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SUMMARY

PROBLEM TO BE SOLVED BY THE DISCLOSURE

[0017]

An objective of the present disclosure is to provide an anti-IGF-I receptor antibody or its fragment or a derivative thereof which specifically binds to an IGF-I receptor of a vertebrate. Another objective of the present disclosure is to provide an antibody which increases the muscle mass or the thickness of growth plate cartilage via the IGF-I receptor while not reducing the blood glucose level.

MEANS TO SOLVE THE PROBLEM

[0018]

The present disclosure relates to the following:

Example [1] An anti-IGF-I receptor antibody or its fragment or a derivative thereof which

specifically binds to an IGF-I receptor of a vertebrate, and exhibits an activity to induce growth of vertebrate-derived cells.

Example [2] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [1], wherein the activity of the antibody, fragment, or derivative to induce growth of vertebrate-derived cells is equal to or higher than the corresponding activity of a wild-type IGF-I.

Example [3] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [1] or Example [2], wherein the EC_{50} value of the antibody, fragment, or derivative for inducing growth of vertebrate-derived cells *in vitro* is 1/20 or less of the corresponding value of a wild-type IGF-I.

Example [4] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [3], wherein when the antibody, fragment, or derivative is contacted with cultured vertebrate-derived cells, the duration of activity of the antibody, fragment, or derivative to induce growth of the culstured cells relative to the duration of contact is improved than a wild-type IGF-I.

Example [5] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [2] to Example [4], wherein the wild-type IGF-I is a human IGF-I having an amino acid sequence defined in SEQ ID NO:1.

Example [6] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [5], wherein the EC_{50} value of the antibody, fragment, or derivative for inducing growth of vertebrate-derived cells *in vitro* is 0.1nmol/L or lower.

Example [7] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [6], which exhibits an activity to induce an increase in the muscle mass and/or the body length of a vertebrate when parenterally administered to the vertebrate.

Example [8] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [7], which is administered to a vertebrate at a frequency of once a week or less.

Aspect [9] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Aspect [1] to Aspect [8], wherein the vertebrate is a human; a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl; or a non-human animal engineered to express a human IGF-I receptor.

Example [10] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [9], which does not induce glucose uptake by differentiated muscle cells when administered at a dosage sufficient to induce growth of vertebrate-derived cells.

Example [11] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to

Example [10], which does not induce glucose uptake by differentiated muscle cells when administered at a dosage of 100 times or more of the EC_{50} value for inducing growth of vertebrate-derived cells *in vitro*.

Example [12] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [10] or Example [11], wherein the vertebrate-derived cells are myoblasts derived from a human or a non-human mammal.

Example [13] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [7] to Example [12], which does not lower the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

Example [14] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [13], which does not change the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage of 10 times or more of an effective dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

Example [15] An anti-IGF-I receptor antibody or its fragment or a derivative thereof, according to any one of Example [1] to Example [14], which binds to a CR domain of an IGF-I receptor.

Example [16] An anti-IGF-I receptor antibody or its fragment or a derivative thereof, which binds to a CR domain of an IGF-I receptor, and inhibits binding of IGF-I or IGF-II to an IGF-I receptor.

Example [17] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [16], which binds to an epitope containing ProSerGlyPheIleArgAsnX_1X_2GlnSerMet (where X_1 represents Gly or Ser and X_2 represents Ser or Thr), or a part in the vicinity thereof, in the sequence of the CR domain of the IGF-I receptor.

Example [18] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [17], which binds to an epitope containing ProSerGlyPheIleArgAsnGlySerGlnSerMet, or a part in the vicinity thereof, in the sequence of the CR domain of the IGF-I receptor.

Example [19] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [18], which has a cross-reactivity with an IGF-I receptor of a human or a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl.

Example [20] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [19], which causes an antigen-antibody reaction with an affinity intensity at a equilibrium dissociation constant (KD) of 1×10^{-8}M or less.

Example [21] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [16] to Example [20], which has at least one of the features of:

1) exhibiting an activity to induce growth of vertebrate-derived cells;

2) exhibiting an activity to induce an increase in the muscle mass and/or the body length of a vertebrate when parenterally administered to the vertebrate;

3) not inducing glucose uptake by differentiated muscle cells when administered at a dosage sufficient to induce growth of vertebrate-derived cells; and

4) not changing the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

Example [22] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [16] to Example [21], which has at least one of the features of:

1) inhibiting growth of vertebrate-derived cells induced by IGF-I;

2) inhibiting IGF-I-induced cell proliferation in a vertebrate suffering a cell proliferative disease when parenterally administered to the vertebrate;

3) not affecting glucose uptake by differentiated muscle cells at a dosage sufficient to inhibit growth of vertebrate-derived cells induced by IGF-I; and

4) not changing the blood glucose level of a vertebrate suffering a cell proliferative disease when parenterally administered to the vertebrate at a dosage sufficient to inhibit IGF-I-induced cell proliferation in the vertebrate.

Example [23] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [22], which is a Fab, scFv, diabody or bispecific antibody, or a derivative thereof.

Example [24] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [23], consisting of an amino acid sequence comprising:

as a heavy chain variable region CDR-1 (CDR-H1) sequence, an amino acid sequence defined in SEQ ID NO:3 or an amino acid sequence derived from SEQ ID NO:3 via substitution, deletion or insertion of any one amino acid residue;

as a heavy chain variable region CDR-2 (CDR-H2) sequence, an amino acid sequence defined in SEQ ID NO:4 or an amino acid sequence derived from SEQ ID NO:4 via substitution, deletion or insertion of any one or two amino acid residues;

as a heavy chain variable region CDR-3 (CDR-H3) sequence, an amino acid sequence defined in SEQ ID NO:5 or an amino acid sequence derived from SEQ ID NO:5 via substitution, deletion or insertion of any one or two amino acid residues;

as a light chain variable region CDR-1 (CDR-L1) sequence, an amino acid sequence defined in SEQ ID NO:6 or an amino acid sequence derived from SEQ ID NO:6 via substitution, deletion or insertion of any one or two amino acid residues;

as a light chain variable region CDR-2 (CDR-L2) sequence, an amino acid sequence defined in SEQ ID NO:7 or an amino acid sequence derived from SEQ ID NO:7 via substitution,

deletion or insertion of any one amino acid residue; and

as a light chain variable region CDR-3 (CDR-L3) sequence, an amino acid sequence defined in SEQ ID NO:8 or an amino acid sequence derived from SEQ ID NO:8 via substitution, deletion or insertion of any one or two amino acid residues.

Example [25] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [24 further comprises a framework sequence of immunoglobulin.

Example [26] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to Example [25], wherein the framework sequence of immunoglobulin is a framework sequence of each class of immunoglobulin from a human or a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, a fowl, a mouse, or a rat.

Example [27] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [26], which consists of an amino acid sequence comprising:

as a heavy chain variable region, an amino acid sequence defined in SEQ ID NO:9 or an amino acid sequence having a similarity of 90% or more to SEQ ID NO:9; and

as a light chain variable region, an amino acid sequence defined in SEQ ID NO:10 or an amino acid sequence having a similarity of 90% or more to SEQ ID NO:10.

Example [28] The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [27] further comprising a constant region of each class of immunoglobulin a human or a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, a fowl, a mouse, or a rat.

Example [29] A nucleic acid molecule consisting of a polynucleotide sequence encoding an anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [28].

Example [30] A cloning vector or expression vector comprising at least one nucleic acid molecule according to Example [29].

Example [31] A recombinant cell derived from a host cell via transfection of a vector according to Example [30].

Example [32] A process of producing an anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [28], comprising:

culturing a recombinant cell according to Example [31]; and

purifying the anti-IGF-I receptor antibody, fragment, or derivative produced from the recombinant cell.

Example [33] A pharmaceutical composition comprising an anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [28], a nucleic acid molecule according to Example [29], a vector according to Example [30], or a recombinant cell according to Example [31].

Example [34] The pharmaceutical composition according to Example [33], further comprising an additional active ingredient other than the anti-IGF-I receptor antibody, fragment, or derivative according to any one of Example [1] to Example [28], the nucleic acid molecule according to Example [29], the vector according to Example [30], or the recombinant cell according to Example [31].

Example [35] The pharmaceutical composition according to Example [34], wherein the active ingredient is one or more selected from a growth hormone or an analog thereof, insulin or an analog thereof, IGF-II or an analog thereof, an anti-myostatin antibody, a myostatin antagonist, an anti-activin type IIB receptor antibody, an activin type IIB receptor antagonist, a 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.

Example [36] The pharmaceutical composition according to Example [34] or Example [35], wherein the active ingredient comprises an ingredient selected from the group consisting of: 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-VEGFantibody, 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.

Example [37] A medical drug for use in the treatment or prevention of a condition associated with IGF-I or IGF-II, comprising comprising an anti-IGF-I receptor antibody or its fragment or a derivative thereof according to any one of Example [1] to Example [28], a nucleic acid molecule according to Example [29], a vector according to Example [30], or a recombinant cell according to Example [31].

Example [38] The medical drug according to Example [37], wherein the condition associated with IGF-I is selected from: disuse muscle atrophy, dwarfism, diabetic nephropathy, chronic renal failure, 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, 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, Turner's syndrome, Prader-Willi syndrome, Silver-Russell syndrome, idiopathic short stature, obesity, multiple sclerosis, fibromyalgia, ulcerous colitis, low muscle mass, myocardial ischemia and decreased bone density.

Example [39] The medical drug according to Example [37] or Example [38], which is parenterally administered.

Example [40] The medical drug according to any one of Example [37] to Example [39], which is a veterinary drug to be administered to a non-human animal.

Example [41] The medical drug according to Example [40], wherein the veterinary drug is administered for the purpose of, increasing muscle mass and/or body length, promoting growth, increasing milk production, promoting reproduction, or preventing aging.

Example [42] The medical drug according to Example [40] or Example [41], wherein the non-human animal is a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl.

Example [43] The medical drug according to any one of Example [37] to Example [42], for the treatment or prevention of a disease caused by an effect of IGF-I or IGF-II on an IGF-I receptor.

Example [44] The medical drug according to Example [43], wherein the disease caused by an effect of IGF-I or IGF-II on an IGF-I receptor is selected from the group consisting of: liver cancer, neuroblastoma, striated muscle sarcoma, bone cancer, childhood cancer, acromegalia, ovary cancer, pancreas cancer, benignant prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervix cancer, synovial sarcoma, 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 ymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatic brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic lupus erythematosus, chronic thyroiditis, myasthenia gravis, autoimmune thyroiditis and Behcet's disease.

Example [45] A method of culturing vertebrate-derived cells *in vitro*, comprising contacting the vertebrate-derived cells with an anti-IGF-I receptor antibody or its fragment or a derivative

thereof according to any one of Example [1] to Example [28], a nucleic acid molecule according to Example [29], a vector according to Example [30], and a recombinant cell according to Example [31] when culturing the cells.

Example [46] The method according to Example [45], wherein said contacting is carried out for the purpose of promoting growth or inducing differentiation of the vertebrate-derived cells.

Example [47] The method according to Example [45] or Example [46], wherein the anti-IGF-I receptor antibody, fragment, or derivative is adsorbed by, or immobilized to, a solid phase.

Example [48] A transgenic animal comprising an IGF-I receptor gene which has been mutated in a CR domain thereof via gene engineering such that the CR domain includes an amino acid sequence represented by ProSerGlyPheIleArgAsnGlySerGlnSerMet.

Example [49] A transgenic animal into which a heterologous IGF-I receptor gene has been transfected, wherein the amino acid sequence encoded by the heterologous IGF-I receptor gene differs from the amino acid sequence encoded by the animal's inherent IGF-I receptor gene in amino acid residue(s) X_1 and/or X_2 of a sequence represented by ProSerGlyPheIleArgAsnX_1X_2GlnSerMet in a CR domain.

Example [50] An anti-IGF-I receptor antibody or its fragment or a derivative thereof as described herein, a nucleic acid molecule as described herein, a vector as described herein, or a recombinant cell as described herein for use in therapy.

Example [51] Use of an anti-IGF-I receptor antibody or its fragment or a derivative thereof as described herein, a nucleic acid molecule as described herein, a vector as described herein, or a recombinant cell as described herein in the manufacture of a medicament for the treatment or prevention of a condition associated with IGF-I or IGF-II.

Example [52] In one aspect, the present disclosure refers to an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof which specifically binds to a wild-type human IGF-I receptor having an amino acid sequence defined in SEQ ID NO:2, and exhibits an activity to induce growth of human-derived cells.

Example [53] In another aspect, the present disclosure refers to an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein, which binds to binding sites including the amino acids at positions 315 and 316 of an amino acid sequence of a wild-type human IGF-I receptor defined in SEQ ID NO:2.

Example [54] In another aspect, the present disclosure refers to a nucleic acid molecule consisting of a polynucleotide sequence encoding an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein.

Example [55] In another aspect, the present disclosure refers to a cloning vector or expression

vector comprising at least one nucleic acid molecule as described herein.

Example [56] In another aspect, the present disclosure refers to a recombinant cell derived from a host cell via transfection of a vector as described herein.

Example [57] In another aspect, the present disclosure refers to a process of producing an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein, comprising: culturing a recombinant cell as described herein; and
purifying the anti-IGF-I receptor antibody, fragment, or derivative produced from the recombinant cell.

Example [58] In another aspect, the present disclosure refers to a pharmaceutical composition comprising an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein, a nucleic acid molecule as described herein, a vector as described herein, or a recombinant cell as described herein.

Example [59] In yet another aspect, the present disclosure refers to an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein, a nucleic acid molecule as described herein, a vector as described herein, or a recombinant cell as described herein for use in therapy.

Example [60] In yet another aspect, the present disclosure refers to a use of the anti-IGF-I receptor antibody or its antigen binding fragment or the derivative thereof as described herein, the nucleic acid molecule as described herein, the vector as described herein, or the recombinant cell as described herein in the manufacture of a medicament for the treatment or prevention of a condition associated with IGF-I, wherein said condition is selected from the group consisting of: disuse muscle atrophy, dwarfism, diabetic nephropathy, chronic renal failure, 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, 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, Turner's syndrome, Prader-Willi syndrome, Silver-Russell syndrome, idiopathic short stature, obesity, multiple sclerosis, fibromyalgia, ulcerous colitis, low muscle mass, myocardial ischemia and decreased bone density.

Example [61] In yet another aspect, the present disclosure refers to a use of the anti-IGF-I receptor antibody or its antigen binding fragment or the derivative thereof as described herein, the nucleic acid molecule as described herein, the vector as described herein, or the recombinant cell as described herein in the manufacture of a medicament for the treatment or prevention of a disease caused by an effect of IGF-I or IGF-II on an IGF-I receptor, wherein said disease is selected from the group consisting of: liver cancer, neuroblastoma, striated muscle sarcoma,

bone cancer, childhood cancer, acromegalia, ovary cancer, pancreas cancer, benignant prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervix cancer, synovial sarcoma, 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 ymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatic brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic lupus erythematosus, chronic thyroiditis, myasthenia gravis, autoimmune thyroiditis and Behcet's disease.

Example [62] In yet another aspect, the present disclosure refers to a method of culturing vertebrate-derived cells *in vitro*, comprising contacting the vertebrate-derived cells with an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof as described herein, a nucleic acid molecule as described herein, a vector as described herein, and a recombinant cell as described herein when culturing the cells.

EFFECT OF THE DISCLOSURE

[0019]

The anti-IGF-I receptor antibody or its fragment or a derivative thereof according to the present disclosure has an effect of specifically binding to an IGF-I receptor of a vertebrate.

BRIEF EXPLANATION OF THE DRAWINGS

[0020]

Figure 1 illustrates aligned amino acid sequences of CR domains of the mouse, rat, human, guinea pig and rabbit IGF-I receptors, in which the amino acid sequences are indicated using the one letter code;

Figure 2 is a graph indicating the results of ELISA using variants of a presumptive epitope of IGF11-16;

Figure 3 is a graph indicating the growth activity of human myoblasts after removal of IGF11-16 and IGF-I;

Figure 4 is a graph indicating the glucose uptake effect by human differentiated muscle cells after addition of IGF-I and IGF11-16;

Figure 5 is a graph indicating the weights of extensor digitorum longus muscles of guinea pigs which received sustained administration of IGF-I using an osmotic pump for two weeks or

CLAIMS

[Claim 1]

An anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof which specifically binds to a wild-type human IGF-I receptor having an amino acid sequence defined in SEQ ID NO:2, and exhibits an activity to induce growth of human-derived cells.

[Claim 2]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 1, wherein the activity of the antibody, fragment, or derivative to induce growth of human-derived cells is equal to or higher than the corresponding activity of a wild-type human IGF-I having an amino acid sequence defined in SEQ ID NO:1.

[Claim 3]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 1 or 2, wherein the EC_{50} value of the antibody, fragment, or derivative for inducing growth of human-derived cells in vitro is 1/20 or less of the corresponding value of a wild type human IGF-I having an amino acid sequence defined in SEQ ID NO:1.

[Claim 4]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 3, wherein when the antibody, fragment, or derivative is contacted with cultured vertebrate-derived cells, the duration of activity of the antibody, fragment, or derivative to induce growth of the cultured cells relative to the duration of contact is longer than a wild human type IGF-I having an amino acid sequence defined in SEQ ID NO:1.

[Claim 5]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 4, wherein the EC_{50} value of the antibody, fragment, or derivative for inducing growth of human-derived cells in vitro is 0.1nmol/L or lower.

[Claim 6]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 5, which exhibits an activity to induce an increase in the muscle mass and/or the body length of a vertebrate when parenterally administered to the vertebrate.

[Claim 7]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 6, which is administered to a vertebrate at a frequency of once a week or less.

[Claim 8]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 7, wherein the vertebrate is a human; a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl; or a non-human animal engineered to express a human IGF-I receptor.

[Claim 9]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 8, which does not induce glucose uptake by differentiated muscle cells when administered at a dosage sufficient to induce growth of vertebrate-derived cells.

[Claim 10]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 9, which does not induce glucose uptake by differentiated muscle cells when administered at a dosage of 100 times or more of the EC_{50} value for inducing growth of vertebrate-derived cells in vitro.

[Claim 11]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 9 or 10, wherein the vertebrate-derived cells are myoblasts derived from a human or a non-human mammal.

[Claim 12]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 6 to 11, which does not lower the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

[Claim 13]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 12, which does not change the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage of 10 times or more of an effective dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

[Claim 14]

An anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof, according to any one of claims 1 to 13, which binds to binding sites including the amino acids at

positions 315 and 316 of an amino acid sequence of a wild-type human IGF-I receptor defined in SEQ ID NO:2.

[Claim 15]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 14, which binds to an epitope containing ProSerGlyPheIleArgAsnX_1X_2GlnSerMet (where X_1 represents Gly or Ser and X_2 represents Ser or Thr), or a part in the vicinity thereof, in the sequence of the CR domain of the IGF-I receptor.

[Claim 16]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 15, which binds to an epitope containing ProSerGlyPheIleArgAsnGlySerGlnSerMet, or a part in the vicinity thereof, in the sequence of the CR domain of the IGF-I receptor.

[Claim 17]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 16, which has a cross-reactivity with an IGF-I receptor of a human or a nonhuman animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl.

[Claim 18]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 17, which causes an antigen-antibody reaction with an affinity intensity at a equilibrium dissociation constant (KD) of 1×10^{-8} M or less.

[Claim 19]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 15 to 18, which has at least one of the features of:

1) exhibiting an activity to induce growth of vertebrate-derived cells;

2) exhibiting an activity to induce an increase in the muscle mass and/or the body length of a vertebrate when parenterally administered to the vertebrate;

3) not inducing glucose uptake by differentiated muscle cells when administered at a dosage sufficient to induce growth of vertebrate-derived cells; and

4) not changing the blood glucose level of a vertebrate when parenterally administered to the vertebrate at a dosage sufficient to induce an increase in the muscle mass and/or the body length of the vertebrate.

[Claim 20]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 15 to 19, which has at least one of the features of:

1) inhibiting growth of vertebrate-derived cells induced by IGF-I;

2) inhibiting IGF-I-induced cell proliferation in a vertebrate suffering a cell proliferative disease when parenterally administered to the vertebrate;

3) not affecting glucose uptake by differentiated muscle cells at a dosage sufficient to inhibit growth of vertebrate-derived cells induced by IGF-I; and

4) not changing the blood glucose level of a vertebrate suffering a cell proliferative disease when parenterally administered to the vertebrate at a dosage sufficient to inhibit IGF-I induced cell proliferation in the vertebrate.

[Claim 21]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 20, which is a Fab, scFv, diabody or bispecific antibody, or a derivative thereof.

[Claim 22]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 21, consisting of an amino acid sequence comprising:

as a heavy chain variable region CDR-1 (CDR-H1) sequence, an amino acid sequence defined in SEQ ID NO:3 or an amino acid sequence derived from SEQ ID NO:3 via substitution, deletion or insertion of any one amino acid residue;

as a heavy chain variable region CDR-2 (CDR-H2) sequence, an amino acid sequence defined in SEQ ID NO:4 or an amino acid sequence derived from SEQ ID NO:4 via substitution, deletion or insertion of any one or two amino acid residues;

as a heavy chain variable region CDR-3 (CDR-H3) sequence, an amino acid sequence defined in SEQ ID NO:5or an amino acid sequence derived from SEQ ID NO:5 via substitution, deletion or insertion of any one or two amino acid residues;

as a light chain variable region CDR-1 (CDR-L1) sequence, an amino acid sequence defined in SEQ ID NO:6 or an amino acid sequence derived from SEQ ID NO:6 via substitution, deletion or insertion of any one or two amino acid residues;

as a light chain variable region CDR-2 (CDR-L2) sequence, an amino acid sequence defined in SEQ ID NO:7 or an amino acid sequence derived from SEQ ID NO:7 via substitution, deletion or insertion of any one amino acid residue; and

as a light chain variable region CDR-3 (CDR-L3) sequence, an amino acid sequence defined in SEQ ID NO:8 or an amino acid sequence derived from SEQ ID NO:8 via substitution, deletion or insertion of any one or two amino acid residues.

[Claim 23]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 24 further comprises a framework sequence of immunoglobulin.

[Claim 24]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to claim 23, wherein the framework sequence of immunoglobulin is a framework sequence of each class of immunoglobulin from a human or a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, a fowl, a mouse, or a rat.

[Claim 25]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 24, which consists of an amino acid sequence comprising:
as a heavy chain variable region, an amino acid sequence defined in SEQ ID NO:9 or an amino acid sequence having a similarity of 90% or more to SEQ ID NO:9; and
as a light chain variable region, an amino acid sequence defined in SEQ ID NO:10 or an amino acid sequence having a similarity of 90% or more to SEQ ID NO:10.

[Claim 26]

The anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 25 further comprising a constant region of each class of immunoglobulin a human or a non-human animal including a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, a fowl, a mouse, or a rat.

[Claim 27]

A nucleic acid molecule consisting of a polynucleotide sequence encoding an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 26.

[Claim 28]

A cloning vector or expression vector comprising at least one nucleic acid molecule according to claim 27.

[Claim 29]

A recombinant cell derived from a host cell via transfection of a vector according to claim 28.

[Claim 30]

A process of producing an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 26, comprising:
culturing a recombinant cell according to claim 29; and
purifying the anti-IGF-I receptor antibody, fragment, or derivative produced from the recombinant cell.

[Claim 31]

A pharmaceutical composition comprising an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 26, a nucleic acid molecule according to claim 27, a vector according to claim 28, or a recombinant cell according to claim 29.

[Claim 32]

The pharmaceutical composition according to claim 31, further comprising an additional active ingredient other than the anti-IGF-I receptor antibody, antigen binding fragment, or derivative according to any one of claims 1 to 26, the nucleic acid molecule according to claim 27, the vector according to claim 28, or the recombinant cell according to claim 29.

[Claim 33]

The pharmaceutical composition according to claim 32, wherein the active ingredient is one or more selected from a growth hormone or an analog thereof, insulin or an analog thereof, IGF-II or an analog thereof, an anti-myostatin antibody, a myostatin antagonist, an anti-activin type IIB receptor antibody, an activin type IIB receptor antagonist, a 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.

[Claim 34]

The pharmaceutical composition according to claim 32 or 33, wherein the active ingredient comprises an ingredient selected from the group consisting of: corticosteroid, antiemetic, ondansetron hydrochloride, granisetron hydrochloride, metoclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, cancer vaccine, GM-CSF inhibitor, GM-CSF DNA vaccine, cellbased 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, antiCCR4

antibody, mogamulizumab, anti-VEGFantibody, 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.

[Claim 35]

An anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 26, a nucleic acid molecule according to claim 27, a vector according to claim 28, or a recombinant cell according to claim 29 for use in therapy.

[Claim 36]

Use of the anti-IGF-I receptor antibody or its antigen binding fragment or the derivative thereof according to any one of claims 1 to 26, the nucleic acid molecule according to claim 27, the vector according to claim 28, or the recombinant cell according to claim 29 in the manufacture of a medicament for the treatment or prevention of a condition associated with IGF-I, wherein said condition is selected from the group consisting of: disuse muscle atrophy, dwarfism, diabetic nephropathy, chronic renal failure, 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, 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, Turner's syndrome, Prader-Willi syndrome, Silver-Russell syndrome, idiopathic short stature, obesity, multiple sclerosis, fibromyalgia, ulcerous colitis, low muscle mass, myocardial ischemia and decreased bone density.

[Claim 37]

The use according to claim 36, wherein the medicament is to be parenterally administered.

[Claim 38]

The use according to claim 36 or 37, wherein the medicament is a veterinary drug to be administered to a non-human animal.

[Claim 39]

The use according to claim 38, wherein the veterinary drug is to be administered for the purpose of, increasing muscle mass and/or body length, promoting growth, increasing milk production, promoting reproduction, or preventing aging.

[Claim 40]

The use according to claim 38 or 39, wherein the non-human animal is a guinea pig, a monkey, a rabbit, a cow, a pig, a horse, a sheep, a dog, or a fowl.

[Claim 41]

Use of the anti-IGF-I receptor antibody or its antigen binding fragment or the derivative thereof according to any one of claims 1 to 26, the nucleic acid molecule according to claim 27, the vector according to claim 28, or the recombinant cell according to claim 29 in the manufacture of a medicament for the treatment or prevention of a disease caused by an effect of IGF-I or IGF-II on an IGF-I receptor, wherein said disease is selected from the group consisting of: liver cancer, neuroblastoma, striated muscle sarcoma, bone cancer, childhood cancer, acromegalia, ovary cancer, pancreas cancer, benignant prostatic hypertrophy, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervix cancer, synovial sarcoma, 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 ymphoblastic leukemia, brain tumor, glioblastoma, non-glioblastomatic brain tumor, meningioma, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, medulloblastoma, astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, gigantism, psoriasis, atherosclerosis, vascular smooth muscle restenosis, inappropriate microvascular growth, diabetic retinopathy, Graves' disease, multiple sclerosis, systemic lupus erythematosus, chronic thyroiditis, myasthenia gravis, autoimmune thyroiditis and Behcet's disease.

[Claim 42]

A method of culturing vertebrate-derived cells *in vitro*, comprising contacting the vertebrate-derived cells with an anti-IGF-I receptor antibody or its antigen binding fragment or a derivative thereof according to any one of claims 1 to 26, a nucleic acid molecule according to claim 27, a vector according to claim 28, and a recombinant cell according to claim 29 when culturing the cells.

[Claim 43]

The method according to claim 42, wherein said contacting is carried out for the purpose of promoting growth or inducing differentiation of the vertebrate-derived cells.

[Claim 44]

The method according to claim 42 or 43, wherein the anti-IGF-I receptor antibody, antigen binding fragment, or derivative is adsorbed by, or immobilized to, a solid phase.