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## SUMMARY OF INVENTION

### PROBLEM TO BE SOLVED BY THE INVENTION

[0019]

An objective of the present ~~invention~~disclosure 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.

[0020]

Specific objectives of the present ~~invention~~disclosure 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 [inventiondisclosure](#)); (3) provision of amino acid substitutions to reduce immunogenicity; and (4) provision of amino acid substitutions to avoid the risk of deamidation.

[0021]

Utilization and application of the present [inventiondisclosure](#) allows for provision of an anti-IGF-1 receptor humanized antibody that can increase muscle mass 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

[0022]

Thus, the present [inventiondisclosure](#) relates to, e.g., the following Aspects:

[Aspect 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.

[Aspect 2]

[A nucleic acid molecule comprising a polynucleotide sequence encoding an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof as disclosed herein.](#)

[Aspect 3]

[A cloning vector or expression vector comprising at least one nucleic acid molecule as disclosed herein.](#)

[Aspect 4]

[A recombinant cell derived from a host cell via introduction of a vector as disclosed herein.](#)

[Aspect 5]

A process of producing an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof as disclosed herein, comprising:

culturing a recombinant cell as disclosed herein; and

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

[Aspect 6]

A pharmaceutical composition comprising, as an active ingredient, an anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof as disclosed herein, a nucleic acid molecule as disclosed herein, a vector as disclosed herein, or a recombinant cell as disclosed herein.

[Aspect 7]

Use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating muscle atrophic disease or dwarfism.

[Aspect 8]

Use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating an IGF-1 receptor associated disease.

[Example 1]

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.

[Example 2Aspect 3]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[\[Example 3 Aspect 4\]](#)

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[\[Example 4 Aspect 5\]](#)

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[\[Example 5Aspect-6\]](#)

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.

[\[Example 6Aspect-7\]](#)

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 6, 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.

[[Example 7](#)~~Aspect 8~~]

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.

[[Example 8](#)~~Aspect 9~~]

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.

[[Example 9](#)~~Aspect 10~~]

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.

[[Example 10](#)~~Aspect 11~~]

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  $1 \times 10^{-7}$  M or less.

[[Example 11](#)~~Aspect 12~~]

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.

[[Example 12](#)~~Aspect 13~~]

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.

[[Example 13](#)~~Aspect 14~~]

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 BIACORE binding assay to recombinant soluble IGF-1 receptor.

[[Example 14](#)~~Aspect 15~~]

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.

[[Example 15](#)~~Aspect 16~~]

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.

[[Example 16](#)~~Aspect 17~~]

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.

[[Example 17](#)~~Aspect 18~~]

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.

[[Example 18](#)~~Aspect 19~~]

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.

[[Example 19](#)~~Aspect 20~~]

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.

[[Example 20](#)~~Aspect 21~~]

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.

[[Example 21](#)~~Aspect 22~~]

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:

- (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.

[[Example 22](#)[Aspect 23](#)]

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.

[[Example 23](#)[Aspect 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.

[[Example 24](#)[Aspect 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 any one of claims 1 to 24.

[[Example 25](#)[Aspect 26](#)]

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

[[Example 26](#)[Aspect 27](#)]

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

[[Example 27](#)[Aspect 28](#)]

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:

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.

[[Example 28](#)[Aspect 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 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.

[[Example 29](#)[Aspect 30](#)]

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

[[Example 30](#)[Aspect 31](#)]

The pharmaceutical composition according to claim 30, wherein the muscle atrophic

disease is disuse muscle atrophy, sarcopenia, or cachexia.

[[Example 31](#)[Aspect 32](#)]

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

[[Example 32](#)[Aspect 33](#)]

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

[[Example 33](#)[Aspect 34](#)]

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, oligodendroglioma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic erythematodes, myasthenia gravis, autoimmune thyroiditis, Hashimoto's thyroiditis, thyroid ophthalmopathy, hyperthyroidism and Behcet's disease.

## **ADVANTAGEOUS EFFECTS OF INVENTION**

[0023]

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**

[0024]

[Figure 1A] Figures 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.

## CLAIMS

### [Claim 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.

### [Claim 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.

### [Claim 3]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[Claim 4]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[Claim 5]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to claim 1 or 2, 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.

[Claim 6]

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.

[Claim 7]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 6, 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.

[Claim 8]

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.

[Claim 9]

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.

[Claim 10]

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.

[Claim 11]

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  $1 \times 10^{-7}$  M or less.

[Claim 12]

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.

[Claim 13]

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.

[Claim 14]

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 equivalent to or higher than that of the mouse parent antibody IGF11-16 in a BIACORE binding assay to recombinant soluble IGF-1 receptor.

[Claim 15]

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.

[Claim 16]

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.

[Claim 17]

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.

[Claim 18]

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.

[Claim 19]

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.

[Claim 20]

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.

[Claim 21]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 20, which has an activity to inhibit cell proliferation in a cancer cell proliferation assay.

[Claim 22]

The anti-IGF-1 receptor humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 21, 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.

[Claim 23]

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.

[Claim 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.

[Claim 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 any one of claims 1 to 24.

[Claim 26]

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

[Claim 27]

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

[Claim 28]

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:

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.

[Claim 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 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.

[Claim 30]

Use of the ~~The~~ pharmaceutical composition according to claim 29 in the manufacture of a medicament for, ~~for use in the treatment of~~ treating muscle atrophic disease or dwarfism.

[Claim 31]

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

[Claim 32]

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

[Claim 33]

Use of the ~~The~~ pharmaceutical composition according to claim 29 in the manufacture of a medicament for treating, ~~for use in the treatment of~~ an IGF-1 receptor associated disease.

[Claim 34]

The ~~pharmaceutical composition~~ use 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, benignant 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, oligodendroglioma, brain room top swell, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic erythematodes, myasthenia gravis, autoimmune thyroiditis, Hashimoto's thyroiditis, thyroid ophthalmopathy, hyperthyroidism and Behcet's disease.