molecule according to claim 25.

27. A recombinant cell derived from a host cell via introduction of a vector according to claim 26.

28. A process of producing an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof, comprising:

- culturing a recombinant cell according to claim 27; and
- purifying the anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof produced by the recombinant cell.

29. A pharmaceutical composition comprising, as an active ingredient, an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1.

30. A method for treating muscle atrophic disease or dwarfism, comprising administering the pharmaceutical composition according to claim 29 to a subject in need thereof.

31. The method according to claim 30, wherein the muscle atrophic disease is disuse muscle atrophy, sarcopenia, or cachexia.

32. The method according to claim 30, wherein the dwarfism is Laron-type dwarfism or growth-hormone resistant dwarfism.

33. A method for treating an IGF-1 receptor associated disease, comprising administering the pharmaceutical composition according to claim 29 to a subject in need thereof.

34. The method according to claim 33, wherein the IGF-1 receptor associated disease is selected from the group consisting of: liver cancer, neuroblastoma, rhabdomyosarcoma, bone cancer, pediatric cancer, acromegalia, ovary cancer, pancreas cancer, benign prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, neck cancer, synoviosarcoma, urinary bladder cancer, stomach cancer, Wilms' tumor, diarrhea associated with metastatic carcinoid and vasoactive intestinal peptide secreting tumor, vipoma, Verner-Morrison syndrome, Beckwith-Wiedemann syndrome, kidney cancer, renal-cell cancer, transitional cell cancer, Ewing's sarcoma, leukemia, acute lymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatous brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, undifferentiated neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendrogloma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic erythematoses, myasthenia gravis, autoimmune thyroiditis, Hashimoto's thyroiditis, thyroid ophthalmopathy, hyperthyroidism and Behcet's disease.

* * * * *