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(54) Title: TREATMENT OF ABNORMAL VISCERAL FAT DEPOSITION USING SOLUBLE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (SFGFR3) POLYPEPTIDES

(57) Abstract: The invention features methods of using sFGFR3 polypeptides to treat abnormal visceral fat deposition and the conditions associated with abnormal visceral fat deposition.

TREATMENT OF ABNORMAL VISCERAL FAT DEPOSITION USING SOLUBLE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (SFGFR3) POLYPEPTIDES

BACKGROUND OF THE INVENTION

Achondroplasia, the most common form of short limb dwarfism, is a rare genetic disease for which there is no cure. In many patients, a G380R substitution in the transmembrane domain of the fibroblast growth factor receptor 3 (FGFR3) (Fgfr3ach) results in a gain-of function, prolonging the intracellular MAPK signaling. In the growth plate, the MAPK signaling is inhibitory and its subsequent constitutive activation results in the inhibition of chondrocyte proliferation and differentiation. Cells expressing the mutant receptor do not mature and are not replaced by mineralized bone matrix, ultimately resulting in abnormally short bones.

Achondroplasia is also characterized by early obesity which represents a major health problem in these patients, affecting approximately 50% of patients during childhood. Obesity increases the morbidity associated with lumbar lordosis, as well as the physical impact of existing orthopedic complications, increasing, for example, bearing weight on already fragile knees. It can also increase the risk of serious complications such as cardiovascular risks, obstructive sleep apnea, or restrictive lung disease. The causes of this increased susceptibility to obesity in achondroplasia patients are not known, but does not appear to be linked to hormonal or neurological dysfunction that can lead to appetite deregulation, such as hyperphagia.

Obese achondroplastic patients may also suffer from associated metabolic complications, such as dyslipidemia, low insulin levels, and glucose dysregulation. It is not clear whether these complications are isolated and related to exogenous factors, such as excessive caloric intake and/or decreased physical activity, or if they indeed reflect an underlying defect in achondroplasia.

Abnormal fat deposition, and, more particularly, abnormal visceral fat deposition, in the general population is also associated with the development of specific diseases, including cardiovascular, metabolic, pulmonary, reproductive and neurologic diseases. There exists a need for therapies to treat or prevent the development of abnormal visceral fat deposition and its associated diseases.

SUMMARY OF THE INVENTION

In a first aspect, the application describes a method of treating or reducing abnormal fat deposition (e.g., visceral fat deposition) in a subject (e.g., a human, such as a fetus, neonate, infant, child, adolescent, or adult) in need thereof by administering a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell that contains the

polynucleotide encoding the same to the subject. In several embodiments, the abnormal visceral fat deposition is associated with or surrounding one or more of the following organs: the heart, liver, spleen, kidneys, pancreas, intestines, reproductive organs, and gall bladder; or the abnormal visceral fat deposition causes disease in one or more of the following organs: the heart, lungs, trachea, liver, pancreas, brain, reproductive organs, arteries, and gall bladder; or the abnormal visceral fat deposition is caused by dysfunction in an endocrine organ, such as an adrenal gland, a pituitary gland, or a reproductive organ, such as an ovary. The method may result in the reduction or elimination of, or decreased risk of developing, one or more conditions associated with the abnormal fat distribution, such as obstructive sleep apnea, pulmonary disease, cardiovascular disease, metabolic disease, neurological disease, dyslipidemia, hypertension, atherosclerosis, myocardial infarction, stroke, dementia, infertility, menstrual irregularities, insulin dysregulation, and glucose dysregulation. In particular, the dyslipidemia is an abnormal level of one or more of triglycerides, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and cholesterol; the cardiovascular disease is heart disease or stroke; the pulmonary disease is asthma and restrictive lung disease; the neurological disease is dementia or Alzheimer's disease; the metabolic disease is type 2 diabetes, glucose intolerance, nonalcoholic fatty liver disease and liver toxicity; the insulin dysregulation is insulin resistance.

In an embodiment, the subject having abnormal fat deposition is not overweight, lacks substantial subcutaneous fat deposition, and/or does may not exhibit substantial abnormal fat deposition outside the abdomen. The abnormal fat deposition may be determined using an anthropometric techniques (e.g., body mass index (BMI) or android:gynoid fat ratio) or imaging (e.g., computed tomography (CT), magnetic resonance imaging (MRI), and dual energy x-ray absorptioometry (DXA), methods which may detect abnormal fat distribution in the absence of other adipose phenotypes.

In other embodiments, the subject may have a skeletal growth retardation disorder, such as an FGFR3-related skeletal disease (e.g., an FGFR3-related skeletal disease that is caused by expression in the patient of a FGFR3 variant that exhibits ligand-dependent overactivation, such as an FGFR3 variant having an amino acid substitution of a glycine residue with an arginine residue at position 358 (G358R), as set forth in SEQ ID NO: 9). The FGFR3-related skeletal disease can include, e.g., achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome (e.g. Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome), and camptodactyly, tall stature, and hearing loss syndrome (CATSHL). The patient with a skeletal growth retardation disorder may have one or more symptoms of the skeletal growth retardation disorder selected from the group consisting of short limbs, short trunk, bowlegs, a waddling gait, skull malformations, cloverleaf skull, craniosynostosis, wormian bones, anomalies of the hands, anomalies of the feet, hitchhiker thumb, and chest anomalies. Excluded from the methods described herein may be a subject

with a skeletal growth retardation disorder, such as those described above, e.g., achondroplasia, after the cessation of bone growth in the patient (e.g., a fetus, neonate, infant, child, and/or adolescent subject).

In an alternative embodiment, the patient does not have a skeletal growth retardation disorder, but can be characterized as having obesity, polycystic ovary syndrome, or a form of hypercortisolism, such as Cushing's disease.

In other embodiments, the sFGFR3 has at least 50 consecutive amino acids of an extracellular domain of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide (e.g., 100-370 consecutive amino acids of an extracellular domain of the naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide or fewer than 350 amino acids of the extracellular domain of the naturally occurring FGFR3 polypeptide). The sFGFR3 polypeptide may have an Ig-like C2-type domain 1, 2, and/or 3 of the naturally occurring FGFR3 polypeptide. The sFGFR3 polypeptide, in particular, lacks a signal peptide and/or a transmembrane domain, such as the signal peptide and/or transmembrane domain of a naturally occurring FGFR3 polypeptide. Alternatively, the sFGFR3 polypeptide is a mature polypeptide. The naturally occurring FGFR3 polypeptide may have the amino acid sequence of Genbank Accession No. NP_000133.

The sFGFR3 polypeptide may have 400 consecutive amino acids or fewer of an intracellular domain of a naturally-occurring FGFR3 polypeptide (e.g., between 5 and 399 consecutive amino acids, such as 175, 150, 125, 100, 75, 50, 40, 30, 20, 15, or fewer consecutive amino acids, of the intracellular domain of a naturally-occurring FGFR3 polypeptide). The sFGFR3 polypeptide may have an amino acid sequence with at least 90%, 92%, 95%, 97%, or 99% sequence identity to amino acids 401 to 413 of SEQ ID NO: 8 (e.g., the sFGFR3 polypeptide may have amino acids 401 to 413 of SEQ ID NO: 8). In several embodiments, the sFGFR3 polypeptide lacks a tyrosine kinase domain of a naturally-occurring FGFR3 polypeptide, lacks an intracellular domain of a naturally-occurring FGFR3 polypeptide, or is fewer than 475, 450, 425, 400, 375, 350, 300, 250, 200, 150, or 100 amino acids in length. In other embodiments, the sFGFR3 polypeptide has an amino acid sequence with at least 85% sequence identity (e.g., 86%-100% sequence identity) to amino acids residues 1 to 280 of SEQ ID NO: 8. In yet other embodiments, the sFGFR3 polypeptide has an amino acid sequence with at least 85% sequence identity (e.g., 86%-100% sequence identity) to the sequence of any one of SEQ ID NOs: 1-7. The sFGFR3 polypeptide may also have a signal peptide, such as a signal peptide of a naturally-occurring FGFR3 polypeptide (e.g., a signal peptide having the amino acid sequence of SEQ ID NO: 21). The sFGFR3 polypeptide may also have a heterologous polypeptide (e.g., a fragment crystallizable region of an immunoglobulin (Fc region) or human serum albumin (HSA)).

In still other embodiments, the polynucleotide encoding the sFGFR3 polypeptide may have a nucleic acid sequence with at least 85% and up to 100% sequence identity to the nucleic acid sequence of any one of SEQ ID NOs: 10-18 (e.g., the polynucleotide may consist of the nucleic acid sequence of any one of SEQ ID NOs: 10-18). The polynucleotide may be an isolated polynucleotide and/or may be in a

vector (e.g., a vector selected from the group consisting of a plasmid, an artificial chromosome, a viral vector, and a phage vector). The vector may be in a host cell (e.g., an isolated host cell, such as a host cell is from the subject or a HEK 293 cell or CHO cell). The host cell may also be transformed with the sFGFR3-encoding polynucleotide.

In other embodiments, the sFGFR3 polypeptide binds to a fibroblast growth factor (FGF), wherein the FGF is selected from the group consisting of fibroblast growth factor 1 (FGF1), fibroblast growth factor 2 (FGF2), fibroblast growth factor 9 (FGF9), fibroblast growth factor 10 (FGF10), fibroblast growth factor 18 (FGF18), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), and fibroblast growth factor 23 (FGF23). The binding to the FGF can be characterized by an equilibrium dissociation constant (K_d) of about 0.2 nM to about 20 nM, or by a K_d of about 1 nM to about 10 nM (e.g., the K_d is about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, about 8 nm, about 9 nm, or about 10 nm).

One aspect of the treatment involves administering an sFGFR3 polypeptide, a polynucleotide encoding an sFGFR3 polypeptide, or a host cell containing a polynucleotide encoding an sFGFR3 polypeptide to a subject, e.g., a human subject, such as a naïve human subject that has not yet been treated with an sFGFR3 polypeptide). The sFGFR3 polypeptide may be administered in a composition containing a pharmaceutically acceptable excipient, carrier, or diluent. Possible doses are from about 0.001 mg/kg to about 30 mg/kg (e.g., about 0.01 mg/kg to about 10 mg/kg). Administration may be daily, weekly, or monthly. Dosing periodicity can be seven times a week, six times a week, five times a week, four times a week, three times a week, twice a week, weekly, every two weeks, or once a month. Route of dosing can be subcutaneous, intravenous, intramuscular, intra-arterial, intrathecal, intraperitoneal, parenteral, enteral, or topical. Repeat administration may be performed.

In other embodiments, the sFGFR3 polypeptide has an *in vivo* half-life of between about 2 hours to about 25 hours.

A second aspect of the invention features a composition containing a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell containing the polynucleotide for treating or reducing abnormal fat distribution in a subject in need thereof (e.g., a human subject), e.g., according to the method of the first aspect of the invention.

A third aspect of the invention features the use of a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell containing a polynucleotide encoding the sFGFR3 polypeptide in the manufacture of a medicament for treating or reducing abnormal fat distribution in a subject in need thereof (e.g., a human subject), e.g., according to the method of the first aspect of the invention.

DEFINITIONS

As used herein, “a” and “an” means “at least one” or “one or more” unless otherwise indicated. In addition, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

The phrase “abnormal visceral fat deposition” refers to a level of fat deposition in the omentum, mesentery, retroperitoneum and pericardium, that is greater than a level of fat deposition observed in a normal subject, as determined by anthropometric techniques or imaging techniques (see, e.g., “Methods of Diagnosis, *infra*., for enumeration of values for each technique defining a cutoff distinguishing normal from abnormal visceral fat deposition). For example, subjects with abnormal visceral fat deposition are those that exhibit a visceral fat deposition value that is equal to or greater than 10% above (for example, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 500%, 750%, 1000% or more above) a cutoff for visceral fat deposition relative to that of a normal subject. Commonly, abnormal visceral fat deposition is associated with a subset of obese patients, e.g., those with a BMI >30 kg/m^2. Abnormal visceral fat deposition can result from a variety of conditions. These include, e.g., skeletal growth retardation syndromes (e.g., achondroplasia), hypercortisolism (e.g., Cushing’s disease), and polycystic ovary syndrome.

As used herein, “about” refers to an amount that is ± 10% of the recited value and is preferably ±5% of the recited value, or more preferably ±2% of the recited value. For instance, the term “about” can be used to modify all dosages or ranges recited herein by ± 10% of the recited values or range endpoints.

The phrase “anthropometric techniques” refers to body composition measurements based on height, weight, waist circumference and hip circumference, including body mass index (BMI), android:gynoid fat ratio, waist circumference, and sagittal diameter (SD); see, e.g., Shuster et al., *Br. J. Radiol.* 85(1009):1-10, 2012).

The phrase “cardiovascular disease” refers to diseases of the heart and blood vessels, in particular, atherosclerosis, myocardial infarction, and hypertension.

The phrase “conditions associated with abnormal visceral fat deposition” refers to diseases observed in patients whose visceral fat deposition is shown to be abnormal relative to normal patients. In particular, these conditions include cardiovascular disease, pulmonary disease, metabolic disease, reproductive disease, and neurologic disease.

The term “domain” refers to a conserved region of the amino acid sequence of a polypeptide (e.g. a FGFR3 polypeptide) having an identifiable structure and/or function within the polypeptide. A domain can vary in length from, e.g., about 20 amino acids to about 600 amino acids. Exemplary domains include the immunoglobulin domains of a FGFR3 (e.g., Ig-like C2-type domain 1, Ig-like C2-type domain 2, and Ig-like C2-type domain 3), the extracellular domain (ECD) of a FGFR3, the intracellular domain (ICD) of a FGFR3, or the transmembrane domain (TM) of a FGFR3, such as a FGFR3 having the sequence set forth in SEQ ID NO: 8).

The term “dosage” refers to a determined quantity of an active agent (e.g., an sFGFR3

polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 or a variant thereof having at least 85% to 100% sequence identity thereto) calculated to produce a desired therapeutic effect (e.g., treatment of abnormal visceral fat deposition, or the conditions associated with visceral fat deposition) when the active agent is administered to a patient (e.g., a patient having abnormal visceral fat deposition, or a condition associated with visceral fat deposition). A dosage may be defined in terms of a defined amount of the active agent or a defined amount coupled with a particular frequency of administration. A dosage form can include an sFGFR3 polypeptide or fragment thereof in association with any suitable pharmaceutical excipient, carrier, or diluent.

The terms “effective amount,” “amount effective to,” and “therapeutically effective amount” refer to an amount of an sFGFR3 polypeptide, a vector encoding an sFGR3, and/or an sFGFR3 composition that is sufficient to produce a desired result, for example, decreased abnormal fat deposition, abnormal visceral fat deposition, or a decrease in symptoms associated with conditions linked to abnormal visceral fat deposition.

The terms “extracellular domain” and “ECD” refer to the portion of a FGFR3 polypeptide that extends beyond the transmembrane domain into the extracellular space. The ECD mediates binding of a FGFR3 to one or more fibroblast growth factors (FGFs). For instance, an ECD includes the Ig-like C2-type domains 1-3 of a FGFR3 polypeptide. In particular, the ECD includes the Ig-like C2-type domain 1 of a wildtype (wt) FGFR3 polypeptide, the Ig-like C2-type domain 2 of a wildtype (wt) FGFR3 polypeptide, and/or the Ig-like C2-type domain 3 of a wt FGFR3 polypeptide. An ECD of a FGFR3 can also include a fragment of the wildtype FGFR3 Ig-like C2-type domain for instance.

The phrase “fat deposition” refers to visceral fat deposition or subcutaneous fat deposition.

The term “FGFR3-related skeletal disease,” as used herein, refers to a skeletal disease that is caused by an abnormal increase in the activation of FGFR3, such as by expression of a gain-of-function mutant of the FGFR3. The phrase “gain-of-function mutant of the FGFR3” refers to a mutant of the FGFR3 exhibiting a biological activity, such as triggering downstream signaling, which is higher than the biological activity of the corresponding wild-type FGFR3 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 8) in the presence of a FGF ligand. FGFR3-related skeletal diseases can include an inherited or a sporadic disease. Exemplary FGFR3-related skeletal diseases include, but are not limited to, achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, a craniosynostosis syndrome (e.g., Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome), and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

The terms “fibroblast growth factor” and “FGF” refer to a member of the FGF family, which includes structurally related signaling molecules involved in various metabolic processes, including endocrine signaling pathways, development, wound healing, and angiogenesis. FGFs play key roles in the

proliferation and differentiation of a wide range of cell and tissue types. The term preferably refers to FGF1, FGF2, FGF9, FGF 10, FGF18, FGF19, FGF21, and FGF23, which have been shown to bind FGFR3. For instance, FGFs can include human FGF1 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 26), human FGF2 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 27), human FGF9 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 28), human FGF10 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 40), human FGF18 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 29), human FGF19 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 30), human FGF21 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 31), and human FGF23 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 41).

The terms “fibroblast growth factor receptor 3,” “FGFR3,” or “FGFR3 receptor,” as used herein, refer to a polypeptide that specifically binds one or more FGFs (e.g., FGF1, FGF2, FGF9, FGF10, FGF18, FGF19, FGF 21, and/or FGF23). The human *FGFR3* gene, which is located on the distal short arm of chromosome 4, encodes an 806 amino acid protein precursor (fibroblast growth factor receptor 3 isoform 1 precursor), which contains 19 exons, and includes a signal peptide (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 21). Mutations in the FGFR3 amino acid sequence that lead to skeletal growth disorders, (e.g., achondroplasia), include, e.g., the substitution of a glycine residue at position 358 with an arginine residue (i.e., G358R; SEQ ID NO: 9). The naturally occurring human FGFR3 gene has a nucleotide sequence as shown in Genbank Accession number NM_000142.4 and the naturally occurring human FGFR3 protein has an amino acid sequence as shown in Genbank Accession number NP_000133, herein represented by SEQ ID NO: 8. The wildtype FGFR3 (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 8) consists of an extracellular immunoglobulin-like membrane domain including Ig-like C2-type domains 1-3, a transmembrane domain, and an intracellular domain. FGFR3s can include fragments and/or variants (e.g., splice variants, such as splice variants utilizing alternate exon 8 rather than exon 9) of the full-length, wild-type FGFR3.

The terms “fragment” and “portion” refer to a part of a whole, such as a polypeptide or nucleic acid molecule that contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more of the entire length of the reference nucleic acid molecule or polypeptide, or a domain thereof (e.g., the ECD, ICD, or TM of a sFGFR3 polypeptide). A fragment or portion may contain, e.g., 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 500, 600, 700, or more consecutive amino acid residues, up to the entire length of the reference polypeptide. For example, a FGFR3 fragment can include any polypeptide having at least about 5 consecutive amino acids to about 300 consecutive amino acids, inclusive of the endpoints, e.g., at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170,

180, 190, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, or 300 consecutive amino acids of any one of SEQ ID Nos: 1-8.

The phrase "glucose dysregulation" refers to a glucose level in the blood that is above or below an acceptable normal range.

As used herein, the term "host cell" refers to a vehicle that includes the necessary cellular components, e.g., organelles, needed to express an sFGFR3 polypeptide from a corresponding polynucleotide. The nucleic acid sequence of the polynucleotide is typically included in a nucleic acid vector (e.g., a plasmid, an artificial chromosome, a viral vector, or a phage vector) that can be introduced into the host cell by conventional techniques known in the art (e.g., transformation, transfection, electroporation, calcium phosphate precipitation, and direct microinjection). A host cell may be a prokaryotic cell, e.g., a bacterial or an archaeal cell, or a eukaryotic cell, e.g., a mammalian cell (e.g., a Chinese Hamster Ovary (CHO) cell or a Human Embryonic Kidney 293 (HEK 293)). Preferably, the host cell is a mammalian cell, such as a CHO cell.

The phrase "imaging techniques" refers to methods of creating visual representations of the interior of a body for the purpose of clinical analysis and medical intervention. Examples of imaging techniques include, e.g., dual energy x-ray absorptiometry (DXA) yielding fat mass index, cross-sectional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), yielding an area of visceral fat in cm^2 at a specified level of the lumbar spine (see, e.g., Shuster et al., *supra*).

The phrase "insulin dysregulation" refers to an insulin level in the blood that is above or below an acceptable normal range.

By "isolated" is meant separated, recovered, or purified from its natural environment. For example, an isolated sFGFR3 polypeptide (e.g., an sFGFR3 polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of any one of SEQ ID Nos: 1-7 or a variant thereof having at least about 85% to up to about 100% sequence identity thereto) can be characterized by a certain degree of purity after isolating the sFGFR3 polypeptide from, e.g., cell culture media. An isolated sFGFR3 polypeptide can be at least 75% pure, such that the sFGFR3 polynucleotide constitutes at least 75% by weight of the total material (e.g., polypeptides, polynucleotides, cellular debris, and environmental contaminants) present in the preparation (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 99%, or at least 99.5% by weight of the total material present in the preparation). Likewise, an isolated polynucleotide encoding an sFGFR3 polypeptide (e.g., a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 10-18 or a variant thereof having at least about 85% to up to about 100% sequence identity thereto), or an isolated host cell (e.g.,CHO cell, a HEK 293 cell, L cell, C127 cell, 3T3 cell, BHK cell, COS-7 cell, or a cell of a subject) containing the polynucleotide can be at least 75% pure, such that the polynucleotide or host cell constitutes at least 75% by weight of the total material (e.g., polypeptides, polynucleotides, cellular debris, and environmental contaminants) present in the preparation (e.g., at least 80%, at least 85%, at least

90%, at least 95%, at least 96%, at least 97%, at least 99%, or at least 99.5% by weight of the total material present in the preparation).

The phrase “metabolic disease” refers to disorders of chemical reactions that help with energy processing , in particular dyslipidemia, insulin dysregulation, glucose dysregulation, non-alcoholic fatty liver, and liver toxicity.

The phrase “neurologic disease” refers to diseases of the brain or nerves, in particular, dementia and stroke.

The terms “parenteral administration,” “administered parenterally,” and other grammatically equivalent phrases, as used herein, refer to a mode of administration of compositions including an sFGFR3 polypeptide (e.g., an sFGFR3 polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 (with or without a signal peptide) other than enteral and topical administration, usually by injection, and include, without limitation, subcutaneous, intradermal, intravenous, intranasal, intraocular, pulmonary, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intrapulmonary, intraperitoneal, transtracheal, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intracerebral, intracranial, intracarotid, and intrasternal injection and infusion.

The terms “patient” and “subject” refer to a mammal, including, but not limited to, a human (e.g., a human having abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition) or a non-human mammal (e.g., a non-human mammal having abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition, such as a bovine, equine, canine, ovine, or feline. Preferably, the patient is a human having abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition), particularly a fetus, a neonate, an infant, a child, an adolescent, or an adult having abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition.

By “pharmaceutical composition” is meant a composition containing an active agent, such as an sFGFR3, formulated with at least one pharmaceutically acceptable excipient, carrier, or diluent. The pharmaceutical composition may be manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of a disease or event (e.g., abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition) in a patient (e.g., a patient having abnormal fat deposition, abnormal visceral fat deposition, or the conditions associated with abnormal visceral fat deposition). Pharmaceutical compositions can be formulated, e.g., for parenteral administration, such as for subcutaneous administration (e.g. by subcutaneous injection) or intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use), or for oral administration (e.g., as a tablet, capsule, caplet, gelcap, or syrup).

By “pharmaceutically acceptable diluent, excipient, carrier, or adjuvant” is meant a diluent, excipient, carrier, or adjuvant, respectively that is physiologically acceptable to the subject (e.g., a human) while retaining the therapeutic properties of the pharmaceutical composition (e.g., an sFGFR3 polypeptide or variant thereof, with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline. Other physiologically acceptable diluents, excipients, carriers, or adjuvants and their formulations are known to one skilled in the art.

“Polynucleotide” and “nucleic acid molecule,” as used interchangeably herein, refers to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or analogs thereof, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide can include modified nucleotides, such as methylated nucleotides and analogs thereof. If present, modification to the nucleotide structure can be imparted before or after assembly of the polymer. The sequence of nucleotides can be interrupted by non-nucleotide components. A polynucleotide can be further modified after synthesis, such as by conjugation with a label.

The phrase “pulmonary disease” refers to diseases of air exchange, in particular, obstructive sleep apnea, restrictive lung disease, and asthma.

The phrase “reproductive disease” refers to diseases of the reproductive system, in particular, infertility and menstrual irregularities.

As used herein, the term “sequence identity” refers to the percentage of amino acid (or nucleic acid) residues of a candidate sequence, e.g., an FGFR3 polypeptide, that are identical to the amino acid (or nucleic acid) residues of a reference sequence, e.g., a wild-type sFGFR3 polypeptide (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 8) or an sFGFR3 polypeptide (e.g., an sFGFR3 polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7) after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity (e.g., gaps can be introduced in one or both of the candidate and reference sequences for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). Alignment for purposes of determining percent identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software, such as BLAST, BLAST-2, BLAST-P, BLAST-N, BLAST-X, WU-BLAST-2, ALIGN, ALIGN-2, CLUSTAL, or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For instance, the percent amino acid (or nucleic acid) sequence identity of a given candidate sequence to, with, or against a given reference sequence (which can alternatively be phrased as a given candidate sequence that has or includes a certain percent amino acid (or nucleic acid) sequence identity to, with, or against a given reference sequence) is calculated as follows: 100 x (fraction of A/B)where A is the number of amino acid (or nucleic acid) residues scored as identical in the alignment

of the candidate sequence and the reference sequence, and where B is the totalnumber of amino acid (or nucleic acid) residues in the reference sequence. In particular, areference sequence aligned for comparison with a candidate sequence can show that the candidate sequence exhibits from, e.g., 50% to 100% identity across the full length of the candidate sequence or a selected portion of contiguous amino acid (or nucleic acid) residues of the candidate sequence. The length of the candidate sequence aligned for comparison purposeis at least 30%, e.g., at least 40%, e.g., at least 50%, 60%, 70%, 80%, 90%, or 100% of the length of the reference sequence. When a position in the candidate sequence is occupied by the same amino acid (or nucleic acid) residue as the corresponding position in the reference sequence, then the molecules are identical at that position.

By “signal peptide” is meant a short peptide (e.g., 5-30 amino acids in length, such as 22 amino acids in length) at the N-terminus of a polypeptide that directs a polypeptide towards the secretory pathway (e.g., the extracellular space). The signal peptide is typically cleaved during secretion of the polypeptide. The signal sequence may direct the polypeptide to an intracellular compartment or organelle, e.g., the Golgi apparatus. A signal sequence may be identified by homology, or biological activity, to a peptide with the known function of targeting a polypeptide to a particular region of the cell. One of ordinary skill in the art can identify a signal peptide by using readily available software (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, or PILEUP/PRETTYBOX programs). A signal peptide can be one that is, for example, substantially identical to the amino acid sequence of SEQ ID NO: 21.

The term “skeletal growth retardation disorder,” as used herein, refers to a skeletal disease characterized by deformities and/or malformations of the bones. These disorders include, but are not limiting to, skeletal growth retardation disorders caused by growth plate (physeal) fractures, idiopathic skeletal growth retardation disorders, or FGFR3-related skeletal diseases. In particular, a patient having a skeletal growth retardation disorder (e.g., achondroplasia) may have bones that are shorter than the bones of a healthy patient. For example, the skeletal growth retardation disorder may include a skeletal dysplasia, e.g., achondroplasia, homozygous achondroplasia, heterozygous achondroplasia, achondrogenesis, acrodysostosis, acromesomelic dysplasia, atelosteogenesis, camptomelic dysplasia, chondrodysplasia punctata, rhizomelic type of chondrodysplasia punctata, cleidocranial dysostosis, congenital short femur, craniosynostosis (e.g., Muenke syndrome, Crouzon syndrome, Apert syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, or Crouzonodermoskeletal syndrome), dactyly, brachydactyly, camptodactyly, polydactyly, syndactyly, diastrophic dysplasia, dwarfism, dyssegmental dysplasia, enchondromatosis, fibrochondrogenesis, fibrous dysplasia, hereditary multiple exostoses, hypochondroplasia, hypophosphatasia, hypophosphatemic rickets, Jaffe-Lichtenstein syndrome, Kniest dysplasia, Kniest syndrome, Langer-type mesomelic dysplasia, Marfan syndrome, McCune-Albright syndrome, micromelia, metaphyseal dysplasia, Jansen-type metaphyseal dysplasia, metatrophic

dysplasia, Morquio syndrome, Nievergelt-type mesomelic dysplasia, neurofibromatosis, osteoarthritis, osteochondrodysplasia, osteogenesis imperfecta, perinatal lethal type of osteogenesis imperfecta, osteopetrosis, osteopoikilosis, peripheral dysostosis, Reinhardt syndrome, Roberts syndrome, Robinow syndrome, short-rib polydactyly syndromes, short stature, spondyloepiphyseal dysplasia congenita, and spondyloepimetaphyseal dysplasia.

The terms "soluble fibroblast growth factor receptor 3," "soluble FGFR3," and "sFGFR3" refer to a FGFR3 that is characterized by the absence or functional disruption of all or a substantial part of the transmembrane domain and any polypeptide portion that would anchor the FGFR3 polypeptide to a cell membrane (e.g., a tyrosine kinase domain). An sFGFR3 polypeptide is a non-membrane bound form of an FGFR3 polypeptide. Thus, an sFGFR3 polypeptide can include a deletion of a portion or all of the amino acid residues of the transmembrane domain of a wild-type FGFR3 polypeptide sequence (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 8). The sFGFR3 polypeptide can further include deletions of the intracellular domain of the wild-type FGFR3 polypeptide.

Exemplary sFGFR3 polypeptides can include, but are not limited to, at least amino acids 1 to 100, 1 to 125, 1 to 150, 1 to 175, 1 to 200, 1 to 205, 1 to 210, 1 to 215, 1 to 220, 1 to 225, 1 to 230, 1 to 235, 1 to 240, 1 to 245, 1 to 250, 1 to 252, 1 to 255, 1 to 260, 1 to 265, 1 to 270, 1 to 275, 1 to 280, 1 to 285, 1 to 290, 1 to 295, or 1 to 300, or 1 to 301 of SEQ ID NOs: 1-8. sFGFR3 polypeptides can include any polypeptide having at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) sequence identity to any of these sFGFR3 polypeptides of SEQ ID NOs: 1-8. Additionally, exemplary sFGFR3 polypeptides can include, but are not limited to, at least amino acids 1 to 100, 1 to 125, 1 to 150, 1 to 175, 1 to 200, 1 to 205, 1 to 210, 1 to 215, 1 to 220, 1 to 225, 1 to 230, 1 to 235, 1 to 240, 1 to 245, 1 to 250, 1 to 255, 1 to 260, 1 to 265, 1 to 270, 1 to 275, 1 to 280, 1 to 285, 1 to 290, 1 to 295, 1 to 300, 1 to 305, 1 to 310, 1 to 315, 1 to 320, 1 to 325, 1 to 330, 1 to 335, 1 to 340, 1 to 345, or 1 to 348 of SEQ ID NOs: 1-8. sFGFR3 polypeptides can include any polypeptide having at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) sequence identity to any of these sFGFR3 polypeptides having the amino acid sequence of SEQ ID NOs: 1-8. Any of the above sFGFR3 polypeptides or variants thereof can optionally include a signal peptide at the N-terminal position, such as amino acids 1 to 22 of SEQ ID NO: 21 (MGAPACALALCVAVAIVAGASS) or amino acids 1 to 19 of SEQ ID NO: 43 (e.g., MMSFVSLLLVGILFHATQA).

The phrase "subcutaneous fat deposition" refers to fat deposition in the hypodermis.

By "treating" and "treatment" is meant a reduction (e.g., by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 99%, or even 100%) in abnormal fat deposition or abnormal visceral fat deposition, or in the progression, severity, or frequency of one or more or a condition associated with abnormal visceral fat deposition (e.g. cardiovascular disease, pulmonary disease,

metabolic disease, or neurological disease) in a patient (e.g., a human, such as a fetus, a neonate, an infant, a child, an adolescent, or an adult). Treatment can occur for a treatment period, in which an sFGFR3 polypeptide is administered for a period of time (e.g., days, months, years, or longer) to treat a patient (e.g., a human, such as a fetus, a neonate, an infant, a child, an adolescent, or an adult) having abnormal fat deposition, abnormal visceral fat deposition, or a condition associated with abnormal visceral fat deposition. Exemplary symptoms of associated with abnormal visceral fat deposition in an achondroplasia patient that can be treated with an sFGFR3 (e.g., an sFGFR3 polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of SEQ ID NOs: 1-7 or a variant thereof) include, but are not limited to, atherosclerosis, hypertension, lipid dysregulation, obstructive sleep apnea, glucose dysregulation or insulin dysregulation (e.g., insulin resistance).

The term "unit dosage form(s)" refers to physically discrete unit(s) suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with any suitable pharmaceutical excipient, carrier, or diluent.

The term "variant," with respect to a polypeptide, refers to a polypeptide (e.g., an sFGFR3 polypeptide or variant thereof, with or without a signal peptide) that differs by one or more changes in the amino acid sequence from the polypeptide from which the variant is derived (e.g., the reference polypeptide, such as, e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7). The term "variant," with respect to a polynucleotide, refers to a polynucleotide that differs by one or more changes in the nucleic acid sequence from the polynucleotide from which the variant is derived (e.g., the reference polynucleotide, such as, e.g., a polynucleotide encoding a sFGFR3 polypeptide having the nucleic acid sequence of any one of SEQ ID NOs: 10-18). The changes in the amino acid or nucleic acid sequence of the variant can be, e.g., amino acid or nucleic acid substitutions, insertions, deletions, N-terminal truncations, or C-terminal truncations, or any combination thereof. In particular, the amino acid substitutions may be conservative and/or non-conservative substitutions. A variant can be characterized by amino acid sequence identity or nucleic acid sequence identity to the reference polypeptide or parent polynucleotide, respectively. For example, a variant can include any polypeptide having at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) sequence identity to the reference polypeptide or polynucleotide.

By "vector" is meant a DNA construct that includes one or more polynucleotides, or fragments thereof, encoding an sFGFR3 polypeptide (e.g., an sFGFR3 polypeptide or variant thereof, such as a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7, or a variant thereof, with our without a signal peptide). The vector can be used to infect a cell (e.g., a host cell or a cell of a patient having a human skeletal growth retardation disorder, such as achondroplasia), which results in the translation of the polynucleotides of the vector into a sFGFR3 polypeptide. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments may

be ligated. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids.

The phrase “visceral fat deposition“ refers to intraabdominal fat depots, including mesenteric and omental, retroperitoneal fat depots, and intrathoracic fat depots, including pericardial.

The recitation herein of numerical ranges by endpoints is intended to include all numbers subsumed within that range (e.g., a recitation of 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

Other features and advantages of the invention will be apparent from the following Detailed Description and from the Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIGS. 1A-1D are tables, an image, and graphs showing that children with achondroplasia develop abdominal obesity without an increase in blood glucose levels. FIG. 1A is a table showing weight, height and BMI measurements and corresponding height-to-age and BMI-to-age z-scores in the three age groups ranging (n = 73 data points in the [0-3] years old group, n = 61 data points in the [4-8] years old group and n = 36 data points in the [9-18] years old group). Results of post hoc analyses: a: significantly different between [0-3] and [4-8] groups; b: significantly different between [0-3] and [9-18] groups; c: significantly different between [4-8] and [9-18] groups. FIG. 1B is an image representation of the different regions of interest (ROI) evaluated by DXA. FIG. 1C is a graph showing android:gynoid fat ratio measurement in the three age groups ranging (n = 4 data points in the [0-3] years old group, n = 6 data points in the [4-8] years old group and n = 9 data points in the [9-18] years old group). FIG. 1D is a graph showing plasmatic fasting glucose concentration in the two age groups ranging [4-8] and [9-18] years old (n = 16 data points in the [4-8] years old group and n = 12 data points in the [9-18] years old group). Horizontal lines represent normal values. Data are represented as mean ± SD, **p<0.01, ***p<0.001.

FIGS. 2A-2H are graphs and images showing that transgenic *Fgfr3*$^{ach/+}$ mice preferentially develop visceral obesity that is prevented upon sFGFR3 treatment (SEQ ID NO: 1). FIG. 2A is a graph showing body weight of vehicle-treated WT and *Fgfr3*$^{ach/+}$ mice and sFGFR3 treated *Fgfr3*$^{ach/+}$ mice after 10 weeks of ND or HFD challenge. FIG. 2B are images and a graph showing the abdominal lean:fat ratio. FIG. 2C is a graph showing epididymal adipose tissue (eAT) weight. FIG. 2D is a graph showing subcutaneous adipose tissue (scAT) weight per gram of body weight. FIG. 2E is a graph showing scAT adipocyte area. FIG. 2F is a graph showing eAT adipocyte area. FIG. 2G is a graph showing scat scattering of adipocytes according to their diameter. Data are presented as mean +/- standard deviation (n=8-10 mice to each group). Data followed normal distribution. *p<0.05, **p<0.01, ***p<0.001 versus vehicle-treated WT, $^{\#}p$<0.05, $^{\#\#}p$<0.01 versus vehicle-treated *Fgfr3*$^{ach/+}$; Student's *t* test. FIG. 2H is a graph showing eAT scattering of adipocytes according to their diameter. Data are presented as mean +/- standard deviation (n=8-10 mice to each group). Data followed normal distribution. *p<0.05, **p<0.01, ***p<0.001 versus vehicle-treated WT, $^{\#}p$<0.05, $^{\#\#}p$<0.01 versus vehicle-treated *Fgfr3*$^{ach/+}$; Student's *t* test.

FIGS. 3A-3B are graphs showing that MSCs isolated from untreated or sFGFR3-treated *Fgfr3*$^{ach/+}$ mice demonstrate preengagement toward adipogenesis with no alteration of the insulin response compared to WT mice. FIG. 3A is a graph showing expression of genes involved in different steps of adipogenesis differentiation (genes listed in Table 1). Expression was normalized to HPRT, RPL6 and RPL13a expression and expressed as percent of change compared to WT. FIG. 3B are graphs showing the results of cells stimulated with 50nM of insulin for 0, 5, 15 or 30 min or with 0, 1, 10, 50 or 100nM of

insulin during 5 min. P-Erk1/2 expression, normalized to Erk1/2 total expression, was expressed as normalized value to WT. Data are represented as mean ± SD. Data followed normal distribution. *p<0.05, **p<0.01, ***p<0.001 versus vehicle-treated WT, $^{\#}p$<0.05, $^{\#\#}p$<0.01 versus vehicle-treated *Fgfr3*$^{ach/+.}$ Two-way ANOVA with Tukey's multiple test.

FIGS. 4A-4E are graphs and microscopy images showing that glucose metabolism is altered in transgenic *Fgfr3ach/+* mice and restored with sFGFR3 treatment. FIG. 4A is a graph showing fasting glycemia and insulinemia of mice following 10 weeks of ND. FIG. 4B is a graph showing fasting glycemia and insulinemia of mice following 10 weeks of HFD. FIG. 4C shows graphs of the results of a HFD glucose tolerance test; glucose levels were normalized to the value of time -15 min and area under the curve corresponding to each group of mice. FIG. 4D first shows microscopy of mice pancreas insulin content (immunohistochemistry of paraffin-embedded sections, red: insulin; green: glucose; blue: DAPI staining). FIG. 4D also shows a graph of mice pancreas insulin content, mean of pancreas islets normalized to total surface and mean of islets number in each group under an HFD condition. FIG. 4E shows microscopy of liver H&E and PAS staining under HFD condition. FIG. 4F shows microscopy of H&E staining of hepatic nodules. Data are represented as mean ± SD (n= 8-10 mice to each group). Data followed normal distribution. **p<0.01, ***p<0.001 versus vehicle-treated WT, $^{\#}p$<0.05, $^{\#\#}p$<0.01 versus vehicle-treated *Fgfr3ach/+*; Student's *t*-test.

FIGS. 5A-5D are graphs showing that untreated transgenic *Fgfr3*$^{ach/+}$ mice draw essentially all their energy from lipids. FIG. 5A shows basal respiratory quotient (RQ = VCO2/VO2) during night or day fasting and feeding periods following 10 weeks of ND challenge. FIG. 5B shows basal carbohydrate and lipid oxidation in WT and *Fgfr3*$^{ach/+}$ ND challenged mice. FIG. 5C shows basal respiratory quotient (RQ = VCO2/VO2) during night or day fasting and feeding periods following 10 weeks of HFD challenge. FIG. 5D shows basal carbohydrate and lipid oxidation in WT and *Fgfr3*$^{ach/+}$ HFD challenged mice. Data are represented as mean ± SD (n= 8-10 mice to each group). Data followed normal distribution. **p<0.01, ***p<0.001 versus vehicle-treated WT, $^{\#}p$<0.05, $^{\#\#}p$<0.01 versus vehicle-treated *Fgfr3*$^{ach/+}$; Student's *t* test.

FIGS. 6A-6B are graphs showing circulating adipokines studied in the serum of untreated or sFGFR3-treated *Fgfr3*$^{ach/+}$ mice. FIG. 6A is a graph showing results of mice challenged with a ND. FIG. 6B is a graph showing results of mice challenged with a HFD. Results were expressed as percent of change compared to WT. AgRP, agoutirelated protein; ANGPT-L3, angiopoietin-3; CRP, C-reactive protein; DPPIV, dipeptidyl peptidase V; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule-1; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; MCP-1, monocyte chemotactic protein-1; M-CSF, macrophage colonystimulating factor; Pref-1, preadipocyte factor 1; RAGE, receptor for advanced glycation endproducts; RANTES, receptor upon activation, normal T-cell expressed and secreted; RBP4, retinol binding protein; TIMP-1, tissue inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor.

FIGS. 7A-7H are graphs showing that transgenic achondroplasia mice displayed normal energy expenditure, cumulative activity, and cumulative rearing during indirect calorimetry. FIG. 7A shows basal oxygen consumption during night or day fasting and feeding periods in WT and *Fgfr3*$^{ach/+}$ ND challenged mice. FIG. 7B shows basal carbon dioxide production during night or day fasting and feeding periods for in WT and *Fgfr3*$^{ach/+}$ ND challenged mice. FIG. 7C shows basal energy expenditure during night or day fasting and feeding periods for in WT and *Fgfr3*$^{ach/+}$ ND challenged mice. FIG. 7D shows basal cumulative activity and rearing in WT and *Fgfr3*$^{ach/+}$ ND challenged mice. FIG. 7E shows basal oxygen consumption during night or day fasting and feeding periods in WT and *Fgfr3*$^{ach/+}$ HFD challenged mice. FIG. 7F shows basal carbon dioxide production during night or day fasting and feeding periods for in WT and *Fgfr3*$^{ach/+}$ HFD challenged mice. FIG. 7G shows basal energy expenditure during night or day fasting and feeding periods for in WT and *Fgfr3*$^{ach/+}$ HFD challenged mice. FIG. 7H shows basal cumulative activity and rearing in WT and *Fgfr3*$^{ach/+}$ HFD challenged mice. Data are represented as mean ± SD (n= 8-10 mice to each group). Data followed normal distribution. ***p*<0.01, ****p*<0.001 versus vehicle-treated WT, $^{\#\#\#}$*p*<0.001 versus vehicle-treated *Fgfr3*$^{ach/+}$; Student's *t* test.

DETAILED DESCRIPTION OF THE INVENTION

We have discovered that soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptides and polynucleotides encoding the sFGFR3 polypeptides, and variants thereof, can be used to treat abnormal visceral fat deposition in a patient (e.g., a human, particularly a fetus, a neonate, a child, an adolescent, and an adult) in need thereof. In particular, sFGFR3 polypeptides that can be used in the methods of treatment described herein include those having an amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof having at least 85% sequence identity thereto. Polynucleotides encoding the sFGFR polypeptides or cells containing the polynucleotides can also be administered in the methods of treatment.

Methods of Treatment

Provided herein are methods for treating a patient with abnormal visceral fat deposition and the conditions associated with abnormal visceral fat deposition. In particular, the patient can have an elevated body mass index, sagittal diameter, android:gynoid fat ratio, fat mass index, and visceral fat area. The patient may also have a skeletal growth retardation syndrome, e.g., achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), hypochondroplasia, and craniosynostosis syndromes (e.g., Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome, camptodactyly, tall stature, and hearing loss syndrome (CATSHL). It may be the case that the patient has a skeletal growth retardation syndrome and a condition associated with abnormal visceral fat deposition (e.g., atherosclerosis, hypertension, myocardial infarction, dyslipidemia, sleep apnea, restrictive lung disease,

asthma, dementia, dysregulation of insulin (e.g., insulin resistance), dysregulation of glucose metabolism, infertility, menstrual irregularities, stroke, and dementia.

Alternatively, the patient may be one that does not have a skeletal growth retardation syndrome, but does have a condition that leads to abnormal visceral fat deposition (e.g., obesity, polycystic ovary syndrome, and hypercortisolism (e.g., Cushing's disease)). For example, the patient may have abnormal visceral fat deposition and a condition associated with abnormal visceral fat deposition (e.g., atherosclerosis, hypertension, myocardial infarction, dyslipidemia, sleep apnea, restrictive lung disease, asthma, dementia, dysregulation of insulin (e.g., insulin resistance), dysregulation of glucose metabolism, infertility, menstrual irregularities, stroke, and dementia). The method may also involve administration of a sFGFR3 to treat a patient with aberrant signaling of FGF10, such as a patient with Cushing's disease caused by pituitary gland dysfunction.

The patient may also be characterized as having visceral fat deposition associated with or surrounding one or more of the following organs: the heart, liver, spleen, kidneys, pancreas, intestines, reproductive organs, and gall bladder

The method involves administering an sFGFR3 polypeptide of the invention, e.g., those described herein, to the patient having abnormal visceral fat deposition. The patient may be a fetus, a neonate, an infant, a child, an adolescent, or an adult at risk for developing abnormal abdominal fat deposition. The patient may also have a skeletal growth retardation syndrome (e.g., achondroplasia), obesity, hypercortisolism (e.g., Cushing's disease), or polycystic ovary syndrome. The patient (e.g., a human) can be treated before signs and symptoms of abnormal visceral fat deposition develop. In particular, patients that can be treated with a sFGFR3 polypeptide of the invention described herein are those exhibiting symptoms including, but not limited to, abnormal fat mass index, abnormal area of visceral fat, elevated BMI, increased waist circumference, increased sagittal diameter, and increased android:gynoid fat ratio. Furthermore, patients that can be treated with a sFGFR3 polypeptide have abnormal visceral fat distribution and conditions associated with abnormal visceral fat deposition (e.g., metabolic, cardiovascular, pulmonary, reproductive or neurologic diseases). Furthermore, treatment with an sFGFR3 polypeptide can result in an improvement in one or more of the aforementioned symptoms related to abnormal visceral fat deposition (e.g., relative to an untreated patient). The patient (e.g., a human) can be diagnosed with abnormal visceral fat deposition, such as one with skeletal growth retardation syndrome (e.g., achondroplasia), obesity, hypercortisolism (e.g., Cushing's disease), and polycystic ovary syndrome, before administration of an sFGFR3 polypeptide. Additionally, the patient having abnormal visceral fat deposition can be one that has not previously been treated with an sFGFR3 polypeptide.

A patient that can be treated with an sFGFR3 polypeptide also includes a patient with, or at risk of developing, diabetes, such as an obese patient. Treatment of this patient may involve locally administering the soluble FGFR3 to the pancreas in order to treat or prevent diabetes development.

Soluble Fibroblast Growth Factor Receptor 3 (sFGFR3) Polypeptides

Soluble FGFR3 polypeptides and variants thereof can be used in the methods of treating a patient having abnormal visceral fat deposition. The sFGFR3 polypeptide can include at least 50 consecutive amino acids of an extracellular domain (ECD) of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide (e.g., the FGFR3 polypeptide having the sequence set forth in Genbank Accession No. NP_000133; see also SEQ ID NO: 8). In particular, the sFGFR3 polypeptide may include 100-370 consecutive amino acids (e.g., fewer than 350 consecutive amino acids) of an ECD of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide. The sFGFR3 polypeptide may also have an Ig-like C2-type domain 1, 2, and/or 3 of a naturally occurring FGFR3 polypeptide.

The sFGFR3 polypeptide may have, or may lack, a signal peptide (e.g., a signal peptide of an FGFR3 polypeptide, such as that corresponding to SEQ ID NO: 21; in particular, the sFGFR3 is a mature polypeptide lacking the signal peptide, which is cleaved during expression and secretion from the cell). The sFGFR3 polypeptide also lacks a transmembrane domain (TM), such as the TM of a naturally occurring FGFR3 polypeptide.

The sFGFR3 polypeptides may also contain all or a portion of an intracellular domain (ICD) of an FGFR3 polypeptide. For example, the sFGFR3 polypeptide may have 400 consecutive amino acids or fewer (e.g., between 5 and 399 consecutive amino acids, such as 175, 150, 125, 100, 75, 50, 40, 30, 20, 15, or fewer consecutive amino acids) of an ICD of a naturally-occurring FGFR3 polypeptide. The ICD of the sFGFR3 polypeptide may also lack a tyrosine kinase domain of a naturally-occurring FGFR3 polypeptide. Alternatively, the sFGFR3 polypeptide may lack any amino acids of an ICD of a naturally-occurring FGFR3 polypeptide (e.g., the FGFR3 polypeptide of SEQ ID NO: 8).

The sFGFR3 polypeptide may also have an amino acid sequence with at least 90%, 92%, 95%, 97%, or 99% sequence identity to, or the sequence of, amino acids 401 to 413 of SEQ ID NO: 8.

An sFGFR3 polypeptide for use in the methods described herein may be fewer than 475, 450, 425, 400, 375, 350, 300, 250, 200, 150, or 100 amino acids in length and/or may have an amino acid sequence with at least 85% sequence identity (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to amino acids residues 1 to 280 of SEQ ID NO: 8. The sFGFR polypeptide may also be one with an amino acid sequence having at least 85% sequence identity (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of any one of SEQ ID NOs: 1-7. In particular, the sFGFR3 has the amino acid sequence of SEQ ID NO: 5 or 6 (e.g., the amino acid sequence of SEQ ID NO: 5). The sFGFR3 polypeptide may also have the sequence of SEQ ID NO: 6, except that the residue at position 253 is an alanine, glycine, proline, or threonine.

sFGFR3 polypeptide variants that can be administered in the methods also include fragments of the amino acid sequence of any one of SEQ ID NOs: 1-8 (e.g., at least amino acids 1 to 200, 1 to 205, 1 to 210, 1 to 215, 1 to 220, 1 to 225, 1 to 235, 1 to 230, 1 to 240, 1 to 245, 1 to 250, 1 to 253, 1 to 255, 1 to 260, 1 to 265, 1 to 275, 1 to 280, 1 to 285, 1 to 290, or 1 to 300, of SEQ ID NO: 8) or polypeptides having at least 50% sequence identity (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity) to any one of SEQ ID NOs: 1-8 (and that, e.g., lack a signal peptide and TM domain).

The sFGFR3 polypeptides of the invention can also be characterized as binding to a fibroblast growth factor (FGF). In particular, the FGF is selected from the group consisting of fibroblast growth factor 1 (FGF1; SEQ ID NO: 26), fibroblast growth factor 2 (FGF2; SEQ ID NO: 27), fibroblast growth factor 9 (FGF9; SEQ ID NO: 28), fibroblast growth fact 10 (FGF10; SEQ ID NO: 40), fibroblast growth factor 18 (FGF18; SEQ ID NO: 29), fibroblast growth factor 19 (FGF19; SEQ ID NO: 30), fibroblast growth factor 21 (FGF21; SEQ ID NO: 31), and fibroblast growth factor 23 (FGF23; SEQ ID NO: 41). The binding is characterized by an equilibrium dissociation constant (K_d) of about 0.2 nM to about 20 nM (e.g., a K_d of about 1 nM to about 10 nM, wherein optionally the K_d is about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, about 8 nm, about 9 nm, or about 10 nm).

Given the results described herein, the invention is not limited to a particular sFGFR3 polypeptide or variant thereof. In addition to the exemplary sFGFR3 polypeptides and variants thereof discussed above, any sFGFR3 polypeptide that binds one or more FGFs with a similar binding affinity as the sFGFR3 polypeptides having the amino acids sequence of SEQ ID NOs: 1-7 are also envisioned as being useful for treating abnormal visceral fat deposition in a subject in need thereof. The sFGFR3 polypeptides can be, for example, fragments of FGFR3 isoform 2 lacking exons 8 and 9 encoding the C-terminal half of the IgG3 domain and exon 10 including the transmembrane domain (e.g., fragments of the amino acid sequence of SEQ ID NO: 8), corresponding to fragments of FGFR3 transcript variant 2 (Accession No. NM_022965).

As noted above, an sFGFR3 polypeptide for use in the methods of the invention can include a signal peptide at the N-terminal position. An exemplary signal peptide can include, but is not limited to, amino acids 1 to 22 of SEQ ID NO: 21 (e.g., MGAPACALALCVAVAIVAGASS). Accordingly, the sFGFR3 polypeptides include both secreted forms, which lack the N-terminal signal peptide, and non-secreted forms, which include the N-terminal signal peptide. For instance, a secreted sFGFR3 polypeptide can include the amino acid sequence of any one of SEQ ID NOs: 1-7, but without an N-terminal signal peptide (e.g., the sequence of SEQ ID NO: 21). Alternatively, the sFGFR3 polypeptide (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7) does include a signal peptide, such as the amino acid sequence of SEQ ID NO: 21. One skilled in the art will appreciate that the position of the N-terminal signal peptide will vary in different sFGFR3 polypeptides and can include, for example, the first 5, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 30, or more amino acid residues on the

N-terminus of the polypeptide. One of skill in the art can predict the position of a signal sequence cleavage site, e.g., by an appropriate computer algorithm such as that described in Bendtsen et al. (*J. Mol. Biol.* 340(4):783-795, 2004) and available on the Web at cbs.dtu.dk/services/SignalP/.

Additionally, sFGFR3 polypeptides of the invention can be glycosylated. In particular, a sFGFR3 polypeptide can be altered to increase or decrease the extent to which the sFGFR3 polypeptide is glycosylated. Addition or deletion of glycosylation sites to an sFGFR3 polypeptide can be accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed. For example, N-linked glycosylation, in which an oligosaccharide is attached to the amide nitrogen of an asparagine residue, can occur at position Asn76, Asn148, Asn169, Asn 203, Asn240, Asn272, and/or Asn 294 of the amino acid sequence of SEQ ID NO: 5 or 6 and variants thereof. One or more of these Asn residues can also be substituted to remove the glycosylation site. For instance, O-linked glycosylation, in which an oligosaccharide is attached to an oxygen atom of an amino acid residue, can occur at position Ser109, Thr126, Ser199, Ser274, Thr281, Ser298, Ser299, and/or Thr301 of the amino acid sequence of SEQ ID NO: 5 or 6 and variants thereof. Additionally, O-linked glycosylation can occur at a serine residue within the sFGFR3. One or more of these Ser or Thr residues can also be substituted to remove the glycosylation site.

sFGFR3 Fusion Polypeptides

sFGFR3 polypeptides of the invention (e.g., sFGFR3 polypeptides having the amino acid sequence of any one of SEQ ID NOs: 1-7 or a variant thereof having at least 85% sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto) can be fused to a functional domain from a heterologous polypeptide (e.g., a fragment crystallizable region (Fc region; such as a polypeptide having the amino acid sequence of SEQ ID NOs: 35 and 36) or human serum albumin (HSA; such as a polypeptide having the amino acid sequence of SEQ ID NO: 37)) to provide a sFGFR3 fusion polypeptide. Optionally, a flexible linker, can be included between the sFGFR3 polypeptide and the heterologous polypeptide (e.g., an Fc region or HSA), such as a serine or glycine-rich sequence (e.g., a poly-glycine or a poly-glycine/serine linker, such as SEQ ID NOs: 38 and 39).

For example, the sFGFR3 polypeptides and variants thereof can be a fusion polypeptide including, e.g., an Fc region of an immunoglobulin at the N-terminal or C-terminal domain. In particular, useful Fc regions can include the Fc fragment of any immunoglobulin molecule, including IgG, IgM, IgA, IgD, or IgE and their various subclasses (e.g., IgG-1, IgG-2, IgG-3, IgG-4, IgA-1, IgA-2) from any mammal (e.g., a human). For instance, the Fc fragment human IgG-1 (SEQ ID NO: 35) or a variant of human IgG-1, such as a variant including a substitution of asparagine at position 297 of SEQ ID NO: 35 with alanine (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 36). The Fc fragments of the invention can include, for example, the CH2 and CH3 domains of the heavy chain and any portion of the hinge region.

The sFGFR3 fusion polypeptides of the invention can also include, e.g., a monomeric Fc, such as a CH2 or CH3 domain. The Fc region may optionally be glycosylated at any appropriate one or more amino acid residues known to those skilled in the art. An Fc fragment as described herein may have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, or more additions, deletions, or substitutions relative to any of the Fc fragments described herein.

Additionally, the sFGFR3 polypeptides can be conjugated to other molecules at the N-terminal or C-terminal domain for the purpose of improving the solubility and stability of the protein in aqueous solution. Examples of such molecules include human serum albumin (HSA), PEG, PSA, and bovine serum albumin (BSA). For instance, the sFGFR3 polypeptides can be conjugated to human HSA (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 37) or a fragment thereof.

The sFGFR3 fusion polypeptides can include a peptide linker region between the sFGFR3 polypeptide and the heterologous polypeptide (e.g., an Fc region or HSA). The linker region may be of any sequence and length that allows the sFGFR3 to remain biologically active, e.g., not sterically hindered. Exemplary linker lengths are between 1 and 200 amino acid residues, e.g., 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, 81-85, 86-90, 91-95, 96-100, 101-110, 111-120, 121-130, 131-140, 141-150, 151-160, 161-170, 171-180, 181-190, or 191-200 amino acid residues. For instance, linkers include or consist of flexible portions, e.g., regions without significant fixed secondary or tertiary structure. Preferred ranges are 5 to 25 and 10 to 20 amino acids in length. Such flexibility is generally increased if the amino acids are small and do not have bulky side chains that impede rotation or bending of the amino acid chain. Thus, preferably the peptide linker of the present invention has an increased content of small amino acids, in particular of glycines, alanines, serines, threonines, leucines and isoleucines.

Exemplary flexible linkers are glycine-rich linkers, e.g., containing at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% glycine residues. Linkers may also contain, e.g., serine-rich linkers, e.g., containing at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% serine residues. In some cases, the amino acid sequence of a linker consists only of glycine and serine residues. For example, the linker can be the amino acid sequence of GGGGAGGGG (SEQ ID NO: 38) or GGGGSGGGGSGGGGS (SEQ ID NO: 39). A linker can optionally be glycosylated at any appropriate one or more amino acid residues. The linker can also be absent, in which the sFGFR3 polypeptide and the heterologous polypeptide (e.g., an Fc region or HSA) are fused together directly, with no intervening residues.

Polynucleotides encoding the sFGFR3 Polypeptides

Polynucleotides encoding the sFGFR3 polypeptides can be used to treat a patient having abnormal visceral fat deposition in a patient (e.g., a human, such as a fetus, a neonate, an infant, a child, an adolescent, or an adult). For example, the polynucleotide can have the nucleic acid sequence of any

one of SEQ ID NOs: 10-18 or a variant thereof having at least 85% sequence identity (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity) to the nucleic acid sequence of any one of SEQ ID NOs: 10-18. Additionally, the polynucleotide can have the nucleic acid sequence of SEQ ID NO: 14 or 15 or a variant having at least 85% sequence identity (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity) to the nucleic acid sequence of SEQ ID NO: 14 or 15.

Also featured are polynucleotides encoding sFGFR3 fusion polypeptides (e.g., a sFGFR3 polypeptide fused to a heterologous polypeptide, such as a Fc region or HSA) and polynucleotides encoding sFGFR3 polypeptides without a signal peptide (e.g., polypeptides having the amino acid sequence of any one of SEQ ID NOs: 1-7) or with a signal peptide (e.g., polypeptides having the amino acid sequence of any one of SEQ ID NOs: 1-7. Additionally, the polynucleotides can have one or more mutations to alter any of the glycosylation sites described herein or known to be present in the polypeptide.

Optionally, the polynucleotides of the invention can be codon optimized to alter the codons in the nucleic acid, in particular to reflect the typical codon usage of the host organism (e.g., a human) without altering the sFGFR3 polypeptide encoded by the nucleic acid sequence of the polynucleotide. Codon-optimized polynucleotides (e.g., a polynucleotide having the nucleic acid sequence of SEQ ID NO: 14 or 16) can, e.g., facilitate genetic manipulations by decreasing the GC content and/or for expression in a host cell (e.g., a HEK 293 cell or a CHO cell). Codon-optimization can be performed by the skilled person, e.g. by using online tools such as the JAVA Codon Adaption Tool (www.jcat.de) or Integrated DNA Technologies Tool (www.eu.idtdna.com/CodonOpt) by simply entering the nucleic acid sequence of the polynucleotide and the host organism for which the codons are to be optimized. The codon usage of different organisms is available in online databases, for example, www.kazusa.or.jp/codon.

Host cells for expression of the sFGFR3 polypeptides

Mammalian cells can be used as host cells for expression of the sFGFR3 polypeptide (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof). Exemplary mammalian cell types useful in the methods include, but are not limited to, human embryonic kidney (HEK; e.g., HEK 293) cells, Chinese Hamster Ovary (CHO) cells, L cells, C127 cells, 3T3 cells, BHK cells, COS-7 cells, HeLa cells, PC3 cells, Vero cells, MC3T3 cells, NS0 cells, Sp2/0 cells, VERY cells, BHK, MDCK cells, W138 cells, BT483 cells, Hs578T cells, HTB2 cells, BT20 cells, T47D cells, NS0 cells, CRL7O3O cells, and HsS78Bst cells, or any other suitable mammalian host cell known in the art. Alternatively, *E. coli* cells can be used as host cells for expression of the sFGFR3 polypeptides. Examples of *E. coli* strains include, but are not limited to, *E. coli* 294 (ATCC® 31,446), *E. coli* λ 1776 (ATCC® 31,537, *E. coli* BL21 (DE3) (ATCC® BAA-1025), *E. coli* RV308 (ATCC® 31,608), or any other suitable *E. coli* strain known in the art.

Vectors including polynucleotides encoding the sFGFR3 polypeptides

Also featured are recombinant vectors including any one or more of the polynucleotides described above (e.g., a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof). The vectors of the invention can be used to deliver a polynucleotide encoding a sFGFR3 polypeptide of the invention and variants thereof, which can include mammalian, viral, and bacterial expression vectors. For example, the vectors can be plasmids, artificial chromosomes (e.g. BAG, PAC, and YAC), and virus or phage vectors, and may optionally include a promoter, enhancer, or regulator for the expression of the polynucleotide. The vectors can also contain one or more selectable marker genes, such as an ampicillin, neomycin, and/or kanamycin resistance gene in the case of a bacterial plasmid or a resistance gene for a fungal vector. Vectors can be used *in vitro* for the production of DNA or RNA or used to transfect or transform a host cell, such as a mammalian host cell for the production of a sFGFR3 polypeptide encoded by the vector. The vectors can also be adapted to be used *in vivo* in a method of gene therapy.

Exemplary viral vectors that can be used to deliver a polynucleotide encoding a sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) include a retrovirus, adenovirus (e.g., Ad2, Ad5, Ad11, Ad12, Ad24, Ad26, Ad34, Ad35, Ad40, Ad48, Ad49, Ad50, and Pan9 (also known as AdC68)), parvovirus (e.g., adeno-associated viruses), coronavirus, negative strand RNA viruses such as orthomyxovirus (e.g., influenza virus), rhabdovirus (e.g., rabies and vesicular stomatitis virus), paramyxovirus (e.g. measles and Sendai), positive strand RNA viruses, such as picornavirus and alphavirus, and double stranded DNA viruses including adenovirus, herpesvirus (e.g., Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus), and poxvirus (e.g., vaccinia, modified vaccinia Ankara (MVA), fowlpox and canarypox). Other viruses useful for delivering polynucleotides encoding sFGFR3 polypeptides include Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, and hepatitis virus. Examples of retroviruses include avian leukosis-sarcoma, mammalian C-type, B-type viruses, D-type viruses, HTLV-BLV group, lentivirus, and spumavirus (Coffin, J. M., Retroviridae: The viruses and their replication, *In Fundamental Virology*, Third Edition, B. N. Fields, et al., Eds., Lippincott-Raven Publishers, Philadelphia, 1996).

Methods of Production

Polynucleotides encoding sFGFR3 polypeptides of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be produced by any method known in the art. For instance, a polynucleotide is generated using molecular cloning methods and is placed within a vector, such as a plasmid, an artificial chromosome, a viral vector, or a phage vector. The vector is used to transform the polynucleotide into a host cell appropriate for the expression of the sFGFR3 polypeptide.

Nucleic acid vector construction and host cells

The sFGFR3 polypeptides of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be produced from a host cell. The polynucleotides (e.g., polynucleotides having the nucleic acid sequence of SEQ ID NO: 14 or 16 and variants thereof) encoding sFGFR3 polypeptides can be included in vectors that can be introduced into the host cell by conventional techniques known in the art (e.g., transformation, transfection, electroporation, calcium phosphate precipitation, direct microinjection, or infection). The choice of vector depends in part on the host cells to be used. Generally, host cells are of either prokaryotic (e.g., bacterial) or eukaryotic (e.g., mammalian) origin.

A polynucleotide encoding an sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be prepared by a variety of methods known in the art. These methods include, but are not limited to, oligonucleotide-mediated (or site-directed) mutagenesis and PCR mutagenesis. A polynucleotide encoding an sFGFR3 polypeptide can be obtained using standard techniques, e.g., gene synthesis. Alternatively, a polynucleotide encoding a wild-type sFGFR3 polypeptide (e.g., a polypeptide having the amino acid sequence of SEQ ID NO: 8) can be mutated to contain specific amino acid substitutions using standard techniques in the art, e.g., QuikChange™ mutagenesis. Polynucleotides encoding an sFGFR3 polypeptide can be synthesized using, e.g., a nucleotide synthesizer or PCR techniques.

Polynucleotides encoding sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be inserted into a vector capable of replicating and expressing the polynucleotide in prokaryotic or eukaryotic host cells. Exemplary vectors useful in the methods can include, but are not limited to, a plasmid, an artificial chromosome, a viral vector, and a phage vector. For example, a viral vector can include the viral vectors described above, such as a retroviral vector, adenoviral vector, or poxviral vector (e.g., vaccinia viral vector, such as Modified Vaccinia Ankara (MVA)), adeno-associated viral vector, and alphaviral vector)) containing the nucleic acid sequence of a polynucleotide encoding the sFGFR3 polypeptide. Each vector can contain various components that may be adjusted and optimized for compatibility with the particular host cell. For example, the vector components may include, but are not limited to, an origin of replication, a selection marker gene, a promoter, a ribosome binding site, a signal sequence, the nucleic acid sequence of the polynucleotide encoding the sFGFR3 polypeptide, and/or a transcription termination sequence.

The above-described vectors may be introduced into appropriate host cells (e.g., HEK 293 cells or CHO cells, or into a host cell of a subject) using conventional techniques in the art, e.g., transformation, transfection, electroporation, calcium phosphate precipitation, and direct microinjection. Once the vectors are introduced into host cells for the production of an sFGFR3 polypeptide of the invention, the host cells are cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting

transformants, or amplifying the polynucleotides encoding the sFGFR3 polypeptide. Methods for expression of therapeutic proteins, such as sFGFR3 polypeptides, are known in the art, see, for example, Paulina Balbas, Argelia Lorence (eds.) *Recombinant Gene Expression: Reviews and Protocols (Methods in Molecular Biology)*, Humana Press; 2nd ed. 2004 (July 20, 2004) and Vladimir Voynov and Justin A. Caravella (eds.) *Therapeutic Proteins: Methods and Protocols (Methods in Molecular Biology)* Humana Press; 2nd ed. 2012 (June 28, 2012), each of which is hereby incorporated by reference in its entirety.

sFGFR3 polypeptide production, recovery, and purification

Host cells (e.g., HEK 293 cells or CHO cells) used to produce the sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be grown in media known in the art and suitable for culturing of the selected host cells. Examples of suitable media for mammalian host cells include Minimal Essential Medium (MEM), Dulbecco's Modified Eagle's Medium (DMEM), Expi293™ Expression Medium, DMEM with supplemented fetal bovine serum (FBS), and RPMI-1640. Examples of suitable media for bacterial host cells include Luria broth (LB) plus necessary supplements, such as a selection agent, e.g., ampicillin. Host cells are cultured at suitable temperatures, such as from about 20 °C to about 39 °C, e.g., from 25 °C to about 37 °C, preferably 37 °C, and CO_2 levels, such as 5 to 10% (preferably 8%). The pH of the medium is generally from about 6.8 to 7.4, e.g., 7.0, depending mainly on the host organism. If an inducible promoter is used in the expression vector, sFGFR3 polypeptide expression is induced under conditions suitable for the activation of the promoter.

An sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be recovered from the supernatant of the host cell. Alternatively, the sFGFR3 polypeptide can be recovered by disrupting the host cell (e.g., using osmotic shock, sonication, or lysis), followed by centrifugation or filtration to remove the sFGFR3 polypeptide. Upon recovery of the sFGFR3 polypeptide, the sFGFR3 polypeptide can then be further purified. An sFGFR3 polypeptide can be purified by any method known in the art of protein purification, such as protein A affinity, other chromatography (e.g., ion exchange, affinity, and size-exclusion column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins (see *Process Scale Purification of Antibodies*, Uwe Gottschalk (ed.) John Wiley & Sons, Inc., 2009, hereby incorporated by reference in its entirety).

Optionally, the sFGFR3 polypeptide of the invention (e.g., a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 1-7 and variants thereof) can be conjugated to a detectable label for purification. Examples of suitable labels for use in purification of the sFGFR3 polypeptides include, but are not limited to, a protein tag, a fluorophore, a chromophore, a radiolabel, a metal colloid, an enzyme, or a chemiluminescent, or bioluminescent molecule. In particular, protein tags that are useful for purification of the sFGFR3 polypeptides can include, but are not limited to, chromatography tags (e.g., peptide tags

consisting of polyanionic amino acids, such as a FLAG-tag, or a hemagglutinin "HA" tag), affinity tags (e.g., a poly(His) tag, chitin binding protein (CBP), maltose binding protein (MBP), or glutathione-S-transferase (GST)), solubilization tags (e.g., thioredoxin (TRX) and poly(NANP)), epitope tags (e.g., V5-tag, Myc-tag, and HA-tag), or fluorescence tags (e.g., GFP, GFP variants, RFP, and RFP variants).

Methods of Diagnosis

A patient with abnormal visceral fat deposition can be identified as being in need of treatment by one of many techniques known in the art. There are two categories of techniques: anthropometric techniques and imaging. Anthropometric techniques rely on measurements based on tape measure and scale. Imaging techniques rely on attenuation of x-ray beams as they travel through a patient or on the magnetic properties of a patient's hydrogen nuclei.

A commonly used anthropometric technique that categorizes patients as normal weight, overweight, or obese, is body mass index (BMI). BMI is calculated by dividing the a patient's weight (in kg) by the square of the patient's height (in m). The cutoff indicating obesity in adults is different from thresholds in children. For adults, obesity is considered to be present when the BMI is 30 kg/m^2 or greater (see, e.g., Nuttall, *Nutr. Today* 50(3):117-28, 2015); for children, the threshold for obesity varies based on age and height (see, e.g., van der Sluis et al., *Arch. Dis. Child*. 87(4):341-347, 2002). The standard tables for BMI in children have limitations when achondroplastic children are considered (see, e.g., Hoover-Fong et al., *Am. J. Clin. Nutr.* 88, 364-371, 2008).

Among anthropometric techniques, BMI does not distinguish between subcutaneous and visceral fat deposition. As a result, abnormal abdominal visceral fat is better identified using waist circumference (measured just above the palpated top of the iliac crest bone), sagittal diameter (the anteroposterior distance from the small of the back to the anterior abdomen), and the android:gynoid fat ratio (the waist circumference divided by the hip circumference).

The cutoff for abnormal waist circumference is, for adult females, greater than 83 cm, and for adult men greater than 90 cm (see, e.g., Zhu et al., *Am. J. Clin. Nutr.* 76(4):743-749, 2002) . For sagittal diameters, the cutoff for women is greater than 20.1 cm, and for men, greater than 23.1 cm; see, e.g., Pimentel et al, *Nutr. Hosp.* 25(4):656-61, 2010. Finally, for the android: gynoid fat ratio, the cutoff for women is greater than 0.85, while for men it is greater than 0.9; see, e.g., Price et al, *Am. J. Clin. Nutr.* 84(2):449-460, 2006).

One imaging technique that relies on x-rays is dual-energy x-ray absorptiometry (DXA), a method in which two x-ray beams of differing energy are used to determine fat (as opposed to lean) mass, and from this determination, a measure called fat mass index (measured fat mass divided by square of height) is derived. The cutoff for abnormal fat deposition in women is greater than 13, and the cutoff for abnormal fat deposition in men is greater than 9; see, e.g. Kelly et al, PLOS One, 4(9): 2009).

Both CT (using x-ray) and MRI (depending on the magnetic properties of the body) can image the abdomen in cross section, and thereby distinguish visceral from subcutaneous fat deposition. With either CT or MRI, the cutoff for abnormal visceral fat deposition in women is 110 cm^2, and for men it is 132 cm^2; see, e.g., Wajchenberg, *Endocr. Rev.* 21(6):697-738, 2000.

Methods of Monitoring Therapy

To assess an effect of therapy, a patient treated with an sFGFR3 polypeptide can be followed using a variety of biomarkers of disease state. For a patient treated to reduce or prevent abnormal visceral fat deposition, monitoring techniques include, e.g., determining improvement in BMI, sagittal diameter, android:gynoid ratio, waist circumference, fat mass index, and area of visceral fat on a standardized cross-sectional image of the abdomen. The effect of therapy can also be assessed using one or more biomarkers found in, e.g., a sample from the patient (e.g., a blood, urine, or sputum sample). In the case of a patient treated to prevent or improve metabolic diseases, such as diabetes or fatty liver, blood tests to monitor an effect of therapy include, e.g., assessing the patient sample for a change in glucose and/or insulin levels, an improvement in glucose tolerance testing, and a decrease in elevated levels of alanine transaminase, aspartate aminotransferase, and/or alkaline phosphatase.

If a patient is receiving sFGFR3 polypeptide therapy to treat or reduce the risk of cardiovascular diseases, a blood test can be performed to show improvement in a level of triglycerides, high density lipoproteins, low density lipoproteins, and/or cholesterol. Alternatively, radioisotope stress testing can be done to show an improvement in a patient's exercise tolerance and/or cardiac perfusion.

For patients treated to improve or reduce the risk of dementia, serial neuropsychology testing can be performed.

In cases in which sFGFR3 polypeptide is administered to treat or reduce the risk of infertility or menstrual irregularities, a level of a blood biomarker, such as follicle-stimulating hormone, luteinizing hormone, estradiol, and prolactin, can be measured.

If a patient is suffering or at risk for sleep apnea, a study that measures, e.g., the sleeping patient's oxygen, respiratory rate, heart rate, snoring, and/or body movement can be performed following therapy with an sFGFR3 polypeptide to assess the effect of therapy.

In a patient for whom an sFGFR3 polypeptide is given to treat or prevent restrictive lung disease or asthma, pulmonary function testing using, e.g., spirometry or plethysmography, can be used to show an improvement in lung measures, such as tidal volume, vital capacity, residual volume, and/or forced vital capacity.

In a case where monitoring techniques indicate that a patient may not be responding to the treatment using an sFGFR3 polypeptide, or for which a greater treatment effect may be desired, administration of an sFGFR3 polypeptide may be repeated one or more times or the frequency of administration may be increased.

Administration of sFGFR3 polypeptides

An sFGFR3 polypeptide can be administered to treat a patient having or at risk of abnormal visceral fat deposition. Examples of sFGFR3 polypeptides include, e.g., sFGFR3 polypeptides having the amino acid sequence of any one of SEQ ID NOs: 1-7 or a variant thereof having at least 85% sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto). The sFGFR3 polypeptide can be administered by any route known in the art, such as by parenteral administration, enteral administration, or topical administration. In particular, the sFGFR3 polypeptide can be administered to the patient having increased visceral fat deposition) subcutaneously (e.g., by subcutaneous injection), intravenously, intramuscularly, intra-arterially, intrathecally, or intraperitoneally.

An sFGFR3 polypeptide can be administered to a patient (e.g., a human) at a predetermined dosage, such as in an effective amount to treat increased visceral fat deposition without inducing significant toxicity. For example, sFGFR3 polypeptides can be administered to a patient having increased visceral fat deposition in individual doses ranging from about 0.002 mg/kg to about 20 mg/kg (e.g., from 0.002 mg/kg to 20 mg/kg, from 0.01 mg/kg to 2 mg/kg, from .2 mg/kg to 20 mg/kg, from 0.01 mg/kg to 10 mg/kg, from 10 mg/kg to 100 mg/kg, from 0.1 mg/kg to 50 mg/kg, 0.5 mg/kg to 20 mg/kg, 1.0 mg/kg to 10 mg/kg, 1.5 mg/kg to 5 mg/kg, or 0.2 mg/kg to 3 mg/kg). In particular, the sFGFR3 polypeptide can be administered in individual doses of, e.g., 0.001 mg/kg to 7 mg/kg, such as 0.3 mg/kg to about 2.5 mg/kg.

Exemplary doses of an sFGFR3 polypeptide of the invention) for administration to a patient (e.g., a human) having increased visceral fat deposition) include, e.g., 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 13, 14, 15, or 20 mg/kg. These doses can be administered one or more times (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more times) per day, week, month, or year. For example, an sFGFR3 polypeptide can be administered to patients in a weekly dosage ranging, e.g., from about 0.0014 mg/kg/week to about 140 mg/kg/week, e.g., about 0.14 mg/kg/week to about 105 mg/kg/week, or, e.g., about 1.4 mg/kg/week to about 70 mg/kg/week (e.g., 5 mg/kg/week).

Gene Therapy

An sFGFR3 polypeptide can be administered to a patient as a nucleic acid molecule. Examples of nucleic acid molecules that can be administered include those that encode sFGFR3 polypeptides having the amino acid sequence of any one of SEQ ID NOs: 1-7 or a variant thereof having at least 85% sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto). For example, the nucleic acid molecules may have the sequence of any one of SEQ ID NOs: 10-18 or a variant thereof with at least 85%

sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto).

The sFGFR3 polypeptide-encoding nucleic acid molecules can be delivered by gene therapy, in which a polynucleotide encoding the sFGFR3 polypeptide is delivered to tissues of interest and expressed *in vivo*. Gene therapy methods are discussed, e.g., in Verme et al. (*Nature* 389:239-242, 1997), Yamamoto et al. (*Molecular Therapy* 17:S67-S68, 2009), and Yamamoto et al., (*J. Bone Miner. Res.* 26: 135-142, 2011), each of which is hereby incorporated by reference.

An sFGFR3 polypeptide of the invention can be produced by the cells of a patient (e.g., a human) having increased visceral fat deposition by administrating a vector (e.g., a plasmid, an artificial chromosome (e.g. BAG, PAC, and YAC), or a viral vector) containing the nucleic acid sequence of a polynucleotide encoding the sFGFR3 polypeptide. For example, a viral vector can be a retroviral vector, adenoviral vector, or poxviral vector (e.g., vaccinia viral vector, such as Modified Vaccinia Ankara (MVA)), adeno-associated viral vector, or alphaviral vector. The vector, once inside a cell of the patient (e.g., a human) having a skeletal growth retardation disorder (e.g., achondroplasia), by, e.g., transformation, transfection, electroporation, calcium phosphate precipitation, or direct microinjection, will promote expression of the sFGFR3 polypeptide, which is then secreted from the cell. The invention further includes cell-based therapies, in which the patient (e.g., a human) is administered a cell expressing the sFGFR3 polypeptide.

Pharmaceutical Compositions

Pharmaceutical compositions that can be administered to treat a subject having abnormal visceral fat deposition, as discussed herein, contain an sFGFR3 polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell that contains the sFGFR3 polynucleotide. The sFGFR3 polypeptide can have the amino acid sequence of any one of SEQ ID NOs: 1-7 or a variant thereof having at least 85% sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto). The nucleic acid molecules may have the sequence of any one of SEQ ID NOs: 10-18 or a variant thereof with at least 85% sequence identity thereto (e.g., 86%-100% sequence identity, such as 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto). Compositions including an sFGFR3 polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell that contains the sFGFR3 polynucleotide can be formulated at a range of dosages, in a variety of formulations, and in combination with pharmaceutically acceptable excipients, carriers, or diluents.

A pharmaceutical composition including an sFGFR3 polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell that contains the sFGFR3 polynucleotide can be formulated at a specific dosage, such as a dosage that is effective for treating a patient (e.g., a human) with increased visceral fat deposition without inducing significant toxicity. For example, the compositions can be

formulated to include between about 1 mg/mL and about 500 mg/mL of the sFGFR3 polypeptide or polynucleotide (e.g., between 10 mg/mL and 300 mg/mL, 20 mg/mL and 120 mg/mL, 40 mg/mL and 200 mg/mL, 30 mg/mL and 150 mg/mL, 40 mg/mL and 100 mg/mL, 50 mg/mL and 80 mg/mL, or 60 mg/mL and 70 mg/mL of the sFGFR3 polypeptide or polynucleotide).

The pharmaceutical compositions including an sFGFR3 polypeptide or polynucleotide can be prepared in a variety of forms, such as a liquid solution, dispersion or suspension, powder, or other ordered structure suitable for stable storage. For example, compositions including an sFGFR3 polypeptide or polynucleotide intended for systemic or local delivery can be in the form of injectable or infusible solutions, such as for parenteral administration (e.g., subcutaneous, intravenous, intramuscular, intra-arterial, intrathecal, or intraperitoneal administration). sFGFR3 compositions for injection (e.g., subcutaneous or intravenous injection) can be formulated using a sterile solution or any pharmaceutically acceptable liquid as a vehicle. Pharmaceutically acceptable vehicles include, but are not limited to, sterile water, physiological saline, and cell culture media (e.g., Dulbecco's Modified Eagle Medium (DMEM), α-Modified Eagles Medium (α-MEM), F-12 medium). Formulation methods are known in the art, see e.g., Banga (ed.) *Therapeutic Peptides and Proteins: Formulation, Processing and Delivery Systems* (2nd ed.) Taylor & Francis Group, CRC Press (2006), which is hereby incorporated by reference in its entirety.

Compositions including an sFGFR3 polypeptide or polynucleotide can be provided to patients (e.g., humans) having increased visceral fat deposition in combination with pharmaceutically acceptable excipients, carriers, or diluents. Acceptable excipients, carriers, or diluents can include buffers, antioxidants, preservatives, polymers, amino acids, and carbohydrates. Aqueous excipients, carriers, or diluents can include water, water-alcohol solutions, emulsions or suspensions including saline, buffered medical parenteral vehicles including sodium chloride solution, Ringer's dextrose solution, dextrose plus sodium chloride solution, Ringer's solution containing lactose, and fixed oils. Examples of non-aqueous excipients, carriers, or diluents are propylene glycol, polyethylene glycol, vegetable oil, fish oil, and injectable organic esters.

Pharmaceutically acceptable salts can also be included in the sFGFR3 compositions . Exemplary pharmaceutically acceptable salts can include mineral acid salts (e.g., hydrochlorides, hydrobromides, phosphates, and sulfates) and salts of organic acids (e.g., acetates, propionates, malonates, and benzoates). Additionally, auxiliary substances, such as wetting or emulsifying agents and pH buffering substances, can be present. A thorough discussion of pharmaceutically acceptable excipients, carriers, and diluents is available in *Remington: The Science and Practice of Pharmacy*, 22nd Ed., Allen (2012), which is hereby incorporated by reference in its entirety.

Pharmaceutical compositions including an sFGFR3 polypeptide or polynucleotide can also be formulated with a carrier that will protect the sFGFR3 polypeptide or polynucleotide against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. For example, the sFGFR3 composition can be entrapped in microcapsules prepared by coacervation

techniques or by interfacial polymerization, such as hydroxymethylcellulose, gelatin, or poly-(methylmethacylate) microcapsules; colloidal drug delivery systems (e.g., liposomes, albumin microspheres, microemulsions, nano-particles, or nanocapsules); or macroemulsions. Additionally, an sFGFR3 composition can be formulated as a sustained-release composition. For example, sustained-release compositions can include semi-permeable matrices of solid hydrophobic polymers containing the sFGFR3 polypeptide or polynucleotide, in which the matrices are in the form of shaped articles, such as films or microcapsules.

EXAMPLES

The following examples are intended to illustrate, rather than limit, the disclosure.

Example 1:

Study design

To evaluate the potential of sFGFR3 therapy (e.g., sFGFR3 having the sequence of SEQ ID NO: 1) to prevent the development of abdominal obesity in achondroplasia, we have first characterized the development of obesity in children by doing a retrospective chart review and have then conducted a study in *Fgfr3ach/+* mice, a mouse model recapitulating most human symptoms. For the chart review, eleven subjects (5 girls and 6 boys) with achondroplasia were followed from birth up to 18 years in the Department of endocrinology, bone diseases, genetic and medical gynecology of the Purpan Children's Hospital in Toulouse, France. This retrospective chart review study was conducted in accordance with the declaration of Helsinki and the French regulations on Biomedical research, not requiring ethics committee approval for a non-interventional study. All patients harbored the G380R FGFR3 mutation (G380R refers to the numbering in the full length FGFR3, including the signal peptide; the residue numbering without the signal peptide is G358R (see SEQ ID NO: 9), confirmed by molecular testing. Patients receiving any growth treatment were excluded. Children were followed in the specialized center every 4 months on average. During each visit, data included the height, weight and subsequent body mass index (BMI=kg/m2). Blood analyses were performed only once a year and dual-energy X-ray absorptiometry (DXA) was performed once. The mouse study was performed on transgenic *Fgfr3ach/+* mice or their wild-type (WT) littermates. For this, litters were treated blindly twice weekly by subcutaneous injections of 2.5 µg/kg of sFGFR3 or vehicle starting at day 3 until day 21. Mice were weaned at age 3 weeks. After one week of acclimation, mice were challenged with normal (ND) or high-fat diet (HFD) for 10 weeks. The development of obesity was evaluated through measures of body composition, indirect calorimetry and classical evaluation of glucose and lipid profiles, as well as hepatic and pancreatic function evaluations. The *n* per group is presented in the figure legends.

Clinical analysis

Anthropometric calculations, including height-to-age z score and BMI-to-age z score, were done using the WHO AnthroPlus software (WHO AnthroPlus for personal computers Manual: Software for assessing growth of the world's children and adolescents. Geneva: WHO, 2009 (www.who.int/growthref/tools/en/); z-scores are based on WHO standards (birth to 60 months) and WHO reference 2007 (61 months to 19 years). Body composition was evaluated by DXA using the Lunar Prodigy device (GE Healthcare). The regions of interest (ROI) for regional body composition were defined using the manufacturer's instructions (**Fig. 1B**). Briefly, the trunk ROI was measured from the pelvis cut (lower boundary) to the neck cut (upper boundary); the android ROI was measured from the pelvis cut (lower boundary) to above the pelvic cut by 20% of the distance between the neck and the pelvis cuts (upper boundary); the umbilicus ROI was defined from the lower boundary of the android by 150% of the android distance; and the gynoid ROI was from the lower boundary of the umbilicus ROI to a line equal to twice the height of the android ROI (lower boundary). Blood samples were drawn after at least a 12-hour fasting period and analyzed at the Federative Institute of Biology (IFB) of the Purpan hospital. Fasting glucose and insulin, total, HDL, and LDL cholesterol, triglyceride, TGO, TGP, gGT concentrations, as well as plasma total calcium, sodium, potassium, bicarbonate, phosphate, chloride and alkaline phosphatase were measured using standard colorimetric or colorimetric enzymatic methods on the Cobas 8000 modular analyzer series, using the C701 module, from Roche Diagnostics. Serum concentration of total 25OH vitamin D was measured by chemiluminescent immunoassay method on the Cobas 8000 modular analyzer series, using the E602 module, from Roche Diagnostics. All values were compared to reference values established for each age group within the Children's hospital and using published references (Mellerio et al., *Pediatrics* 129: e1020-1029 (2012); Fischer et al., *Ann. Clin. Biochem.* 49:546-553, 2012; and Haine et al., *J. Bone Miner. Res.* 30:1369-1376, 2015). After 12h overnight fast, OGTT was performed in patients per the established recommendations (Alberti et al., *Diabet. Med.* 15:539-553, 1998). Following oral administration of 1.75g/kg of glucose, blood samples were drawn at baseline and after 30 and 120 min to measure glucose concentration using hexokinase method. Glucose regulation was assessed according to the American Diabetes Association guidelines: normal glucose regulation was defined as fasting glucose <5.6 mmol/L and 120 min glucose <7.8 mmol/L and impaired fasting glucose as fasting glucose
5.6 – 6.9 mmol/L, impaired glucose tolerance as 120 min glucose 7.8 – 11.0 mmol/L.

Animals and treatment

Experiments were performed on transgenic Fgfr3ach/+ mice (Naski et al., *Development* 125: 4977-4988, 1998). At weaning, ear biopsies were used to verify mice genotype by PCR of genomic DNA as previously described (Garcia et al., *Science Translational Medicine* 5:203ra124, 2013).

During the experiment, mice were housed in standard laboratory conditions and were allowed access food and water ad libitum. The study was approved by the local Institutional Ethic Committee for

the use of Laboratory Animals (CIEPAL Azur) (approvals # NCE-2012-52 and NCE-2015-225). At day 3, newborn mice were treated with 2.5 mg/kg of FLAG-tagged sFGFR3 as described previously (Garcia et al., *Science Translational Medicine* 5:203ra124, 2013). Control litters received 10 µl of PBS containing 50% glycerol (vehicle). From age day 3 to day 22, *Fgfr3ach/+* mice received 6 subcutaneous injections of sFGFR3 or vehicle. One week after weaning at 4 weeks of age, treated and untreated mice were divided into two groups and challenged for 10 weeks with normal (ND, A03, SAFE) or high fat diet (HFD, 52% kcal as fat, custom made, containing 54% lipids, SAFE), respectively. After 6 hours fasting, blood was taken from the tail vein. Glycemia was measured with a glucometer (Abbot) and serum insulin contents were determined by ELISA (Mercodia). Glucose tolerance tests (GTT) were performed on mice after 10 weeks of ND or HFD challenge. After 6 hours fasting mice were injected with an intra-peritoneal glucose solution (1g/kg). Blood was taken from the tail vein and glucose levels were monitored over time using a glucometer or using EnzyChrom Glucose Assay Kit (BioAssay Systems). Glucose levels were normalized to the value of time -15 min of each mouse.

Indirect calorimetry was studied on mice challenged for 10 weeks with normal (ND) or high fat (HFD) diet. As stated above, mice were treated during the growth period with 2.5 mg/kg of sFGFR3 or vehicle, were subjected to the diet challenge for 2 weeks and were then subjected to the metabolic chambers. After 24 h of acclimatization in individual metabolic cages, O2 consumption (VO2) and CO2 production (VCO2) were measured (Oxylet; Panlab-Bioseb) in individual mice at 32 min intervals during a 24 h period with unrestricted access on food followed by one night fasted. The respiratory quotient was calculated and analyzed as follows: RQ=VCO2/VO2, RQ=1 correspond to carbohydrate oxidation and RQ~0.7 correspond to fat oxydation. Energy expenditure (kcal/day/weighx0.75=1.44xVO2x[3.815+1.232xRQ]), carbohydrate (g/min/kg0.75= [4.55xVCO2]-[3.21xVO2]) and lipid (g/min/kg0.75=[1.67xVO2]- [1.67xVCO2]) oxidations were calculated. Ambulatory activities and rearing of the mice were monitored by a weight transducer technology or an infrared photocell beam interruption method (Oxylet; Panlab-Bioseb).

Body composition was determined using a SkyScan 1178 X-ray micro-CT system. Four and 10 weeks old mice were anesthetized and scanned using the same parameters: 104 µm of pixel size, 49 kV, 0.5 mm thick aluminum filter, 0.9° of rotation step. Total adipose tissue volume was determined between the tip of the snout and the top of the tail and abdominal adipose tissue volume was determined between the lumbar L1 and the sacral S1. Then, adipose tissue quantification was carried out more precisely. Body compositionanalysis is based on the delimitation of region of interest after 3D reconstruction of scanned images. 3-D reconstructions analyses were performed using NRecon and CTAn software (Skyscan).

At sacrifice, animals were weighted and several tissues and organs (subcutaneous, epididymal adipose tissue, liver, pancreas) were harvested for further analysis by histochemistry or qPCR. In some groups, bone-marrow-derived mesenchymal stem cells were harvested by flushing the femurs (Zhu et al., *Nat Protoc* 5:550-560, 2010).

Lipid profile was evaluated by taking intracardiac blood. Total cholesterol, triglycerides (TG), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) were measured on serum using a Beckman AU 2700 Analyzer. Sera were analyzed for protein levels of selected adipokines related to inflammation, obesity, insulin pathway or FGFs using the Mouse Adipokine Array (#ARY013, R&D Systems) according to the manufacturer's instructions on nitrocellulose membranes. Following streptavidin-HRP and chemiluminescent detection the proteins bound to each captured antibody were quantified using densitometry and levels were compared to percent change from WT mice.

Mesenchymal stem cell studies

Mesenchymal stem cells were isolated from femoral bone marrow providing from untreated or sFGFR3-treated 6 to 8 weeks old mice by flushing the femurs (Zhu et al., *Nat. Protoc.* 5:550-560, 2010) and cultivated to 80% confluence in medium supplemented with 10% serum. Then, medium was replaced with adipogenic medium (DMEM F12 supplemented with 2% serum, 1% antiobiotics, 66mM insulin, 1nM triiodothyronine, 100mM cortisol, 10µg/ml transferrin and 3µM rosiglitazone in DMEM-F12). Total RNAs were extracted using Trizol Reagent (Life Technologies) and Chloroform (Sigma). One microgram of total RNA was reverse transcribed into cDNA using random hexamers and the Superscript II Reverse Transcriptase kit (Invitrogen). Real-time qPCR was performed on a StepOne Plus Real-Time PCR System (Applied Biosystems) with Fast SYBR Green Master Mix (Sigma) using a custom RT2 Profiler PCR Array (CAPM13080). Studied genes are listed in **Table 1**. Gene expression was normalized to HPRT, RPL13a and RPL6 housekeeper gene. FGFRs expression was performed using the following primers: FGFR1, For-5' CAGATGCACTCCCATCCTCG 3' Rev-5' TCT GGGGATGTCCAGTAGGG 3'; FGFR2 For-5' TGGCAGTGAAGATGTTGAAAG 3' Rev-5' ATCATCTTCATCATCTCCATCTCTTG 3'; FGFR3 For-5' TTATCCTTGGCTCCTGGGTG 3' Rev-5' CTGGAAGGTAGCAGTGGGAA 3'; FGFR4 For-5' GCTCGGAGGTAGAGGTCTTGT 3' Rev-5' CCACGCTGACTGGTAGGAA 3'; HSP90 For-5' TTTGGTGGACACAGGCATTG 3' Rev-5' CAAACTGCCCGATCATGGAG 3'.

Table 1. List of genes studied using custom RT2 Profiler PCR Array in mesenchymal stem cells.

Gene Symbol	Official Full Name	Refseq #
Adipoq	Adiponectin, C1Q and collagen domain containing	NM_009605
Cebpa	CCAAT/enhancer binding protein (C/EBP), alpha	NM_007678
Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	NM_009883
Cebpd	CCAAT/enhancer binding protein (C/EBP), delta	NM_007679
Dlk1	Delta-like 1 homolog (Drosophila)	NM_010052
Fabp4	Fatty acid binding protein 4, adipocyte	NM_024406
Fasn	Fatty acid synthase	NM_007988
Gata3	GATA binding protein 3	NM_008091
Hprt	Hypoxanthine guanine phosphoribosyl transferase	NM_013556
Lep	Leptin	NM_008493
Lipe	Lipase, hormone sensitive	NM_010719
Lpl	Lipoprotein lipase	NM_008509
Pparg	Peroxisome proliferator activated receptor gamma	NM_011146
Ppargc1a	Peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	NM_008904
Rpl13a	Ribosomal protein L13a	NM_009438
Rpl6	Ribosomal protein L6	NM_011290
Scd1	Stearoyl-Coenzyme A desaturase 1	NM_009127
Slc2a4	Solute carrier family 2 (facilitated glucose transporter), member 4	NM_009204
Srebf1	Sterol regulatory element binding transcription factor 1	NM_011480
Ucp1	Uncoupling protein 1 (mitochondrial, proton carrier)	NM_009463
Wnt1	Wingless-related MMTV integration site 1	NM_021279

For insulin signaling experiments, 24h after isolation, cells were depleted during 6h and then stimulated with 50nM insulin for 0, 5, 15, 30 min, or with 0, 1, 10, 50, 100nM for 5min. Cells extracts were processed for Western Blot analysis. For this, cells were lysed in RIPA lysis buffer (Millipore) and homogenized from 30 min using a vortex. Proteins were pelleted by centrifugation 1400 g from 15 min and total protein contents were evaluated using the BCA Protein Assay Kit (ThermoScientific). Samples were diluted in Sample Reducing Buffer (Life Technology), boiled, and processed for immunoblotting by using a standard procedure. Monoclonal antibodies were used as follows: anti p44/42 MAPK (Erk1/2) (4695S, Cell Signaling), anti phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (4370S, Cell Signaling). Results were normalized to HSP90 expression (4877S, Cell Signaling).

Histology and immunohistochemistry

Histology analyses were performed on adipose tissue, liver and pancreas of 12 weeks old mice. Organs were fixed in 4% formalin for 24 h, paraffin-embedded and 5 µm sections are stained with hematoxylin and eosin. Adipocyte diameters were measured in one or two different sections in each sample (from 100 to 300 adipocytes were counted in each section).

Pancreatic islet numbers and area were measured in one section using Fiji Image J system (islet area was normalized to total pancreas area). Liver glycogen content was evaluated by Periodic acid-Shiff (PAS) staining. Immunohistochemistry was performed on 5µm sections of pancreas. Sections were blocked 45 min with PBS 1% BSA, incubated over night with anti-insulin monoclonal primary antibody (4µg/ml) (Santa Cruz, sc-9168), anti-glucagon polyclonal antibody (4µg/ml) (Santa Cruz, sc-7779) and 1h with Alexa Fluor 594 secondary antibody (2µg/ml) (Life Technologies, A-21442) and Alexa Fluor 488 secondary antibody (4µg/ml) (Life Technologies, A-21467) in wet chamber. Sections were counterstained with DAPI solution (Santa Cruz), treated with autofluorescence eliminator reagent and visualized under fluorescence microscopy. Staining without secondary antibody was used as a negative control.

Statistical analysis

Statistical analyses were performed with GraphPad Prism 6.0 software. Data were expressed as mean ± SD. To verify normality and equal variance, an Agostino and Pearson omnibus normality test (a = 0.05), a Shapiro-Wilk normality test (a = 0.05) and a KS normality test (a = 0.05) were performed. Significance was determined by using unpaired two-tailed Student *t* test or Tukey's multiple comparison test. In patients, the raw results of height and BMI were transformed to age-specific z-score from the average in the reference population using reference data. The expected mean result of these values in a healthy population is 0. P values < 0,05 were considered significant (* P< 0,05; ** P< 0,01; *** P< 0,001).

Example 2:

Achondroplasia patients develop an excess of abdominal adipose tissue without classical complications

Subjects were children and adolescents with achondroplasia. They were included in a longitudinal, retrospective study conducted by the same observer for an average of 8.6 ± 5.6 years. Anthropometric measures and body composition were recorded from birth on during follow up visits and compared between three age groups ranging from [0-3], [4-8] and [9-18] years old. Several metabolic blood parameters were measured and compared in the different age groups. Blood values for visits under age of 3 were not considered because of the difficulty to restrict food intake in infants and thus control metabolic parameters at this young age.

It is known that achondroplasia patients not only display impaired growth but that they also have a tendency to gain excessive weight leading to overweight or even obesity (Hoover-Fong et al., *Am. J. Med. Genet. A.* 143A:2227-2235, 2007). As seen in **Fig. 1A**, the BMI of patients with achondroplasia significantly increased during childhood, to reach a value of about 30 kg/m2 in the [9-18] years old group ($P = 0.2407$ between [0-3] and [4-8] groups, $P<0.0001$ comparing the [9-18] group to both other groups, Tukey's multiple comparisons test). A negative correlation was observed between BMI and height (Pearson r coefficient=-0.5660, P=0.0021), with a tendency for the smallest children to have the highest BMI. To study their metabolic status and its evolution, densitometry analyses were first performed to determine body fat and lean mass distribution in the different age groups (**Fig. 1B**). We observed that up to 8 years old, the total fat:lean ratio was relatively constant and that it rose significantly during adolescence, from 0.21 ± 0.02 and 0.20 ± 0.05 in the [0-3] and [4-8] age groups to 0.84 ± 0.29 in the [9-18] age group, respectively ($P=0.9954$ between [0-3] and [4-8] groups, $P=0.0053$ and $P<0.0001$ comparing [9-18] to [0-3] and [4-8] age groups, respectively, Tukey's multiple comparisons test) (**Table 2**).

Table 2. Densitometry results of achondroplasia patients in the three age groups. Values are mean ± SD (range). The p values represent the significance of the difference between the three groups (one way ANOVA test followed by Tukey's multiple comparison tests, ns = non-significant). Results of post hoc analyses: a significantly different between [0-3] and [4-8] groups; b significantly different between [0-3] and [9-18] groups; c significantly different between [4-8] and [9-18] groups.

Age (yrs)	**[0-3]**		**[4-8]**		**[9-18]**			
Variables	**Mean ± SD**	**Range (min-max)**	**Mean ± SD**	**Range (min-max)**	**Mean ± SD**	**Range (min-max)**		
Fat and lean mass repartition (kg)							*P*	
Total body fat mass	1.52 ± 0.32	(1.29-1.76)	2.64 ± 0.73	(1.98-4.06)	19.78 ± 7.98	(8.56-30.15)	< 0.0001	b, c
Total body lean mass	0.88 ± 0.04	(0.86-0.91)	0.84 ± 0.09	(0.75-0.90)	0.46 ± 0.01	(0.46-0.68)	0.001	b, c
Trunk mass	3.67 ± 0.45	(3.38-4.02)	6.93 ± 1.46	(4.83-8.68)	21.19 ± 5.53	(14.08-28.72)	< 0.0001	b, c
Trunk fat mass	0.41 ± 0.12	(0.32-0.49)	0.83 ± 0.44	(0.23-1.64)	9.74 ± 4.42	(3.97-15.65)	0.001	b, c
Trunk lean mass	3.29 ± 0.33	(3.06-3.53)	6.11 ± 1.15	(4.35-7.08)	11.4 ± 1.50	(9.67-13.42)	< 0.0001	a, b, c
Leg mass	1.77 ± 0.28	(1.57-1.97)	4.61 ± 1.29	(3.12-7.21)	13.89 ± 3.36	(8.86-18.24)	< 0.0001	b, c
Leg fat mass	0.65 ± 0.12	(0.57-0.73)	1.22 ± 0.31	(0.86-1.69)	7.46 ± 2.61	(3.39-10.72)	< 0.0001	b, c
Leg lean mass	1.11 ± 0.16	(0.99-1.23)	3.39 ± 1.04	(2.26-5.52)	6.31 ± 0.98	(4.81-7.51)	< 0.0001	a, b, c
Arm mass	0.65 ± 0.04	(0.62-0.68)	1.21 ± 0.23	(0.99-1.53)	3.74 ± 1.03	(2.38-5.12)	< 0.0001	b, c
Arm fat mass	0.09 ± 0.06	(0.08-0.10)	0.21 ± 0.09	(0.12-0.35)	1.57 ± 0.76	(0.56-2.54)	0.004	b, c
Arm lean mass	0.56 ± 0.04	(0.53-0.58)	0.99 ± 0.18	(0.66-1.18)	2.16 ± 0.34	(1.62-2.65)	0.001	b, c
Fat and lean mass repartition (% of total body weight)								
Total body fat mass	19.04 ± 0.74	(18.51-19.57)	16.08 ± 3.10	(11.86-21.40)	42.93 ± 9.11	(28.36-52.89)	< 0.0001	b, c
Total body lean mass	88.29 ± 3.51	(85.81-90.77)	83.89 ± 9.25	(74.75-90.43)	46.19 ± 0.79	(45.63-68.49)	< 0.0001	b, c
Trunk mass	46.47 ± 2.57	(44.64-48.29)	47.26 ± 4.08	(28.42-50.15)	50.35 ± 0.06	(45.00-50.40)	ns	
Trunk fat mass	5.01 ± 0.64	(4.56-5.46)	5.60 ± 1.74	(1.37-8.65)	27.11 ± 0.50	(13.16-27.46)	< 0.0001	b, c
Trunk lean mass	41.47 ± 3.22	(39.19-43.74)	41.66 ± 5.82	(27.05-45.78)	23.24 ± 0.44	(22.71-33.47)	0.004	b, c
Leg mass	22.14 ± 0.37	(21.88-22.40)	25.22 ± 0.28	(25.03-42.45)	31.13 ± 1.24	(29.68-32.32)	0.0285	c
Leg fat mass	8.17 ± 0.02	(8.16-8.19)	6.94 ± 0.87	(5.95-9.95)	18.05 ± 1.08	(11.23-19.32)	< 0.0001	b, c
Leg lean mass	13.97 ± 0.40	(13.69-14.26)	18.28 ± 0.60	(17.64-32.50)	13.07 ± 0.16	(12.96-18.44)	0.0122	c
Arm mass	8.21 ± 0.88	(7.59-8.83)	7.33 ± 0.21	(6.66-8.07)	8.89 ± 0.14	(7.60-8.99)	0.0032	c
Arm fat mass	<0.001	(10^{-6}-10^{-5})	1.08 ± 0.42	(0.78-1.88)	4.40 ± 0.09	(1.86-4.46)	< 0.0001	b, c
Arm lean mass	7.05 ± 0.76	(6.51-7.59)	6.25 ± 0.21	(5.44 ± 6.60)	4.49 ± 0.23	(4.25-6.04)	0.0005	b, c
Gynoid and android body composition (% total tissue)								
Gynoid body fat	43.75 ± 0.07	(43.70-43.80)	33.97 ± 3.00	(29.30-38.40)	52.91 ± 6.37	(40.60-58.80)	0.0007	c
Android body fat	13.45 ± 3.47	(11.00-15.90)	14.73 ± 4.02	(8.90-19.50)	44.79 ± 11.39	(29.90-55.90)	< 0.0001	b, c
Gynoid body lean	56.25 ± 0.07	(56.20-56.30)	67.52 ± 4.70	(60.90-74.91)	47.10 ± 6.38	(40.50-58.70)	ns	
Android body lean	86.6 ± 3.40	(84.20-89.00)	85.27 ± 3.97	(80.52-91.07)	55.21 ± 11.39	(44.10-69.20)	ns	

Interestingly, as seen in **Fig. 1C**, the increase in fat mass was not homogeneous and patients preferentially developed abdominal (android) fat mass (+204%) over hip (gynoid) fat mass (+55%) (P=0.0974 between [0-3] and [4-8] groups, P=0.0002 and P=0.001 comparing [9-18] to [0-3] and [4-8] age groups, respectively, Tukey's multiple comparisons test). Concurrently, both android and gynoid lean masses did not vary during this period (Table 1). Consequently, the fat:lean ratio significantly increased in the abdominal area throughout childhood (P=0.3187 between [0-3] and [4-8] groups, P=0.0924 and P<0.0001 comparing [9-18] to [0-3] and [4-8] age groups, respectively, Tukey's multiple comparisons test). The trunk, legs and arms followed a very similar trend with an increase in percent fat mass and decrease in percent lean mass from infancy to adulthood (Table 1). Spinal bone mineral density (BMD) was determined between L1 and L4 after age of 3. In both age groups, BMD was found to be below age-appropriate normal range value (van der Sluis et al., *Arch. Dis. Child.* 87:341-347, 2002) (0.511 ± 0.065 g/cm2 and 0.898 ± 0.223 g/cm^2 in the [4-8] and [9-18] age groups, respectively, compared to 0.645 ± 0.071 g/cm2 and 0.913 ± 0.199 g/cm2 in the same age referenced groups).

Different blood parameters were compared between the [4-8] and [9-18] age groups. Unexpectedly, in both age groups and independently of their BMI, achondroplasia children displayed a tendency to low plasmatic total cholesterol (3.38 ± 0.36 mmol/L and 3.73 ± 0.44 mmol/L in the [4-8] and [9-18] age groups, respectively, with normal values being comprised between 3.90 and 5.70 mmol/L in children), and low triglycerides (0.56 ± 0.14 mmol/L and 0.63 ± 0.13 mmol/L in the [4-8] and [9-18] age groups, respectively, with normal values being comprised between 0.60 and 1.70 mmol/L in children). Similarly, fasting blood glucose (**Fig. 1D**) and insulin levels were not increasing with age and remained within normal range (7.3 ± 5.4 mUI/L and 13.4 ± 3.4 mUI/L in the [4-8] and [9-18] age groups, respectively, with normal values being comprised between 2.6 and 16 mUI/L in children). These results were confirmed by glucose levels obtained during oral glucose tolerance test (OGTT), that showed normal glucose levels at 0, 30 and 120 minutes following oral administration (4.53 ± 0.22 mmol/l at 0 min, 7.97 ± 1.72 mmol/l at 30 min and 5.17 mmol/l at 120 min). No statistical differences were found between both age groups. Due to high levels of hemolysis during the OGTT, no data were unfortunately available regarding insulin levels. All other blood parameters were within normal range (data not shown).

Metabolic alterations are observed in lean and obese Fgfr3ach/+ mice and are corrected by sFGFR3 treatment

To determine the role of FGFR3ach in this preferential development of visceral obesity in achondroplasia, transgenic *Fgfr3ach/+* mice carrying the G380R mutation or their wild-type (WT) littermates were treated with sFGFR3 or vehicle for 3 weeks starting at day 3. Mice were then challenged with normal (ND) or high fat diet (HFD) starting at 4 weeks of age for a duration of 10 weeks to evaluate the development of obesity.

After weaning, at 4 weeks of age, as expected, untreated *Fgfr3ach*/+ mice had a 20.4% decrease in body weight compared to their WT littermates. This was associated with reduced lean and fat tissues (50% and 33.9% respectively). Treated animals displayed a 14.1% decrease in body weight compared to WT mice ($P<0.0001$).

After 10 weeks of diet challenge, all HFD groups showed a significant increase in body weight compared to ND (**Fig. 2A**). Interestingly however body composition was different in both genotypes. Untreated *Fgfr3ach*/+ mice had an higher abdominal lean:fat ratio, measured between L1 and S1, compared to WT mice, independently of the diet (**Fig. 2B**). When fed with ND, untreated *Fgfr3ach*/+ mice had less epididymal (visceral) and subcutaneous adipose tissues than WT animals (**Figs. 2C and 2D**). However, after 10 weeks of HFD challenge, untreated *Fgfr3ach*/+ mice developed more epididymal adipose tissue compared to WT animals that preferentially developed subcutaneous fat depot (**Fig. 2C and 2D**). These data showed that, like achondroplasia patients, *Fgfr3ach*/+ mice were prone to developed visceral adipose tissue.

sFGFR3 treatment has no effect on body weight gain (**Fig. 2A**). However, body composition was significantly impacted by sFGFR3 treatment with a significant decrease in abdominal lean:fat ratio in mice fed with ND (**Fig. 2B**), caused by a decrease in lean masses and an increase in fat masses respectively. Very interestingly, sFGFR3-treated *Fgfr3ach*/+ mice displayed fat depot distributions that were like those of WT animals whether they were fed with ND or HFD (**Figs. 2C and 2D**).

After the HFD challenge, histological analyses showed smaller adipocytes in the subcutaneous area and a greater proportion of these small adipocytes in untreated *Fgfr3ach*/+ mice compared to WT (**Figs. 2E and 2G**). No difference in size or dispersion was observed in epididymal adipocytes between both genotypes (**Figs. 2F and 2H**). sFGFR3 treatment restored the subcutaneous adipocytes size and scattering and induced a slight increase in epididymal adipocyte size (**Fig. 2E-2H**). Because increased proportion of small adipose cells has been associated with inflammation (Kursawe et al., *Diabetes* 59: 2288-2296, 2010; and Lafontan, *Diabetes Metab.* 40:16-28, 2014), several circulating adipokines were measured to evaluate the extent of systemic inflammation in these animals (**Figs. 6A and 6B**). Adipokines were sorted into four categories – pro-inflammatory, obesity-related, insulin-pathway and FGFs – all of which were increased in transgenic mice compared to WT littermates (**Table 3**). Untreated *Fgfr3ach*/+ mice displayed a low-grade inflammatory baseline compared to WT animals, that was exacerbated under HFD challenge (**Table 3**). Treated Fgfr3ach/+ animals under ND or HFD has a systemic profile that resembled that of their WT littermates. In vitro, mesenchymal stem cells (MSCs) isolated from *Fgfr3ach/+* mice showed that early and intermediary genes of the differentiation process such as Srebf-1, CEBP/d, CEPB/a and PPARg were already expressed (**Fig. 3A**). Very interestingly, MSCs isolated from sFGFR3-treated *Fgfr3ach/+* mice showed significant increase in anti-adipogenic markers and brow tissue activation markers as well as decreased expression of genes involved in the functions of mature adipocytes (**Fig.**

3A). Together with the in vivo data, this suggests a predisposition to adipogenesis in *Fgfr3ach/+* mice that can be prevented by sFGFR3 treatment.

Table 3. Untreated *Fgfr3*$^{ach/+}$ mice displayed an elevated inflammatory baseline prevented by sFGFR3 treatment. Pro-inflammatory, obesity, insulin pathway and FGF circulating adipokines expression performed into vehicle-treated WT and *Fgfr3*$^{ach/+}$ mice and sFGFR3 treated *Fgfr3*$^{ach/+}$ after 10 weeks of ND or HFD challenge. '-' = <2 arbitrary units (A.U.), '+' = 10-30 A.U., '++' = 30-100 A.U., '+++' >100 A.U.

	ND			HFD		
	WT	*Fgfr3* $^{ach/+}$		WT	*Fgfr3* $^{ach/+}$	
markers (n)	vehicle	vehicle	2.5 mg/kg sFGFR3	vehicle	vehicle	2.5 mg/kg sFGFR3
Pro-inflammatory (14)	+	++	+	+	++	+
Obesity (15)	++	+++	+	++	+++	++
Insulin pathway (7)	++	++	++	++	+++	++
FGF (2)	+	+	-	-	++	-

Compared to their WT littermates, mice carrying the FGFR3 mutation had low fasting glycemia and very low baseline levels of insulin (**Fig. 4A**). When challenged with a HFD diet (**Fig. 4B**), glycemic levels raised but remained under those of the WT animals. Insulin levels remained extremely low. In sFGFR3-treated *Fgfr3ach/+* animals, glycemia was restored and insulin levels significantly increased compared to untreated Fgfr3ach/+mice (**Figs. 4A and 4B**).

To evaluate the development of glucose intolerance, glucose tolerance tests (GTT) were performed after 10 weeks of diet challenge. Untreated *Fgfr3ach/+* mice displayed higher glucose levels and AUC compared to their WT littermates (Cmax 320.9 ± 32.0 mg/dL and 273.3 ± 23.9 mg/dL, AUC 1.2x104 ± 0.7x104 and 1.7x104 ± 0.4x104, respectively), showing some basal glucose intolerance even under ND. This was further exacerbated under HFD (**Fig. 4C**). When *Fgfr3ach/+* mice were treated with 2.5 mg/kg sFGFR3, normal GTT responses were restored (**Fig 4C**). We attempted to perform insulin tolerance test in transgenic mice under ND or HFD but, because of their lower basal glycemic levels, *Fgfr3ach/+* mice did not support insulin injection and died rapidly. Analysis of insulin sensitivity of mesenchymal stem cells isolated from *Fgfr3ach/+* or WT mice showed no differences in Erk1/2 phosphorylation levels suggesting similar response to insulin stimulation in both type of mice (**Fig. 3B**). These results suggest that *Fgfr3ach/+* mice do not appear more sensitive to insulin regulation but that

insulin injection during the ITT probably induced lethal hypoglycemia because of their low basal glycemia. Pancreas analyses showed smaller and more islets of Langerhans with lower insulin and glucagon contents in untreated *Fgfr3ach*/+ mice (**Fig. 4D**) suggesting an alteration of insulin production and/or storage. This was partially restored in treated animals (**Figs. 3B and 4A-4C**). Glucose storage also appeared impaired in the liver of untreated *Fgfr3ach*/+ animals as seen by the decrease in glycogen in liver sections (**Fig. 4E**). As expected, following 10 weeks of HFD challenge, WT mice developed grade III macrovesicular steatosis with more than 75% of hepatocytes displayed lipid vacuoles that were larger than the nucleus (**Fig. 4E**). In contrast, after 10 weeks of HFD, untreated *Fgfr3ach*/+ mice developed reversible benign hepatic nodules (**Fig. 4F**) and a grade II microvesicular steatosis: less than 50% of hepatocytes displayed small vacuoles (**Fig. 4E**). Interestingly, sFGFR3 treatment restored a normal hepatic response in treated *Fgfr3ach*/+ mice (**Fig. 4E**) and no nodules were observed.

The basal energy metabolic rate of *Fgfr3ach*/+ mice was evaluated by indirect calorimetry. We found that while lean WT animals fed with normal diet (ND) drew energy from carbohydrate sources (respiratory quotient RQ near 1), fed transgenic achondroplasia mice drew their energy essentially from lipid sources (RQ near 0.7) (**Fig. 5A**). In fasting episode, as expected, both types of animals drew their energy from lipid sources. This preferential lipid utilization was confirmed by the calculation of carbohydrate and lipid oxidation, which were respectively lower and higher in *Fgfr3ach*/+ mice compared to WT animals (**Fig. 5B**). Over a 24-hour period, *Fgfr3ach*/+ mice tend to eat constantly not only during the nocturnal period, however energy expenditure and food intake were not significantly different between both genotypes (**Figs. 7A-D**). As expected under HFD, all animals drew their energy from lipid sources, leading to similar carbohydrate and lipid oxidation indexes (**Figs. 5C-D, Figs. 7E-H**). Very interestingly, *Fgfr3ach*/+ animals that received sFGFR3 treatment during the growth period behaved like untreated WT mice after weaning whether they were fed with ND or HFD, suggesting the restoration of glucose metabolism capacities during the treatment period (**Fig. 5 and Figs. 7A-H**).

Variations in adipose tissue deposition in the different body sites can be assessed to evaluate the severity of obesity in achondroplasia. Compared to BMI z-scores and skinfold measurements, the android:gynoid ratio is closely related to all risk factors in overweight and obese children. In achondroplasia, children display higher android:gynoid ratio that develops very early during childhood. Our findings in *Fgfr3ach/+* mice suggests a predisposition to preferential visceral obesity in these patients. Indeed, cells derived from the mesenchymal lineage appeared more prone to adipogenesis than cells isolated from WT animals and seem pre-engaged in the differentiation process towards adipocytes. Moreover, different adipocyte distribution was observed with a greater proportion of small adipocytes in the subcutaneous adipose tissue of *Fgfr3ach/+* mice compared to WT animals. The number of fat cells is set during childhood and adolescence and remains constant during adulthood. Obesity in achondroplasia patients may be set very early during childhood and monitoring as early as 4-8 years old using, e.g., DXA scans, may be warranted.

The development of an abdominal obesity is usually considered to be the most deleterious type of obesity (Smith, *J. Clin. Invest.* 125:1790-1792, 2015). Our results suggest that abdominal obesity is likely a consequence of the mutation affecting FGFR3. Currently, three members of the FGFs family have been linked to obesity (Nies et al., *Front. Endocrinol. (Lausanne)* 6:193, 2015): FGF1, FGF15/19 and FGF21. FGF1 is regulated by PPARg and is notably highly upregulated in WAT (*28*). FGF1 is known to promote pre-adipocyte proliferation and differentiation through Erk1/2 signaling. It also triggers acute blood lowering effect that seem to be dependent on FGFR2 signaling in WAT. FGF15/19 is considered as a regulator of the feeding responses. It binds to FGFR4/bklotho receptor complex on the cell membrane of hepatocytes ultimately leading to repression of gluconeogenesis (Tomlinson et al., *Endocrinology* 143:1741-1747, 2002). FGF21 mainly binds to FGFR1 and regulates the adaptive fasting response through PPARa (Kharitonenkov et al., *J. Clin. Invest.* 115:1627-1635, 2005). In *Fgfr3ach/+* mice, overexpression of FGFR3ach during embryogenesis could modify FGFs signaling in different cell types. In accordance with this, we found that mesenchymal stem cells from *Fgfr3ach/+* mice express high levels of FGFR3 compared to their WT littermates. Similarly, newborn *Fgfr3ach/+* mice express increased levels of FGFR2 and FGFR4 in AT and liver. Altogether these data could explain the low glycemia associated with abdominal obesity in *Fgfr3ach/+* mice. Along this line, we also observed that patients even tended to lower fasting glycemia and insulinemia and no patients had glucose intolerance, suggesting that similar mechanisms could apply in human.

sFGFR3 treatment was applied immediately after birth and prevented most metabolic complications, including the development of abdominal obesity. Treated *Fgfr3ach/+* mice were not protected against obesity *per se* but behave essentially like WT animals with the development of homogeneous obesity and the restoration of glucose metabolism leading to glucose resistance under HFD. This suggests that, if apply early in life, treatment could revert the effect of the Fgfr3ach mutation on these atypical metabolic tissues.

In conclusion, our data establish that the development of a nonconforming obesity is preferentially abdominal and appears to be triggered by the FGFR3 mutation. Our data also indicate that the treatment for achondroplastic patients having abnormal visceral fat deposition may be applied to other patient populations with abnormal visceral fat deposition and conditions stemming therefrom. Patients having skeletal growth retardation disorders may be treated to control abnormal visceral fat deposition and conditions associated therewith, for example, after the conclusion of bone growth when sFGFR3 polypeptides would not otherwise be considered a relevant therapy. Patients may also benefit from monitoring for co-morbities of obesity, such as diabetes and CVS risks.

OTHER EMBODIMENTS

All publications, patents, and patent applications mentioned in the above specification are hereby incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Various modifications and variations of the described methods, pharmaceutical compositions, and kits of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific embodiments, it will be understood that it is capable of further modifications and that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the art are intended to be within the scope of the invention. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known customary practice within the art to which the invention pertains and may be applied to the essential features herein before set forth.

SPECIFIC EMBODIMENTS

The following specific embodiments also describe the present invention:

1. A method of treating or reducing abnormal fat deposition in a subject in need thereof comprising administering a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising the polynucleotide to the subject.

2. The method of 1, wherein the abnormal fat deposition comprises visceral fat deposition.

3. The method of 2, wherein:

a) the abnormal visceral fat deposition is associated with or surrounding one or more of the following organs: the heart, liver, spleen, kidneys, pancreas, intestines, reproductive organs, and gall bladder;

b) the abnormal visceral fat deposition causes disease in one or more of the following organs: the heart, lungs, trachea, liver, pancreas, brain, reproductive organs, arteries, and gall bladder; or

c) the abnormal visceral fat deposition is caused by dysfunction in an endocrine organ, such as an adrenal gland, a pituitary gland, or a reproductive organ, such as an ovary.

4. The method of any one of 1 to 3, wherein the method reduces or eliminates one or more conditions associated with the abnormal fat distribution.

5. The method of 4, wherein the one or more conditions are selected from the group consisting of obstructive sleep apnea, pulmonary disease, cardiovascular disease, metabolic disease, neurological disease, dyslipidemia, hypertension, atherosclerosis, myocardial infarction, stroke, dementia, infertility, menstrual irregularities, insulin dysregulation, and glucose dysregulation.

6. The method of 5, wherein the dyslipidemia comprises an abnormal level of one or more of triglycerides, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and cholesterol.

8. The method of 5, wherein the cardiovascular disease is heart disease or stroke.

9. The method of 5, wherein the pulmonary disease is asthma and restrictive lung disease.

10. The method of 5, wherein the neurological disease is dementia or Alzheimer's disease.

11. The method of 5, wherein the metabolic disease is type 2 diabetes, glucose intolerance, nonalcoholic fatty liver disease and liver toxicity.

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12. The method of 5, wherein the insulin dysregulation is insulin resistance.

13. The method of any one of 1 to 12, wherein the subject is not overweight or lacks substantial subcutaneous fat deposition.

14. The method of any one of 1 to 13, wherein the abnormal fat deposition is determined using an anthropometric techniques, or imaging.

15. The method of 14, wherein the anthropometric technique is body mass index (BMI) or android:gynoid fat ratio.

16. The method of 14, wherein the imaging comprises computed tomography (CT), magnetic resonance imaging (MRI), and dual energy x-ray absorptioometry (DXA).

18. The method of any one of 1 to 18, wherein the patient does not exhibit substantial abnormal fat deposition outside the abdomen.

19. The method of any one of 1 to 18, wherein the subject is a fetus, a neonate, an infant, a child, a juvenile, an adolescent, or an adult.

20. The method of any one of 1 to 19, wherein the method reduces visceral fat deposition.

21. The method of any one of 1 to 20, wherein the sFGFR3 polypeptide comprises at least 50 consecutive amino acids of an extracellular domain of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide.

22. The method of 21, wherein the sFGFR3 polypeptide comprises 100-370 consecutive amino acids of an extracellular domain of the naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide.

23. The method of 21 or 22, wherein the sFGFR3 polypeptide comprises fewer than 350 amino acids of the extracellular domain of the naturally occurring FGFR3 polypeptide.

24. The method of any one of 21 to 23, wherein the sFGFR3 polypeptide comprises an Ig-like C2-type domain 1, 2, and/or 3 of the naturally occurring FGFR3 polypeptide.

25. The method of any one of 1 to 24, wherein the sFGFR3 polypeptide lacks a signal peptide and/or a transmembrane domain, such as the signal peptide and/or transmembrane domain of a naturally occurring FGFR3 polypeptide.

26. The method of any one of 1 to 25, wherein the sFGFR3 polypeptide is a mature polypeptide.

27. The method of any one of 1 to 26, wherein the sFGFR3 polypeptide comprises 400 consecutive amino acids or fewer of an intracellular domain of a naturally-occurring FGFR3 polypeptide.

28. The method of 27, wherein the sFGFR3 polypeptide comprises between 5 and 399 consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide, such as 175, 150, 125, 100, 75, 50, 40, 30, 20, 15, or fewer consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide.

29. The method of 28, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 90%, 92%, 95%, 97%, or 99% sequence identity to amino acids 401 to 413 of SEQ ID NO: 8.

30. The method of 29, wherein the sFGFR3 polypeptide comprises amino acids 401 to 413 of

SEQ ID NO: 8.

31. The method of any one of 1 to 30, wherein the sFGFR3 polypeptide lacks a tyrosine kinase domain of a naturally-occurring FGFR3 polypeptide.

32. The method of any one of 1 to 31, wherein the sFGFR3 polypeptide lacks an intracellular domain of a naturally-occurring FGFR3 polypeptide.

33. The method of any one of 1 to 33, wherein the sFGFR3 polypeptide comprises fewer than 475, 450, 425, 400, 375, 350, 300, 250, 200, 150, or 100 amino acids in length.

34. The method of any one of 1 to 33, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 85% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

35. The method of 34, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

36. The method of any one of 1 to 35, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 85% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

37. The method of 36, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

38. The method of any one of 1 to 37, wherein the subject has a skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

39. The method of 38, wherein the skeletal growth retardation disorder is a FGFR3-related skeletal disease.

40. The method of 39, wherein the FGFR3-related skeletal disease is selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

41. The method of 40, wherein the skeletal growth retardation disorder is achondroplasia.

42. The method of 40, wherein the craniosynostosis syndrome is selected from the group consisting of Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome.

43. The method of any one of 38 to 42, wherein the FGFR3-related skeletal disease is caused by expression in the patient of a FGFR3 variant that exhibits ligand-dependent overactivation.

44. The method of 43, wherein the FGFR3 variant comprises an amino acid substitution of a glycine residue with an arginine residue at position 358 (G358R) as set forth in SEQ ID NO: 9.

45. The method of any one of 38 to 44, wherein the subject has been diagnosed with the skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

46. The method of any one of 38 to 45, wherein the subject exhibits one or more symptoms of the skeletal growth retardation disorder selected from the group consisting of short limbs, short trunk, bowlegs, a waddling gait, skull malformations, cloverleaf skull, craniosynostosis, wormian bones, anomalies of the hands, anomalies of the feet, hitchhiker thumb, and chest anomalies.

47. The method of any one of 1 to 37, wherein the subject does not have a skeletal growth retardation disorder, such as a FGFR3-related skeletal disease.

48. The method of 47, wherein the subject does not have an FGFR3-related skeletal disease is selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

49. The method of any one of 21 to 25 and 27-32, wherein the naturally-occurring human FGFR3 polypeptide comprises the amino acid sequence of Genbank Accession No. NP_000133.

50. The method of any one of 1 to 49, wherein the sFGFR3 polypeptide binds to a fibroblast growth factor (FGF).

51. The method of 50, wherein the FGF is selected from the group consisting of fibroblast growth factor 1 (FGF1), fibroblast growth factor 2 (FGF2), fibroblast growth factor 9 (FGF9), fibroblast growth

factor 10 (FGF10), fibroblast growth factor 18 (FGF18), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), and fibroblast growth factor 23 (FGF23).

52. The method of 50 or 51, wherein the binding is characterized by an equilibrium dissociation constant (K_d) of about 0.2 nM to about 20 nM.

53. The method of 52, wherein the binding is characterized by a K_d of about 1 nM to about 10 nM, wherein optionally the K_d is about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, about 8 nm, about 9 nm, or about 10 nm.

54. The method of any one of 1 to 53, wherein the amino acid sequence of the sFGFR3 polypeptide is set forth in SEQ ID NO: 5.

55. The method of any one of 1 to 54, wherein the sFGFR3 polypeptide comprises a signal peptide, such as a signal peptide of a naturally-occurring FGFR3 polypeptide.

56. The method of 55, wherein the signal peptide comprises the amino acid sequence of SEQ ID NO: 21.

57. The method of any one of 1 to 56, wherein the sFGFR3 polypeptide comprises a heterologous polypeptide.

58. The method of 57, wherein the heterologous polypeptide is a fragment crystallizable region of an immunoglobulin (Fc region) or human serum albumin (HSA).

59. The method of any one of 1 to 59, wherein the polynucleotide encoding the sFGFR3 polypeptide comprises a nucleic acid sequence having at least 85% and up to 100% sequence identity to the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

60. The polypeptide of 59, wherein the polynucleotide consists of the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

61. The method of 59 or 60, wherein the polynucleotide is an isolated polynucleotide.

62. The method of 59 or 60, wherein the polynucleotide is in a vector.

63. The method of 62, wherein the vector is selected from the group consisting of a plasmid, an artificial chromosome, a viral vector, and a phage vector.

64. The method of 62 or 63, wherein vector is in the host cell.

65. The method of 64, wherein the host cell is an isolated host cell.

66. The method of 65, wherein the host cell is from the subject.

67. The method of 66, wherein the host cell has been transformed with the polynucleotide.

68. The method of 64 or 65, wherein the host cell is a HEK 293 cell or CHO cell.

69. The method of any one of 1 to 68, wherein the sFGFR3 is administered as a composition comprising a pharmaceutically acceptable excipient, carrier, or diluent.

70. The method of 69, wherein the composition is administered to the subject at a dose of about 0.001 mg/kg to about 30 mg/kg of the sFGFR3 polypeptide.

71. The method of 70, wherein the composition is administered at a dose of about 0.01 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide.

72. The method of any one of 69 to 71, wherein the composition is administered daily, weekly, or monthly.

73. The method of any one of 69 to 72, wherein the composition is administered seven times a week, six times a week, five times a week, four times a week, three times a week, twice a week, weekly, every two weeks, or once a month.

74. The method of 73, wherein the composition is administered at a dose of about 2.5 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide once or twice a week.

75. The method of any one of 69 to 74, wherein the composition is administered by parenteral administration, enteral administration, or topical administration.

76. The method of 75, wherein the composition is administered by subcutaneous

administration, intravenous administration, intramuscular administration, intra-arterial administration, intrathecal administration, or intraperitoneal administration.

77. The method of 76, wherein the composition is administered by subcutaneous administration.

78. The method of any one of 1 to 77, wherein the subject has not been previously administered the sFGFR3 polypeptide.

79. The method of any one of 1 to 78, wherein the subject is a human.

80. The method of any one of 1 to 79, wherein the sFGFR3 polypeptide has an in vivo half-life of between about 2 hours to about 25 hours.

81. A composition comprising a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising the polynucleotide for treating or reducing abnormal fat distribution in a subject in need thereof, such as by the method of any one of 1 to 80.

82. Use of a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising a polynucleotide encoding the sFGFR3 polypeptide in the manufacture of a medicament for treating or reducing abnormal fat distribution in a subject in need thereof, such as by the method of any one of 1 to 80.

CLAIMS

1. A method of treating or reducing abnormal fat deposition in a subject in need thereof comprising administering a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising the polynucleotide to the subject.

2. The method of claim 1, wherein the abnormal fat deposition comprises visceral fat deposition.

3. The method of claim 2, wherein:

a) the abnormal visceral fat deposition is associated with or surrounding one or more of the following organs: the heart, liver, spleen, kidneys, pancreas, intestines, reproductive organs, and gall bladder;

b) the abnormal visceral fat deposition causes disease in one or more of the following organs: the heart, lungs, trachea, liver, pancreas, brain, reproductive organs, arteries, and gall bladder; or

c) the abnormal visceral fat deposition is caused by dysfunction in an endocrine organ, such as an adrenal gland, a pituitary gland, or a reproductive organ, such as an ovary.

4. The method of any one of claims 1 to 3, wherein the method reduces or eliminates one or more conditions associated with the abnormal fat distribution.

5. The method of claim 4, wherein the one or more conditions are selected from the group consisting of obstructive sleep apnea, pulmonary disease, cardiovascular disease, metabolic disease, neurological disease, dyslipidemia, hypertension, atherosclerosis, myocardial infarction, stroke, dementia, infertility, menstrual irregularities, insulin dysregulation, and glucose dysregulation.

6. The method of claim 5, wherein the dyslipidemia comprises an abnormal level of one or more of triglycerides, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and cholesterol.

7. The method of claim 5, wherein the cardiovascular disease is heart disease or stroke.

8. The method of claim 5, wherein the pulmonary disease is asthma and restrictive lung disease.

9. The method of claim 5, wherein the neurological disease is dementia or Alzheimer's disease.

10. The method of claim 5, wherein the metabolic disease is type 2 diabetes, glucose intolerance, nonalcoholic fatty liver disease and liver toxicity.

11. The method of claim 5, wherein the insulin dysregulation is insulin resistance.

12. The method of any one of claims 1-11, wherein the subject is not overweight or lacks substantial subcutaneous fat deposition.

13. The method of any one of claims 1-12, wherein the abnormal fat deposition is determined using an anthropometric ~~techniques~~ technique, or imaging.

14. The method of claim 13, wherein the anthropometric technique is body mass index (BMI) or android:gynoid fat ratio.

15. The method of claim 13, wherein the imaging comprises computed tomography (CT), magnetic resonance imaging (MRI), and dual energy x-ray absorptioometry (DXA).

16. The method of any one of claims 1-15, wherein the subject does not exhibit substantial abnormal fat deposition outside the abdomen.

17. The method of any one of claims 1-16, wherein the subject is a fetus, a neonate, an infant, a child, a juvenile, an adolescent, or an adult.

18. The method of any one of claims 1-17, wherein the method reduces visceral fat deposition.

19. The method of any one of claims 1-18, wherein the sFGFR3 polypeptide comprises at least 50 consecutive amino acids of an extracellular domain of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide.

20. The method of claim 19, wherein the sFGFR3 polypeptide comprises 100-370 consecutive amino acids of an extracellular domain of the naturally occurring FGFR3 polypeptide.

21. The method of claim 19 or 20, wherein the sFGFR3 polypeptide comprises fewer than 350 amino acids of the extracellular domain of the naturally occurring FGFR3 polypeptide.

22. The method of any one of claims 19-21, wherein the sFGFR3 polypeptide comprises an Ig-like

C2-type domain 1, 2, and/or 3 of the naturally occurring FGFR3 polypeptide.

23. The method of any one of claims 1-22, wherein the sFGFR3 polypeptide lacks a signal peptide and/or a transmembrane domain, such as the signal peptide and/or transmembrane domain of a naturally occurring FGFR3 polypeptide.

24. The method of any one of claims 1-23, wherein the sFGFR3 polypeptide is a mature polypeptide.

25. The method of any one of claims 1-24, wherein the sFGFR3 polypeptide comprises 400 consecutive amino acids or fewer of an intracellular domain of a naturally-occurring FGFR3 polypeptide.

26. The method of claim 25, wherein the sFGFR3 polypeptide comprises between 5 and 399 consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide, such as 175, 150, 125, 100, 75, 50, 40, 30, 20, 15, or fewer consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide.

27. The method of claim 26, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 90%, 92%, 95%, 97%, or 99% sequence identity to amino acids 401 to 413 of SEQ ID NO: 8.

28. The method of claim ~~29~~ 27, wherein the sFGFR3 polypeptide comprises amino acids 401 to 413 of SEQ ID NO: 8.

29. The method of any one of claims 1-28, wherein the sFGFR3 polypeptide lacks a tyrosine kinase domain of a naturally-occurring FGFR3 polypeptide.

30. The method of any one of claims 1-29, wherein the sFGFR3 polypeptide lacks an intracellular domain of a naturally-occurring FGFR3 polypeptide.

31. The method of any one of claims 1-30, wherein the sFGFR3 polypeptide comprises fewer than 475, 450, 425, 400, 375, 350, 300, 250, 200, 150, or 100 amino acids in length.

32. The method of any one of claims 1-31, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 85% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

33. The method of claim 32, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

34. The method of any one of claims 1-33, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 85% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

35. The method of claim 34, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

36. The method of any one of claims 1-35, wherein the subject has a skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

37. The method of claim 36, wherein the skeletal growth retardation disorder is a FGFR3-related skeletal disease.

38. The method of claim 37, wherein the FGFR3-related skeletal disease is selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

39. The method of claim 38, wherein the FGFR3-related skeletal disease is achondroplasia.

40. The method of claim 38, wherein the craniosynostosis syndrome is selected from the group consisting of Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome.

41. The method of any one of claims 37-40, wherein the FGFR3-related skeletal disease is caused by expression in the subject of a FGFR3 variant that exhibits ligand-dependent overactivation.

42. The method of claim 41, wherein the FGFR3 variant comprises an amino acid substitution of a glycine residue with an arginine residue at position 358 (G358R) as set forth in SEQ ID NO: 9.

43. The method of any one of claims 36-42, wherein the subject has been diagnosed with the skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

44. The method of any one of claims 36-43, wherein the subject exhibits one or more symptoms of the skeletal growth retardation disorder selected from the group consisting of short limbs, short trunk, bowlegs, a waddling gait, skull malformations, cloverleaf skull, craniosynostosis, wormian bones, anomalies of the hands, anomalies of the feet, hitchhiker thumb, and chest anomalies.

45. The method of any one of claims 1-35, wherein the subject does not have a skeletal growth retardation disorder, such as a FGFR3-related skeletal disease.

46. The method of claim 45, wherein the subject does not have an FGFR3-related skeletal disease is selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

47. The method of any one of claims 19-23 and 25-30, wherein the naturally-occurring human FGFR3 polypeptide comprises the amino acid sequence of Genbank Accession No. NP_000133.

48. The method of any one of claims 1-47, wherein the sFGFR3 polypeptide binds to a fibroblast growth factor (FGF).

49. The method of claim 48, wherein the FGF is selected from the group consisting of fibroblast growth factor 1 (FGF1), fibroblast growth factor 2 (FGF2), fibroblast growth factor 9 (FGF9), fibroblast growth factor 10 (FGF10), fibroblast growth factor 18 (FGF18), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), and fibroblast growth factor 23 (FGF23).

50. The method of claim 48 or 49, wherein the binding is characterized by an equilibrium dissociation constant (K_d) of about 0.2 nM to about 20 nM.

51. The method of claim 50, wherein the binding is characterized by a K_d of about 1 nM to about 10 nM, wherein optionally the K_d is about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, about 8 nm, about 9 nm, or about 10 nm.

52. The method of any one of claims 1-51, wherein the amino acid sequence of the sFGFR3 polypeptide is set forth in SEQ ID NO: 5.

53. The method of any one of claims 1-52, wherein the sFGFR3 polypeptide comprises a signal

peptide, such as a signal peptide of a naturally-occurring FGFR3 polypeptide.

54. The method of claim 53, wherein the signal peptide comprises the amino acid sequence of SEQ ID NO: 21.

55. The method of any one of claims 1-54, wherein the sFGFR3 polypeptide comprises a heterologous polypeptide.

56. The method of claim 55, wherein the heterologous polypeptide is a fragment crystallizable region of an immunoglobulin (Fc region) or human serum albumin (HSA).

57. The method of any one of claims 1-56, wherein the polynucleotide encoding the sFGFR3 polypeptide comprises a nucleic acid sequence having at least 85% and up to 100% sequence identity to the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

58. The polypeptide of claim 57, wherein the polynucleotide consists of the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

59. The method of claim 57 or 58, wherein the polynucleotide is an isolated polynucleotide.

60. The method of claim 57 or 58, wherein the polynucleotide is in a vector.

61. The method of claim 60, wherein the vector is selected from the group consisting of a plasmid, an artificial chromosome, a viral vector, and a phage vector.

62. The method of claim 60 or 61, wherein vector is in the host cell.

63. The method of claim 62, wherein the host cell is an isolated host cell.

64. The method of claim 63, wherein the host cell is from the subject.

65. The method of claim 64, wherein the host cell has been transformed with the polynucleotide.

66. The method of claim 62 or 63, wherein the host cell is a HEK 293 cell or CHO cell.

67. The method of any one of claims 1-66, wherein the sFGFR3 is administered as a composition comprising a pharmaceutically acceptable excipient, carrier, or diluent.

68. The method of claim 67, wherein the composition is administered to the subject at a dose of about 0.001 mg/kg to about 30 mg/kg of the sFGFR3 polypeptide.

69. The method of claim 68, wherein the composition is administered at a dose of about 0.01 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide.

70. The method of any one of claims 67-69, wherein the composition is administered daily, weekly, or monthly.

71. The method of any one of claims 67-70, wherein the composition is administered seven times a week, six times a week, five times a week, four times a week, three times a week, twice a week, weekly, every two weeks, or once a month.

72. The method of claim 71, wherein the composition is administered at a dose of about 2.5 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide once or twice a week.

73. The method of any one of claims 67-72, wherein the composition is administered by parenteral administration, enteral administration, or topical administration.

74. The method of claim 73, wherein the composition is administered by subcutaneous administration, intravenous administration, intramuscular administration, intra-arterial administration, intrathecal administration, or intraperitoneal administration.

75. The method of claim 74, wherein the composition is administered by subcutaneous administration.

76. The method of any one of claims 1-75, wherein the subject has not been previously administered the sFGFR3 polypeptide.

77. The method of any one of claims 1-76, wherein the subject is a human.

78. The method of any one of claims 1-77, wherein the sFGFR3 polypeptide has an in vivo half-life of between about 2 hours to about 25 hours.

79. A composition comprising a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising the polynucleotide for treating or reducing abnormal fat distribution in a subject in need thereof.

80. The composition of claim 79, wherein the abnormal fat deposition comprises visceral fat deposition.

81. The composition of claim 80, wherein:

a) the visceral fat deposition is associated with or surrounding one or more of the following organs: the heart, liver, spleen, kidneys, pancreas, intestines, reproductive organs, and gall bladder;

b) the visceral fat deposition causes disease in one or more of the following organs: the heart, lungs, trachea, liver, pancreas, brain, reproductive organs, arteries, and gall bladder; or

c) the visceral fat deposition is caused by dysfunction in an endocrine organ, such as an adrenal gland, a pituitary gland, or a reproductive organ, such as an ovary.

82. The composition of any one of claims 79-81, wherein the composition reduces or eliminates one or more conditions associated with the abnormal fat distribution.

83. The composition of claim 82, wherein the one or more conditions are selected from the group consisting of obstructive sleep apnea, pulmonary disease, cardiovascular disease, metabolic disease, neurological disease, dyslipidemia, hypertension, atherosclerosis, myocardial infarction, stroke, dementia, infertility, menstrual irregularities, insulin dysregulation, and glucose dysregulation.

84. The composition of claim 83, wherein the dyslipidemia comprises an abnormal level of one or more of triglycerides, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and cholesterol.

85. The composition of claim 83, wherein the cardiovascular disease is heart disease or stroke.

86. The composition of claim 83, wherein the pulmonary disease is asthma and restrictive lung disease.

87. The composition of claim 83, wherein the neurological disease is dementia or Alzheimer's disease.

88. The composition of claim 83, wherein the metabolic disease is type 2 diabetes, glucose intolerance, nonalcoholic fatty liver disease and liver toxicity.

89. The composition of claim 83, wherein the insulin dysregulation is insulin resistance.

90. The composition of any one of claims 79-89, wherein the subject is not overweight or lacks substantial subcutaneous fat deposition.

91. The composition of any one of claims 79-90, wherein the abnormal fat deposition is determined using an anthropometric technique, or imaging.

92. The composition of claim 91, wherein the anthropometric technique is body mass index (BMI) or android:gynoid fat ratio.

93. The composition of claim 91, wherein the imaging comprises computed tomography (CT), magnetic resonance imaging (MRI), and dual energy x-ray absorptioometry (DXA).

94. The composition of any one of claims 79-93, wherein the subject does not exhibit substantial abnormal fat deposition outside the abdomen.

95. The composition of any one of claims 79-94, wherein the subject is a fetus, a neonate, an infant, a child, a juvenile, an adolescent, or an adult.

96. The composition of any one of claims 79-95, wherein the composition reduces visceral fat deposition.

97. The composition of any one of claims 79-96, wherein the sFGFR3 polypeptide comprises at least 50 consecutive amino acids of an extracellular domain of a naturally occurring fibroblast growth factor receptor 3 (FGFR3) polypeptide.

98. The composition of claim 97, wherein the sFGFR3 polypeptide comprises 100-370 consecutive amino acids of an extracellular domain of the naturally occurring FGFR3 polypeptide.

99. The composition of claim 97 or 98, wherein the sFGFR3 polypeptide comprises fewer than 350 amino acids of the extracellular domain of the naturally occurring FGFR3 polypeptide.

100. The composition of any one of claims 97-99, wherein the sFGFR3 polypeptide comprises an Ig-like C2-type domain 1, 2, and/or 3 of the naturally occurring FGFR3 polypeptide.

101. The composition of any one of claims 79-100, wherein the sFGFR3 polypeptide lacks a signal peptide and/or a transmembrane domain, such as the signal peptide and/or transmembrane domain of a naturally occurring FGFR3 polypeptide.

102. The composition of any one of claims 79-101, wherein the sFGFR3 polypeptide is a mature polypeptide.

103. The composition of any one of claims 79-102, wherein the sFGFR3 polypeptide comprises 400 consecutive amino acids or fewer of an intracellular domain of a naturally-occurring FGFR3 polypeptide.

104. The composition of claim 103, wherein the sFGFR3 polypeptide comprises between 5 and 399 consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide, such as 175, 150, 125, 100, 75, 50, 40, 30, 20, 15, or fewer consecutive amino acids of the intracellular domain of a naturally-occurring FGFR3 polypeptide.

105. The composition of claim 104, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 90%, 92%, 95%, 97%, or 99% sequence identity to amino acids 401 to 413 of SEQ ID NO: 8.

106. The composition of claim 105, wherein the sFGFR3 polypeptide comprises amino acids 401 to 413 of SEQ ID NO: 8.

107. The composition of any one of claims 79-106, wherein the sFGFR3 polypeptide lacks a tyrosine kinase domain of a naturally-occurring FGFR3 polypeptide.

108. The composition of any one of claims 79-107, wherein the sFGFR3 polypeptide lacks an intracellular domain of a naturally-occurring FGFR3 polypeptide.

109. The composition of any one of claims 79-108, wherein the sFGFR3 polypeptide comprises fewer than 475, 450, 425, 400, 375, 350, 300, 250, 200, 150, or 100 amino acids in length.

110. The composition of any one of claims 79-109, wherein the sFGFR3 polypeptide comprises

an amino acid sequence having at least 85% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

111. The composition of claim 110, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to amino acids residues 1 to 280 of SEQ ID NO: 8.

112. The composition of any one of claims 79-111, wherein the sFGFR3 polypeptide comprises an amino acid sequence having at least 85% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

113. The composition of claim 112, wherein the amino acid sequence of the sFGFR3 polypeptide has 86%-100% sequence identity to the sequence of any one of SEQ ID NOs: 1-7.

114. The composition of any one of claims 79-113, wherein the subject has a skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

115. The composition of claim 114, wherein the skeletal growth retardation disorder is a FGFR3-related skeletal disease.

116. The composition of claim 115, wherein the FGFR3-related skeletal disease is selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

117. The composition of claim 116, wherein the FGFR3-related skeletal disease is achondroplasia.

118. The composition of claim 116, wherein the craniosynostosis syndrome is selected from the group consisting of Muenke syndrome, Crouzon syndrome, and Crouzonodermoskeletal syndrome.

119. The composition of any one of claims 115-118, wherein the FGFR3-related skeletal disease is caused by expression in the subject of a FGFR3 variant that exhibits ligand-dependent overactivation.

120. The composition of claim 119, wherein the FGFR3 variant comprises an amino acid substitution of a glycine residue with an arginine residue at position 358 (G358R) as set forth in SEQ ID NO: 9.

121. The composition of any one of claims 114-120, wherein the subject has been diagnosed with the skeletal growth retardation disorder, obesity, polycystic ovary syndrome, or hypercortisolism, such as Cushing's disease.

122. The composition of any one of claims 114-121, wherein the subject exhibits one or more symptoms of the skeletal growth retardation disorder selected from the group consisting of short limbs, short trunk, bowlegs, a waddling gait, skull malformations, cloverleaf skull, craniosynostosis, wormian bones, anomalies of the hands, anomalies of the feet, hitchhiker thumb, and chest anomalies.

123. The composition of any one of claims 79-113, wherein the subject does not have a skeletal growth retardation disorder, such as a FGFR3-related skeletal disease.

124. The composition of claim 123, wherein the subject does not have an FGFR3-related skeletal disease selected from the group consisting of achondroplasia, thanatophoric dysplasia type I (TDI), thanatophoric dysplasia type II (TDII), severe achondroplasia with developmental delay and acanthosis nigricans (SADDEN), hypochondroplasia, a craniosynostosis syndrome, and camptodactyly, tall stature, and hearing loss syndrome (CATSHL).

125. The composition of any one of claims 97-101 and 103-108, wherein the naturally-occurring human FGFR3 polypeptide comprises the amino acid sequence of Genbank Accession No. NP_000133.

126. The composition of any one of claims 79-125, wherein the sFGFR3 polypeptide binds to a fibroblast growth factor (FGF).

127. The composition of claim 126, wherein the FGF is selected from the group consisting of fibroblast growth factor 1 (FGF1), fibroblast growth factor 2 (FGF2), fibroblast growth factor 9 (FGF9), fibroblast growth factor 10 (FGF10), fibroblast growth factor 18 (FGF18), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), and fibroblast growth factor 23 (FGF23).

128. The composition of claim 126 or 127, wherein the binding is characterized by an equilibrium dissociation constant (K_d) of about 0.2 nM to about 20 nM.

129. The composition of claim 128, wherein the binding is characterized by a K_d of about 1 nM to about 10 nM, wherein optionally the K_d is about 1 nm, about 2 nm, about 3 nm, about 4 nm, about 5 nm, about 6 nm, about 7 nm, about 8 nm, about 9 nm, or about 10 nm.

130. The composition of any one of claims 79-129, wherein the amino acid sequence of the sFGFR3 polypeptide is set forth in SEQ ID NO: 5.

131. The composition of any one of claims 79-130, wherein the sFGFR3 polypeptide comprises a signal peptide, such as a signal peptide of a naturally-occurring FGFR3 polypeptide.

132. The composition of claim 131, wherein the signal peptide comprises the amino acid sequence of SEQ ID NO: 21.

133. The composition of any one of claims 79-132, wherein the sFGFR3 polypeptide comprises a heterologous polypeptide.

134. The composition of claim 133, wherein the heterologous polypeptide is a fragment crystallizable region of an immunoglobulin (Fc region) or human serum albumin (HSA).

135. The composition of any one of claims 79-134, wherein the polynucleotide encoding the sFGFR3 polypeptide comprises a nucleic acid sequence having at least 85% and up to 100% sequence identity to the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

136. The composition of claim 135, wherein the polynucleotide consists of the nucleic acid sequence of any one of SEQ ID NOs: 10-18.

137. The composition of claim 135 or 136, wherein the polynucleotide is an isolated polynucleotide.

138. The composition of claim 135 or 136, wherein the polynucleotide is in a vector.

139. The composition of claim 138, wherein the vector is selected from the group consisting of a plasmid, an artificial chromosome, a viral vector, and a phage vector.

140. The composition of claim 138 or 139, wherein vector is in the host cell.

141. The composition of claim 140, wherein the host cell is an isolated host cell.

142. The composition of claim 141, wherein the host cell is from the subject.

143. The composition of claim 142, wherein the host cell has been transformed with the polynucleotide.

144. The composition of claim 140 or 141, wherein the host cell is a HEK 293 cell or CHO cell.

145. The composition of any one of claims 79-144, further comprising a pharmaceutically acceptable excipient, carrier, or diluent.

146. The composition of claim 145, wherein the composition is formulated for administration to the subject at a dose of about 0.001 mg/kg to about 30 mg/kg of the sFGFR3 polypeptide.

147. The composition of claim 146, wherein the composition is formulated for administration to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide.

148. The composition of any one of claims 145-147, wherein the composition is formulated for administration to the subject daily, weekly, or monthly.

149. The composition of any one of claims 145-148, wherein the composition is formulated for administration to the subject seven times a week, six times a week, five times a week, four times a week, three times a week, twice a week, weekly, every two weeks, or once a month.

150. The composition of claim 149, wherein the composition is formulated for administration to the subject at a dose of about 2.5 mg/kg to about 10 mg/kg of the sFGFR3 polypeptide once or twice a week.

151. The composition of any one of claims 145-150, wherein the composition is formulated for administration to the subject by parenteral administration, enteral administration, or topical administration.

152. The composition of claim 151, wherein the composition is formulated for administration to the subject by subcutaneous administration, intravenous administration, intramuscular administration, intra-arterial administration, intrathecal administration, or intraperitoneal administration.

153. The composition of claim 152, wherein the composition is formulated for administration to the subject by subcutaneous administration.

154. The composition of any one of claims 79-153, wherein the subject has not been previously administered the sFGFR3 polypeptide.

155. The composition of any one of claims 79-154, wherein the subject is a human.

156. The composition of any one of claims 79-155, wherein the sFGFR3 polypeptide has an in vivo half-life of between about 2 hours to about 25 hours.

157. Use of a soluble fibroblast growth factor receptor 3 (sFGFR3) polypeptide, a polynucleotide encoding the sFGFR3 polypeptide, or a host cell comprising a polynucleotide encoding the sFGFR3 polypeptide in the manufacture of a medicament for treating or reducing abnormal fat distribution in a subject in need thereof, such as by the method of any one of claims 1-78.

FIG. 1A

Age (yrs)	[0-3]		[4-8]		[9-18]		p	
Variables	Mean ± SD	Range (min-max)	Mean ± SD	Range (min-max)	Mean ± SD	Range (min-max)		
Weight (kg)	7.30 ± 2.56	(2.50-13.10)	16.95 ± 3.35	(11.40-29.10)	43.93 ± 10.33	(26.00-63.40)	< 0.0001	a, b, c
Height (cm)	63.17 ± 9.34	(44.00-82.00)	91.41 ± 5.50	(77.00-106.10)	118.50 ± 5.74	(104.50-126.50)	0.001	b, c
Heigth-to-age z-score (median)	-3.07 SD		-4.29 SD		-5.85 SD			
BMI (kg/m^2)	17.64 ± 2.05	(12.68-21.21)	20.10 ± 1.95	(14.18-25.85)	30.85 ± 4.87	(23.81-39.62)	0.001	b, c
BMI-to-age z-score (median)	+1.70 SD		+3.54 SD		+2.71 SD			

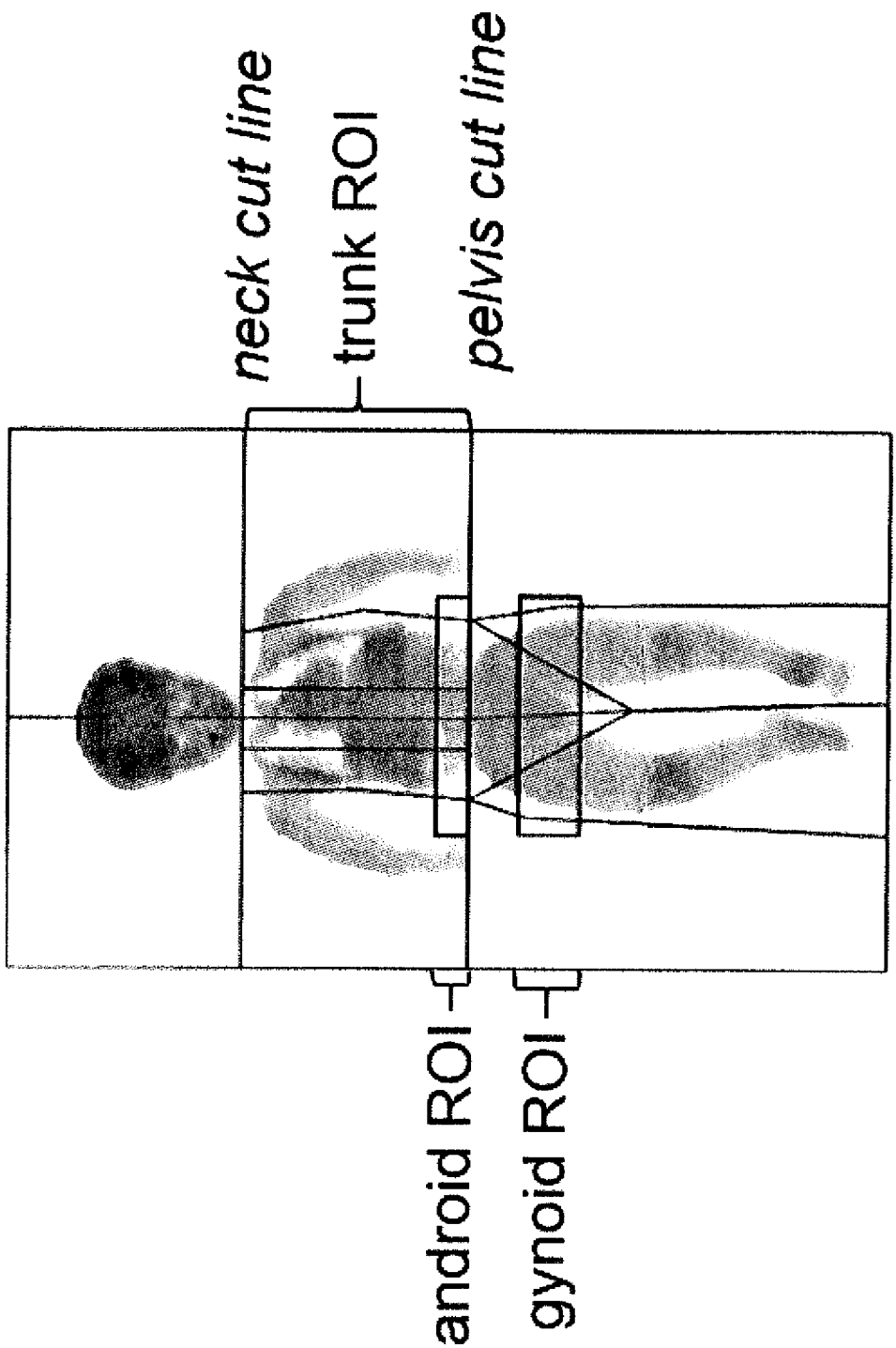

neck cut line
trunk ROI
pelvis cut line
android ROI
gynoid ROI

FIG. 1B

FIG. 1C

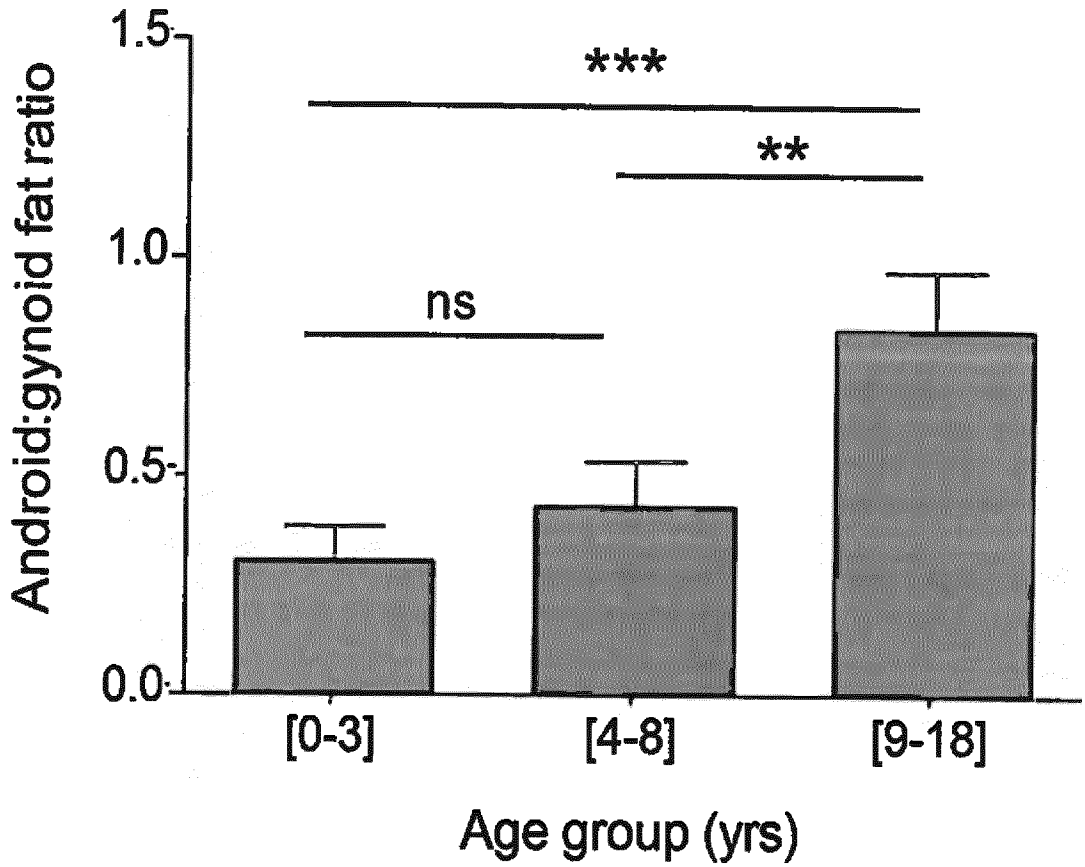


FIG. 1D

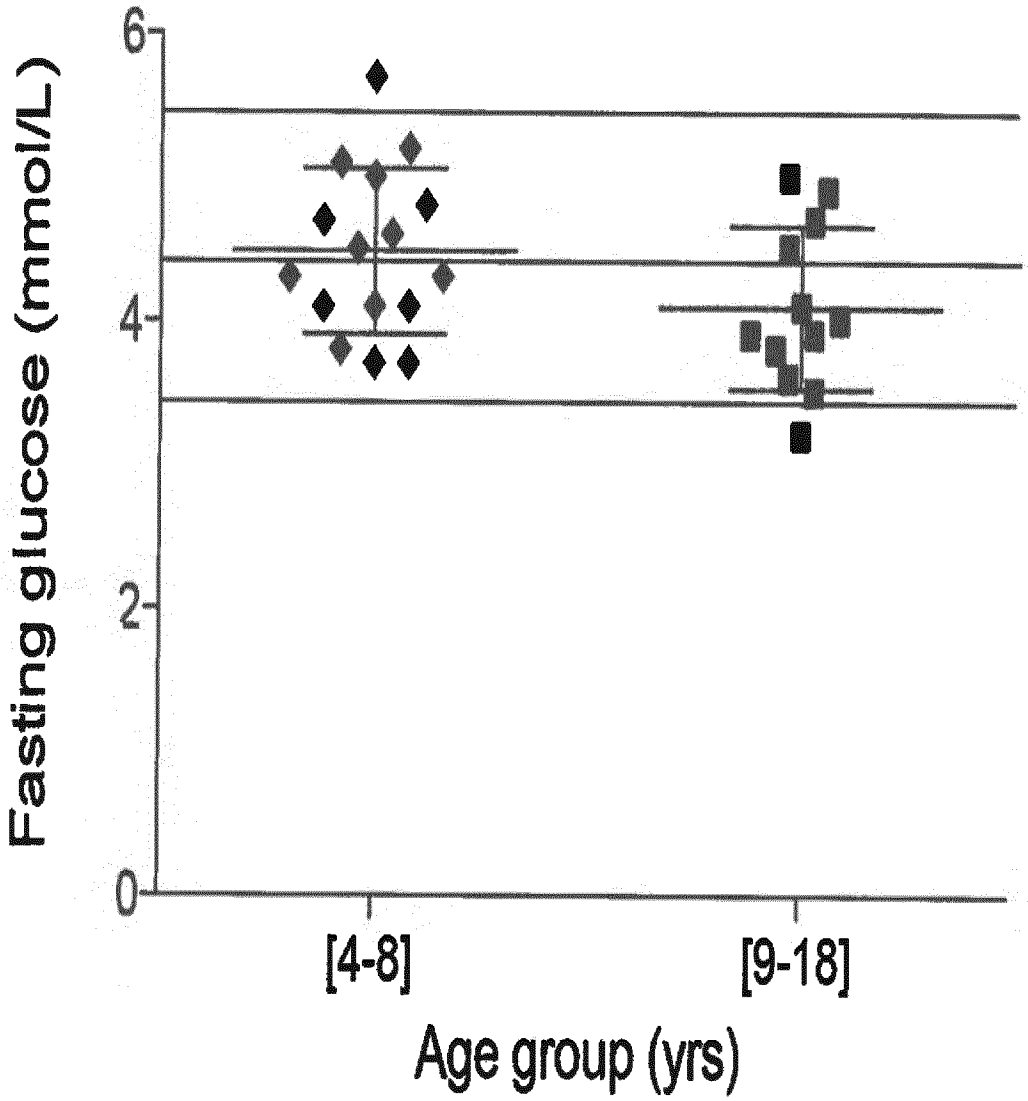
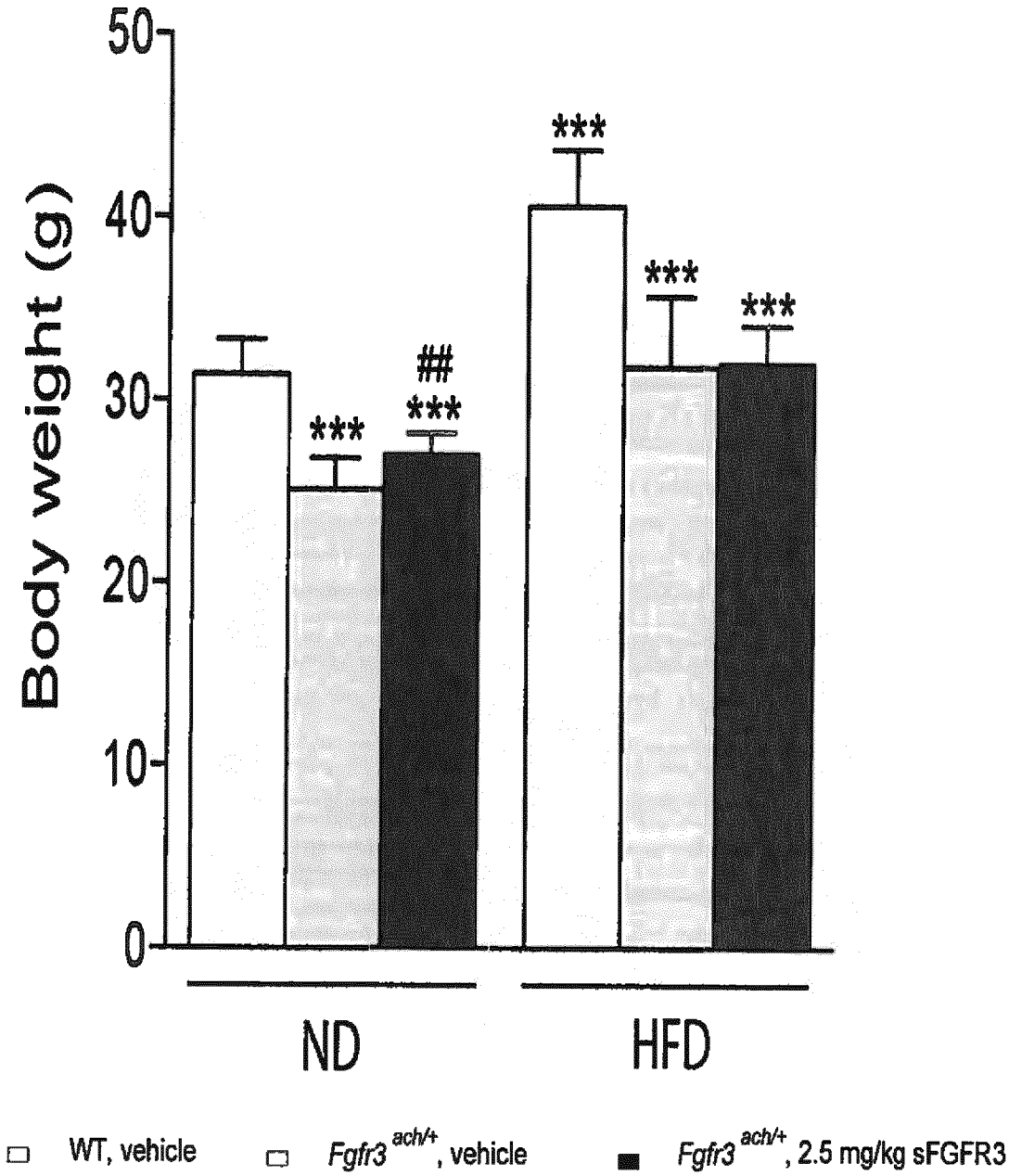


FIG. 2A


Body weight (g)
50
40
30
20
10
0
***
***
***
##
***
ND
HFD
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

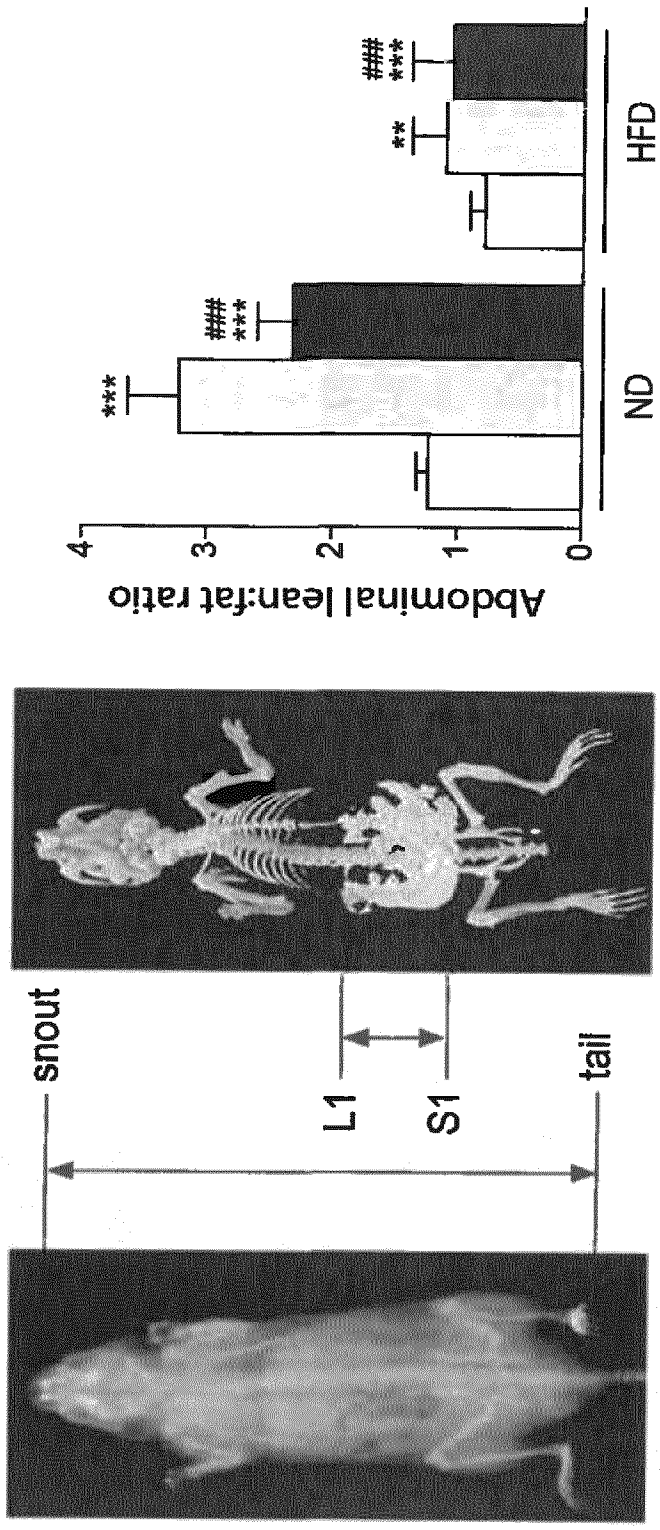

WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3
snout
tail
L1
S1
Abdominal lean:fat ratio
0
1
2
3
4
***
###
***
**
###
***
ND
HFD

FIG. 2B

FIG. 2C

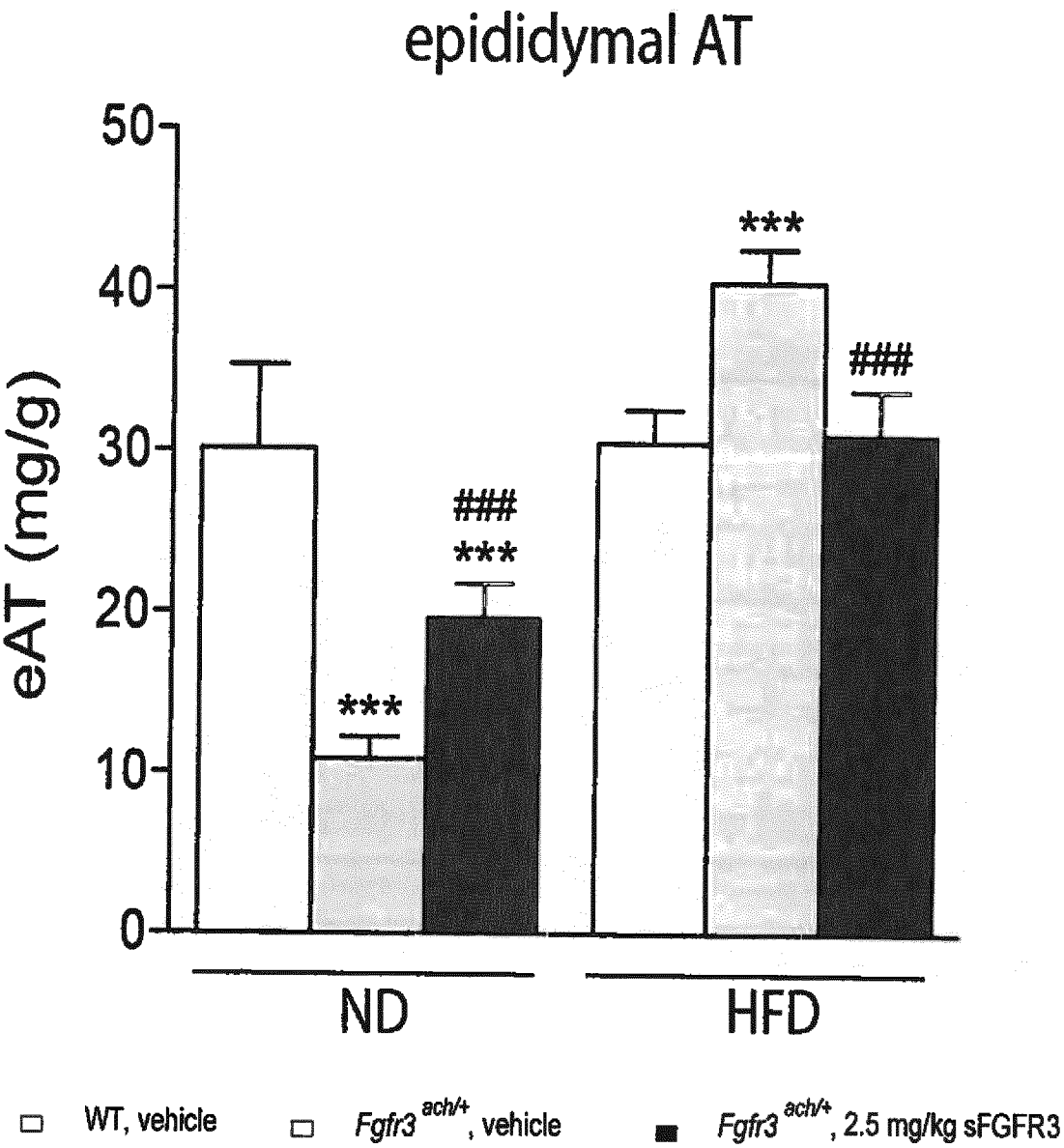

epididymal AT
eAT (mg/g)
50
40
30
20
10
0
***
###
***
***
###
ND
HFD
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 2D

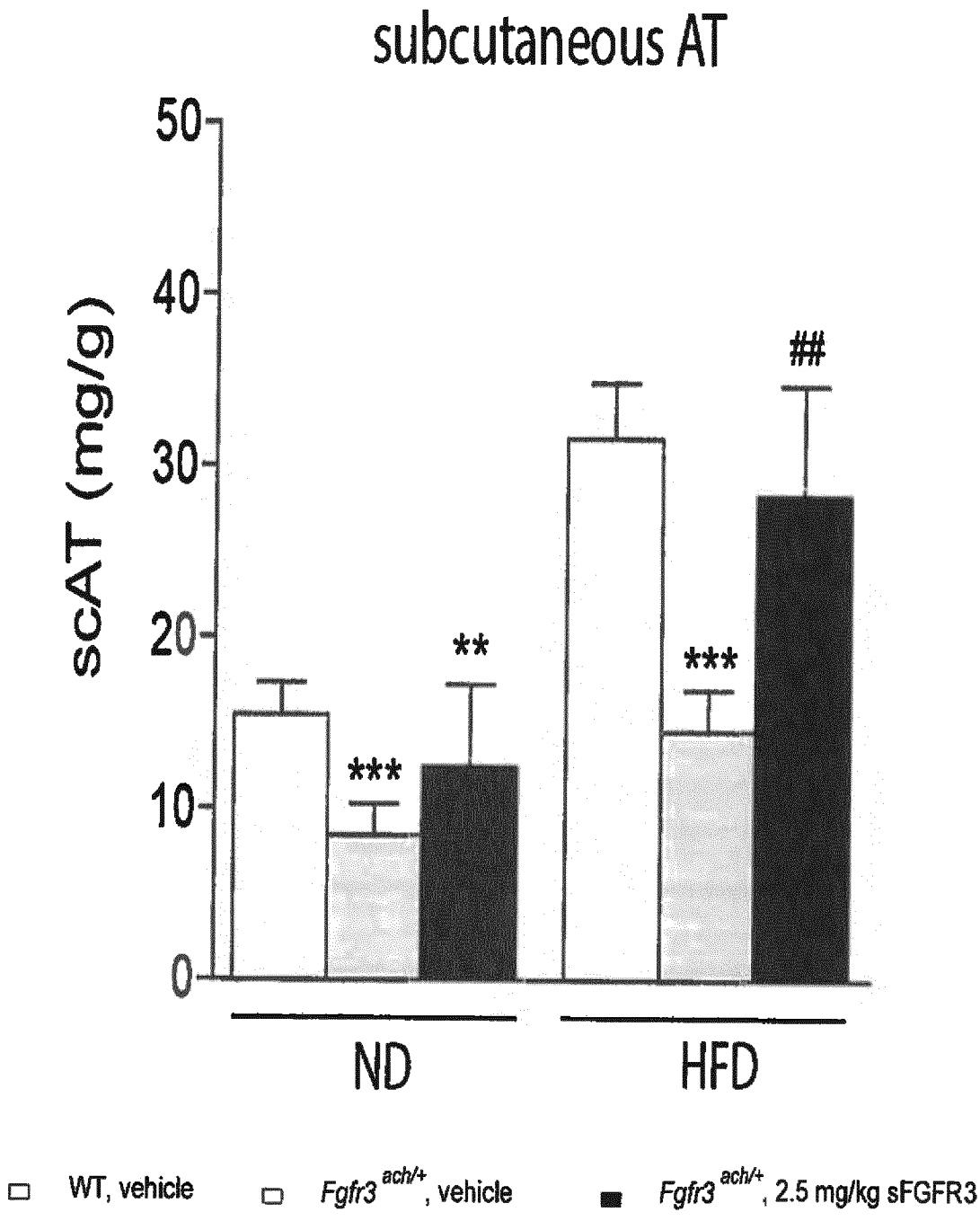

subcutaneous AT
scAT (mg/g)
50
40
30
20
10
0
**
***
***
##
ND
HFD
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 2E

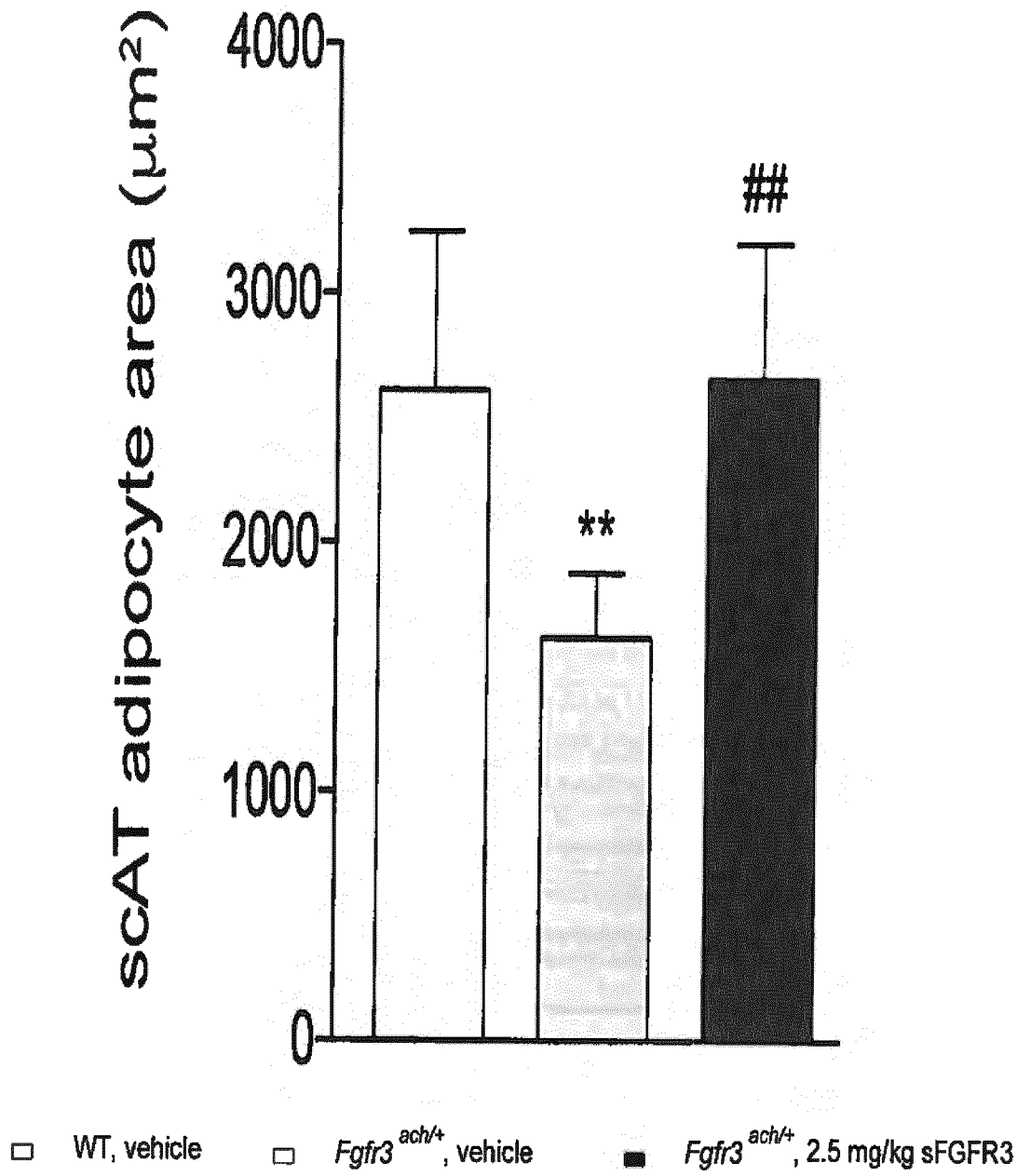
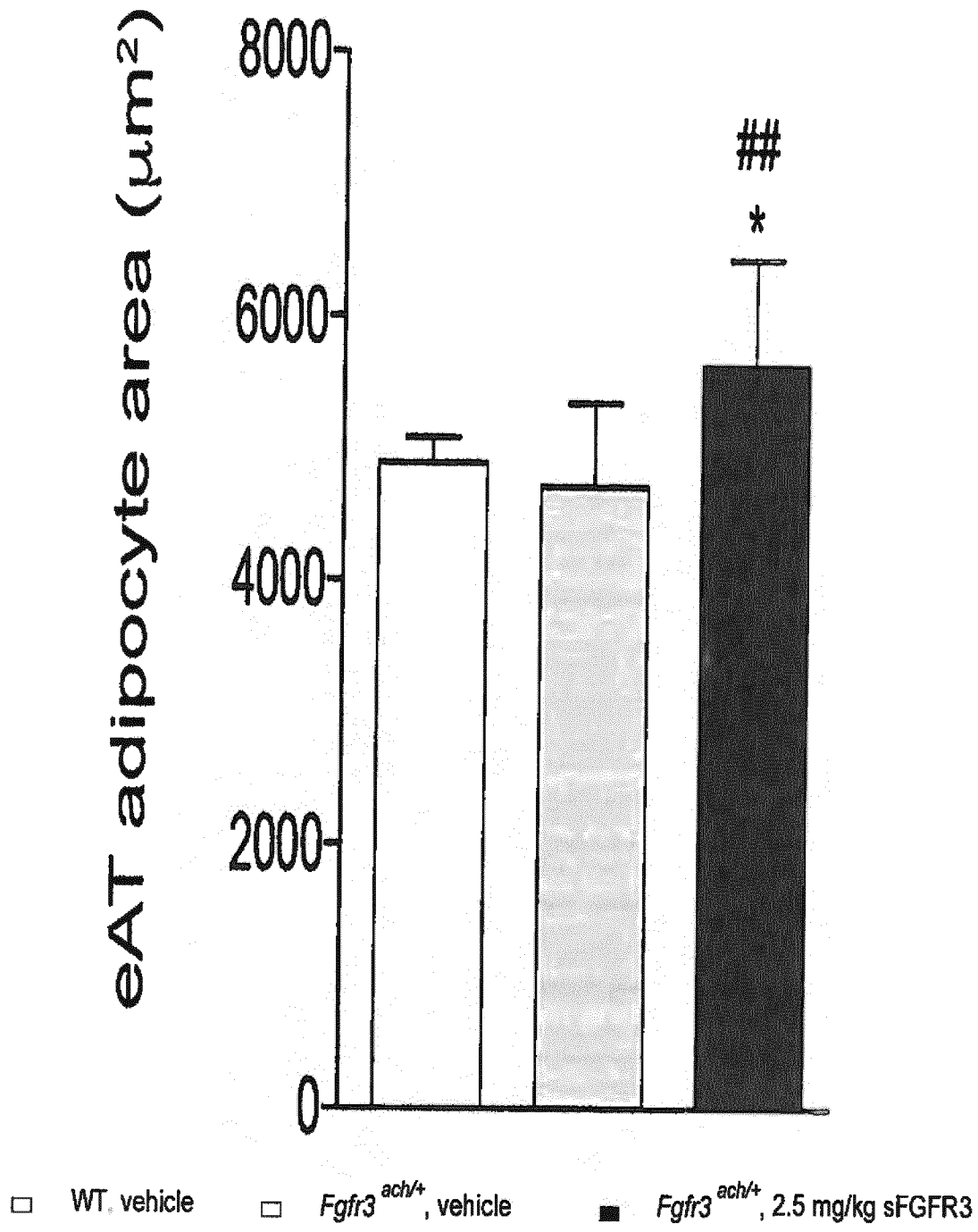

scAT adipocyte area (µm²)
4000
3000
2000
1000
0
**
##
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 2F


eAT adipocyte area (µm²)
8000
6000
4000
2000
0
##
*
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

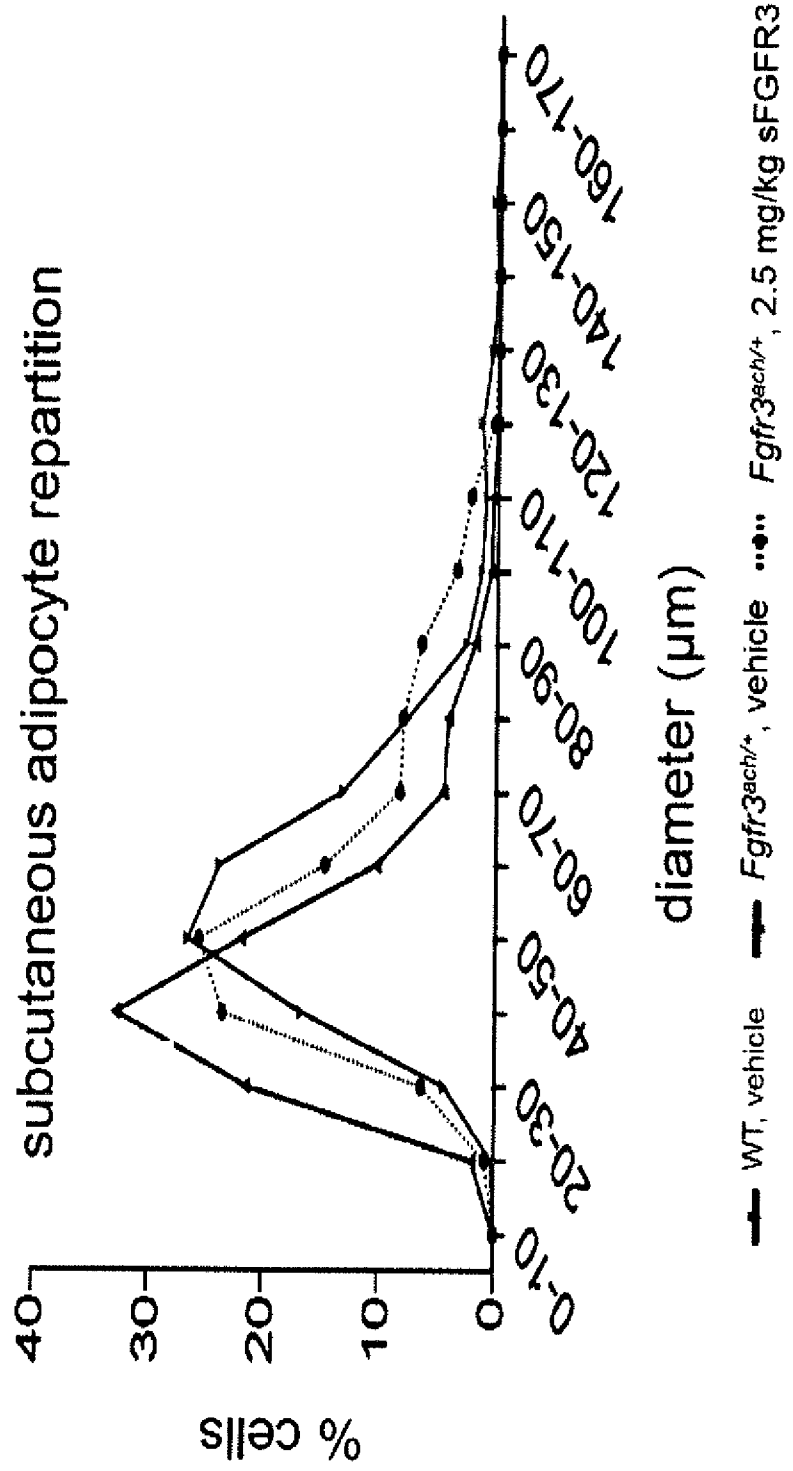

subcutaneous adipocyte repartition
% cells
40
30
20
10
0
0-10
20-30
40-50
60-70
80-90
100-110
120-130
140-150
160-170
diameter (µm)
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 2G

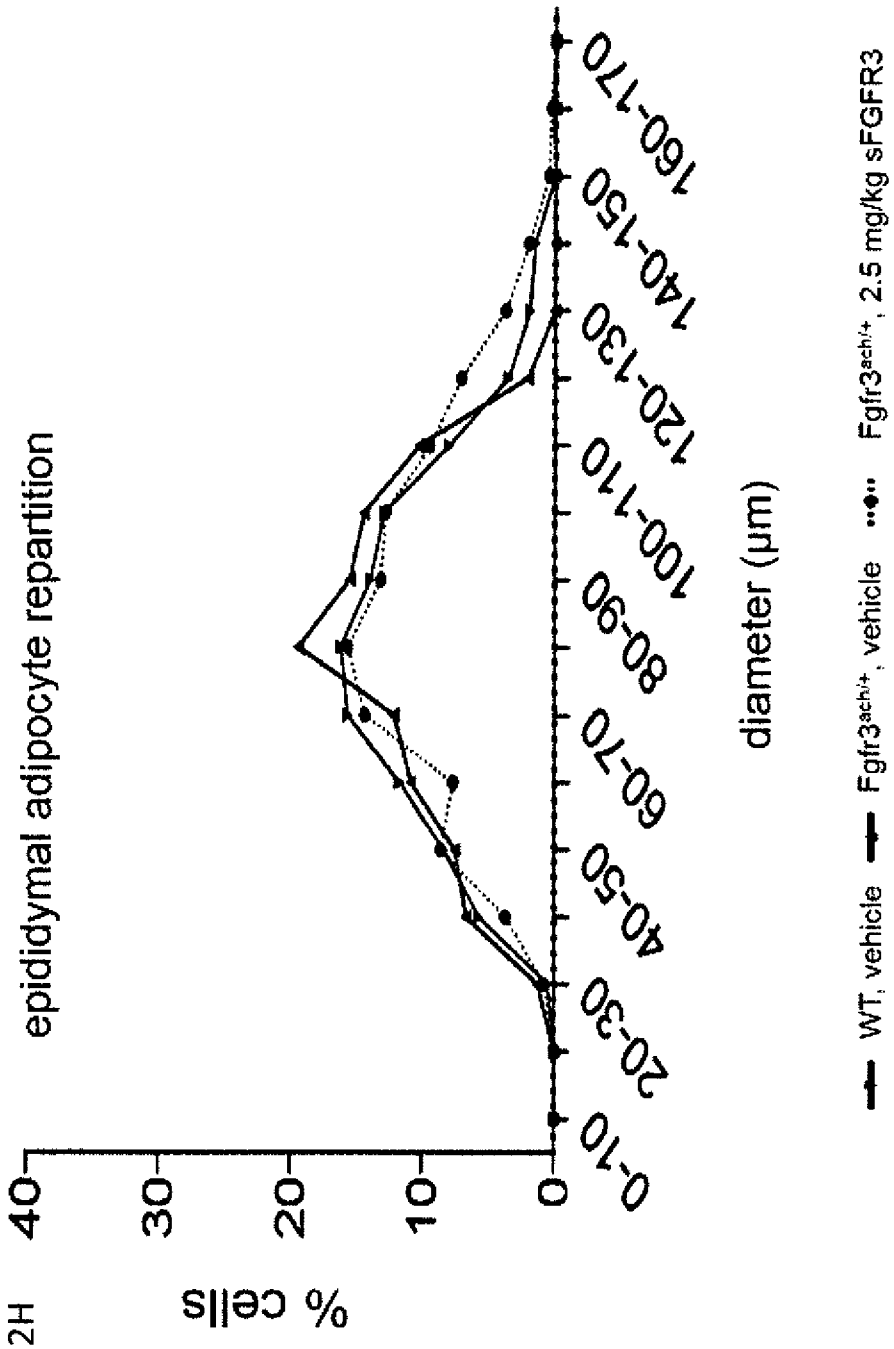

epididymal adipocyte repartition
% cells
0
10
20
30
40
0-10
20-30
40-50
60-70
80-90
100-110
120-130
140-150
160-170
diameter (µm)
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 2H

FIG. 3A

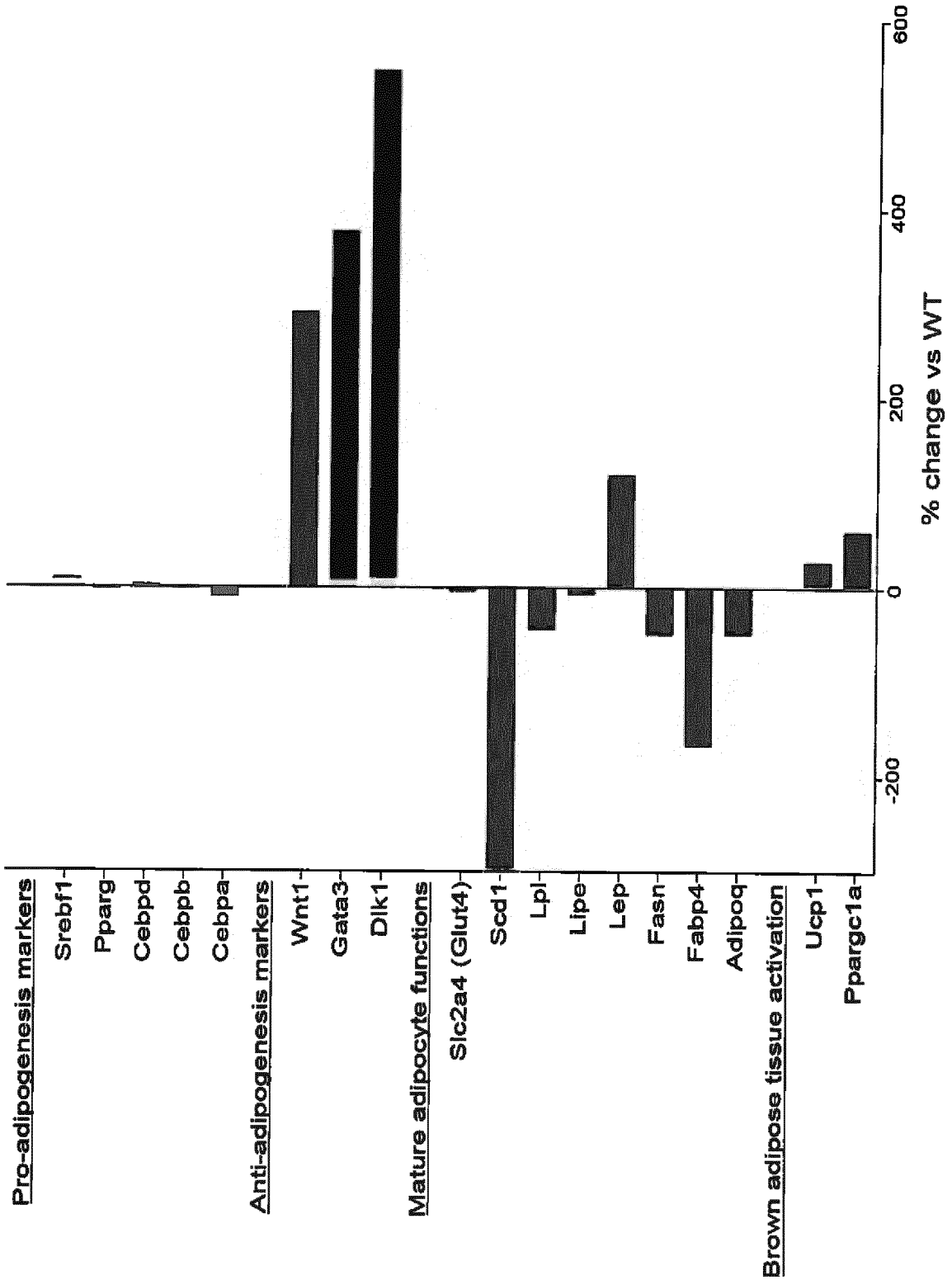

Pro-adipogenesis markers
Srebf1
Pparg
Cebpd
Cebpb
Cebpa
Anti-adipogenesis markers
Wnt1
Gata3
Dlk1
Mature adipocyte functions
Slc2a4 (Glut4)
Scd1
Lpl
Lipe
Lep
Fasn
Fabp4
Adipoq
Brown adipose tissue activation
Ucp1
Ppargc1a
-200
0
200
400
600
% change vs WT

FIG. 3B

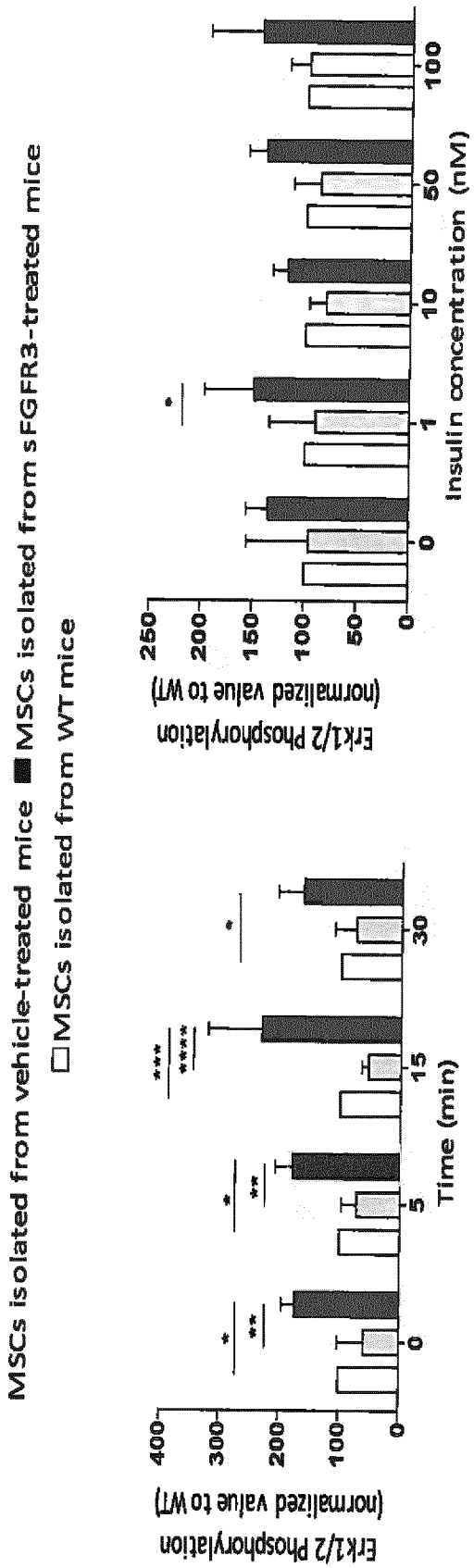

MSCs isolated from vehicle-treated mice
MSCs isolated from sFGFR3-treated mice
MSCs isolated from WT mice
Erk1/2 Phosphorylation (normalized value to WT)
Time (min)
Insulin concentration (nM)

FIG. 4A

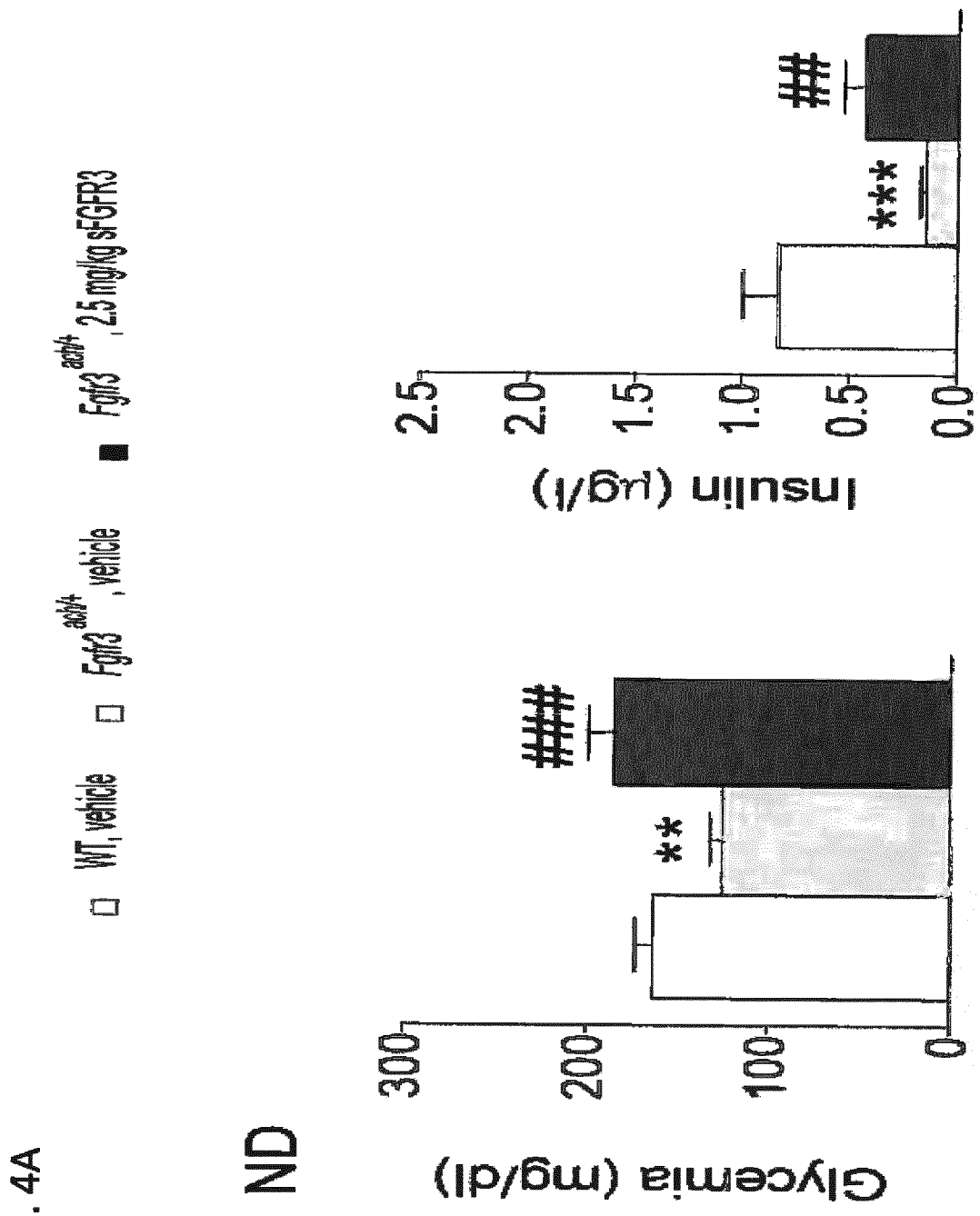
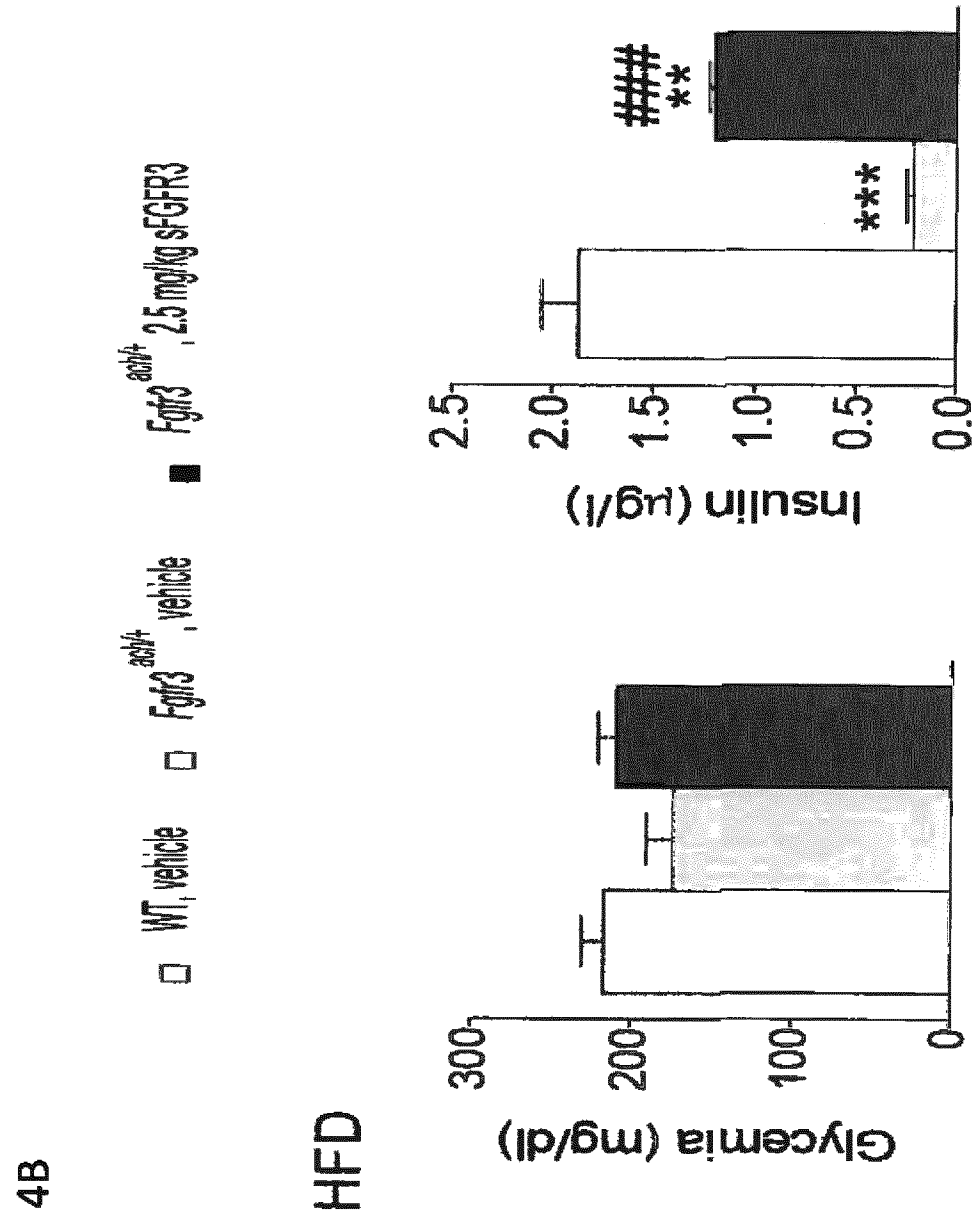

WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3
ND
Glycemia (mg/dl)
300
200
100
0
**
#####
Insulin (µg/l)
2.5
2.0
1.5
1.0
0.5
0.0
***
###

FIG. 4B


HFD
Glycemia (mg/dl)
300
200
100
0
Insulin (µg/l)
2.5
2.0
1.5
1.0
0.5
0.0
***
**
####
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

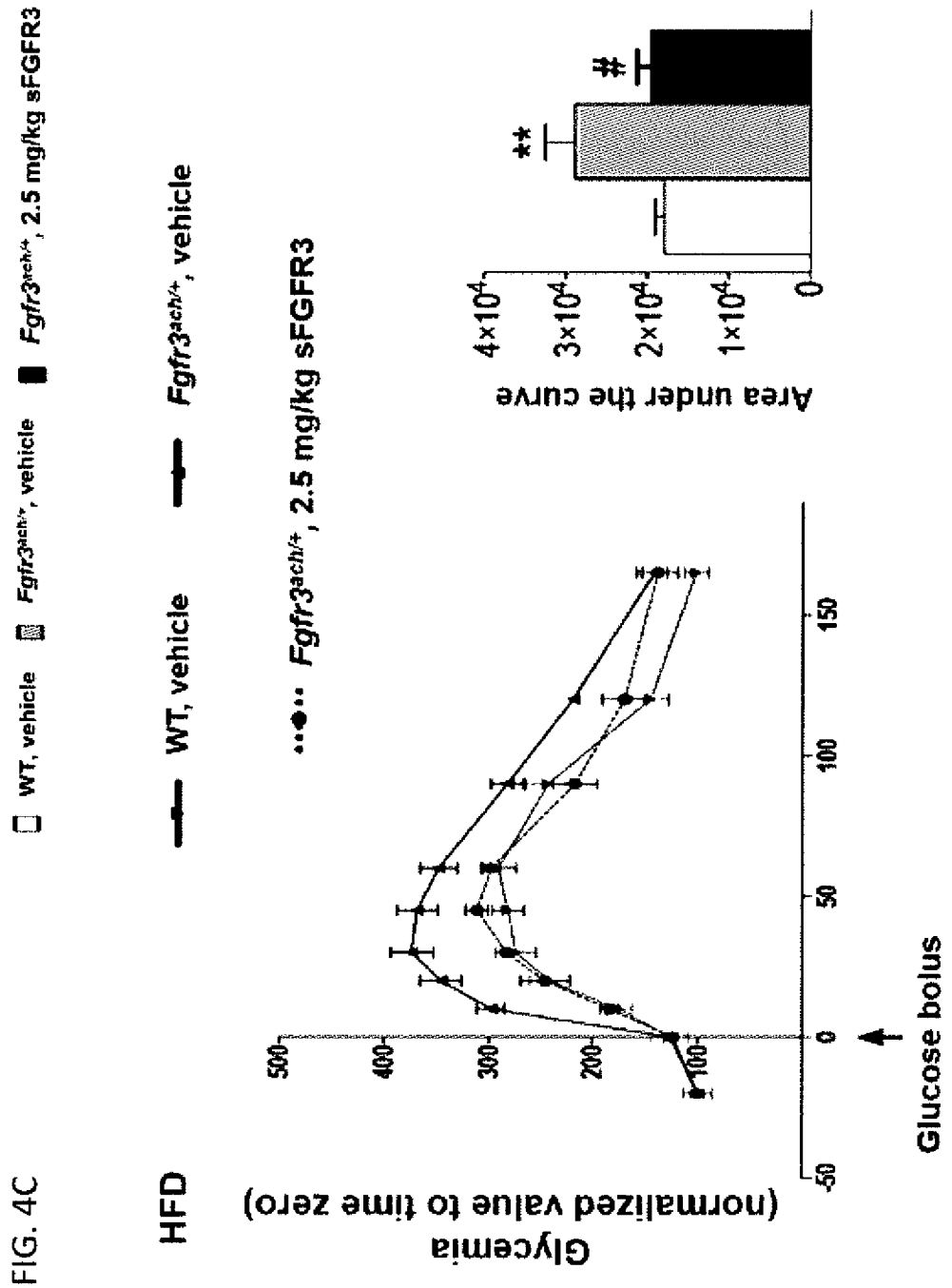

WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3
HFD
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3
Glycemia
(normalized value to time zero)
500
400
300
200
100
-50
0
50
100
150
Glucose bolus
Area under the curve
4×10^4
3×10^4
2×10^4
1×10^4
0
**
#

FIG. 4C

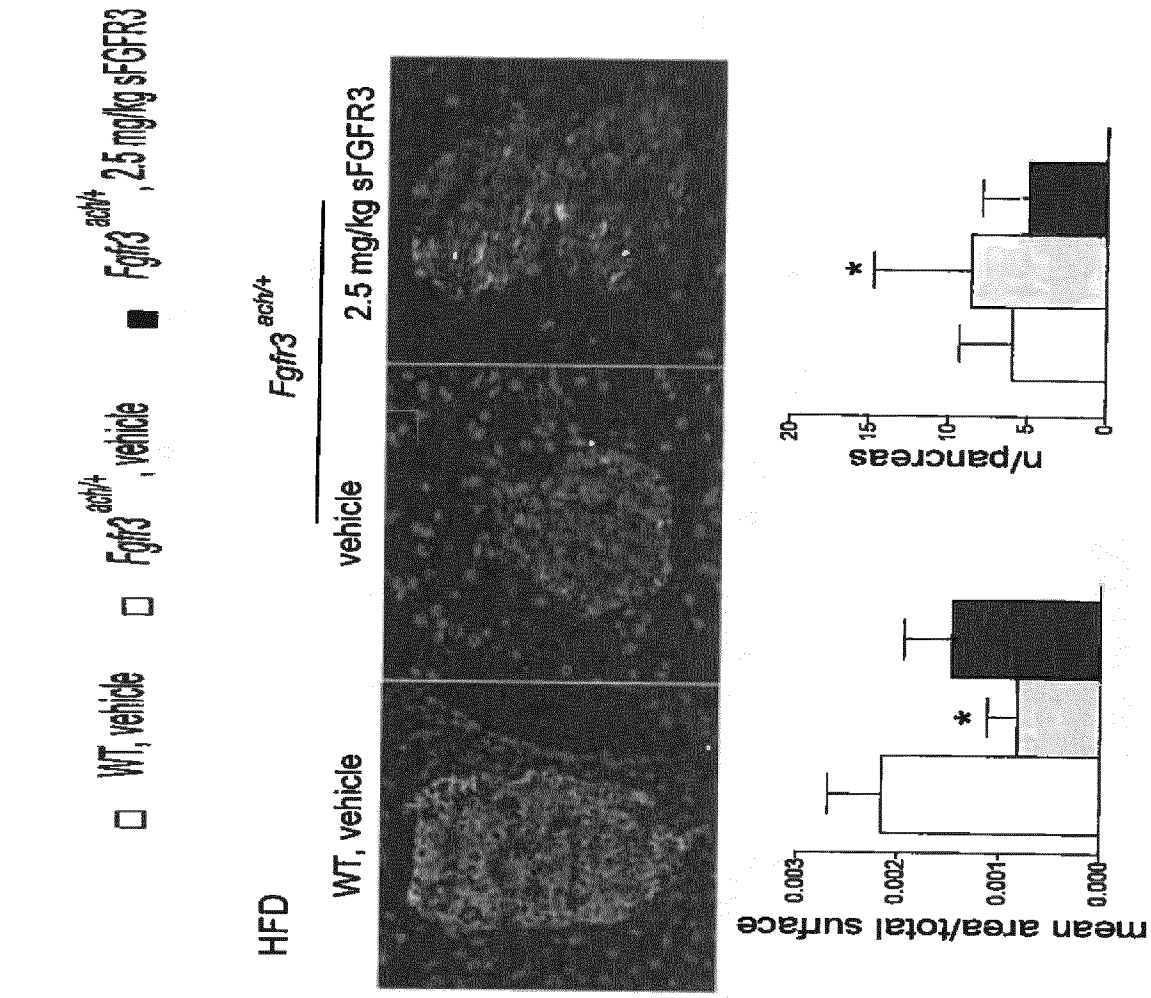

WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3
HFD
Fgfr3 ach/+
WT, vehicle
vehicle
2.5 mg/kg sFGFR3
mean area/total surface
0.003
0.002
0.001
0.000
*
n/pancreas
20
15
10
5
0
*

FIG. 4D

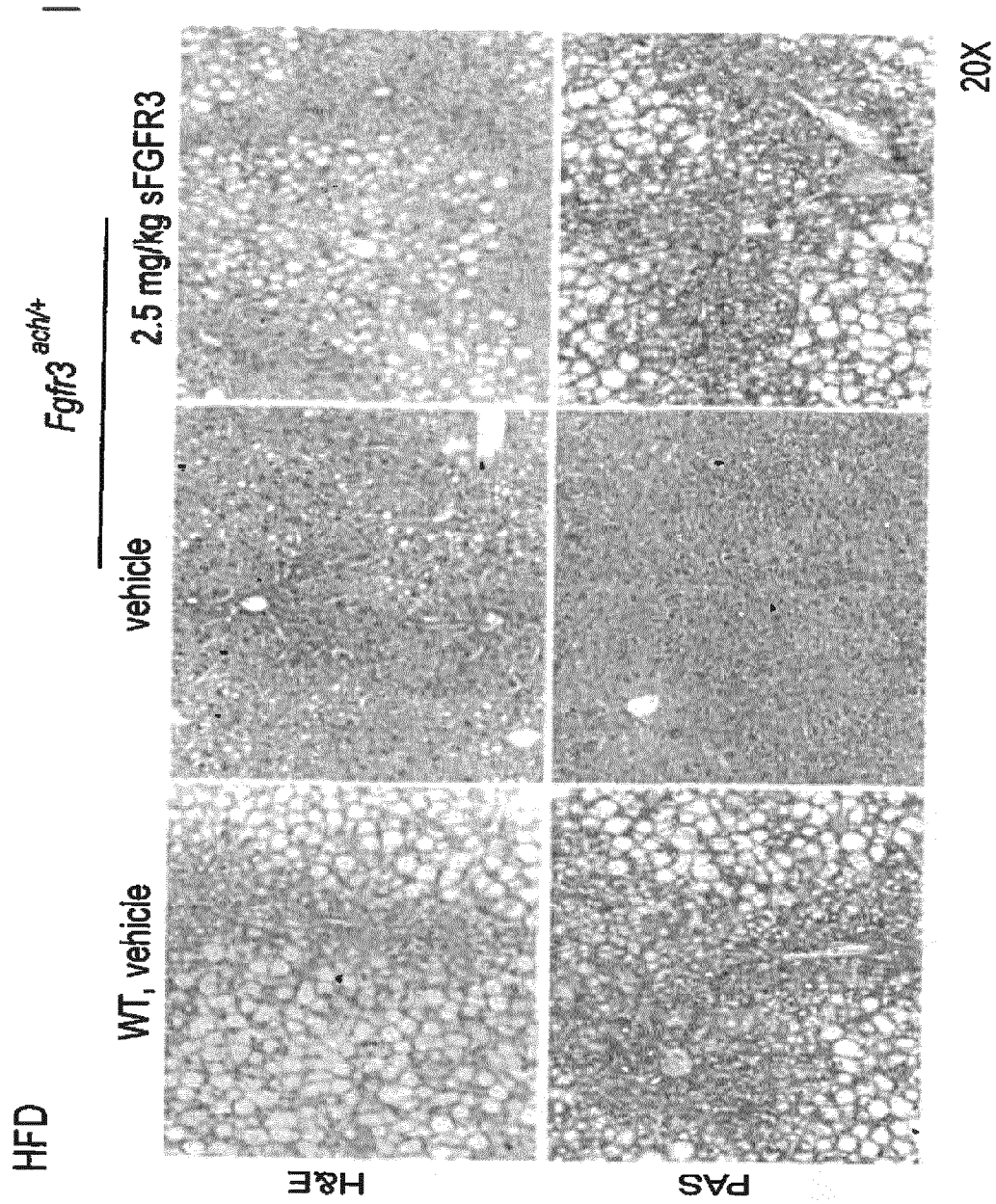


FIG. 4E

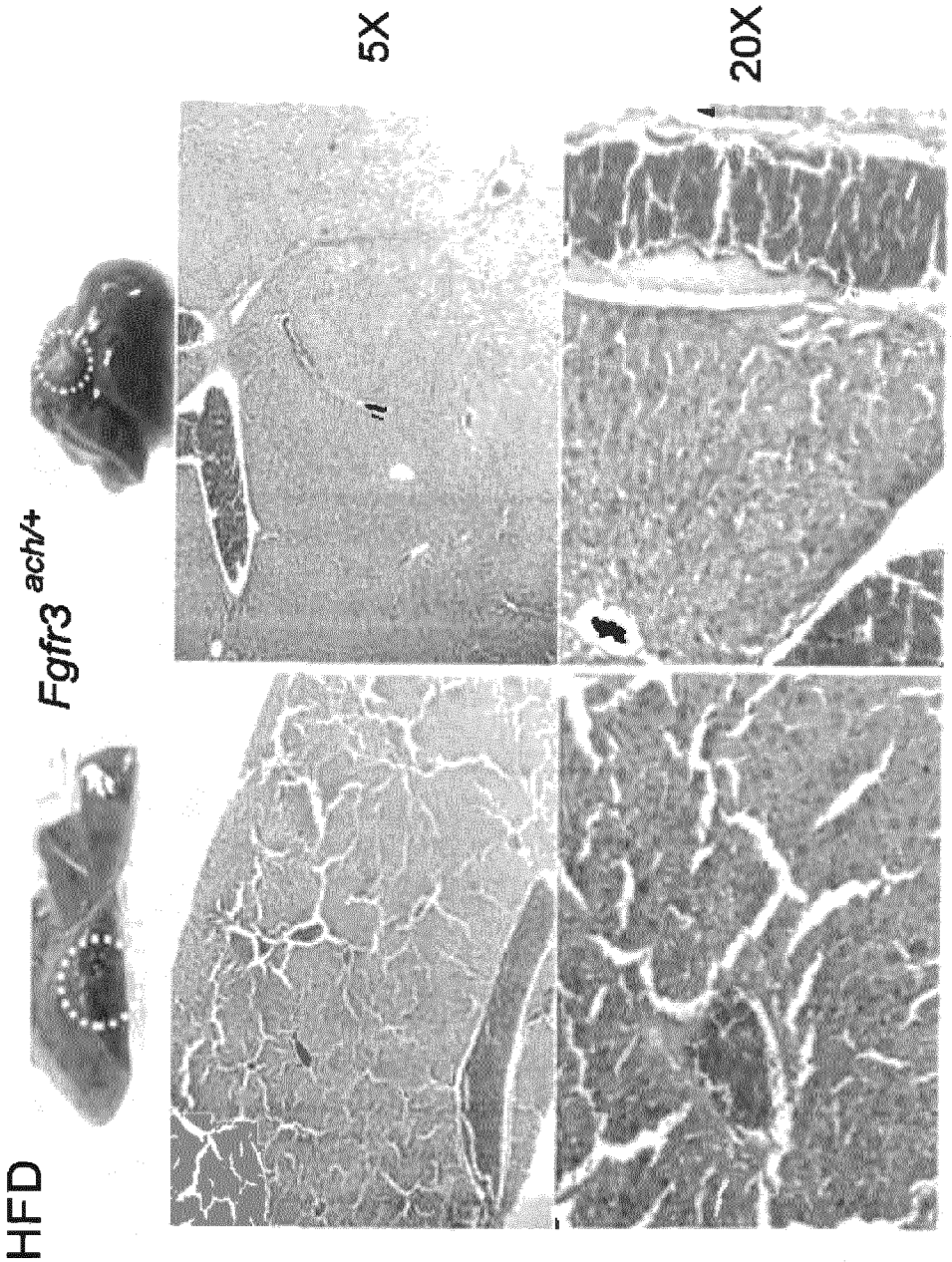


FIG. 4F

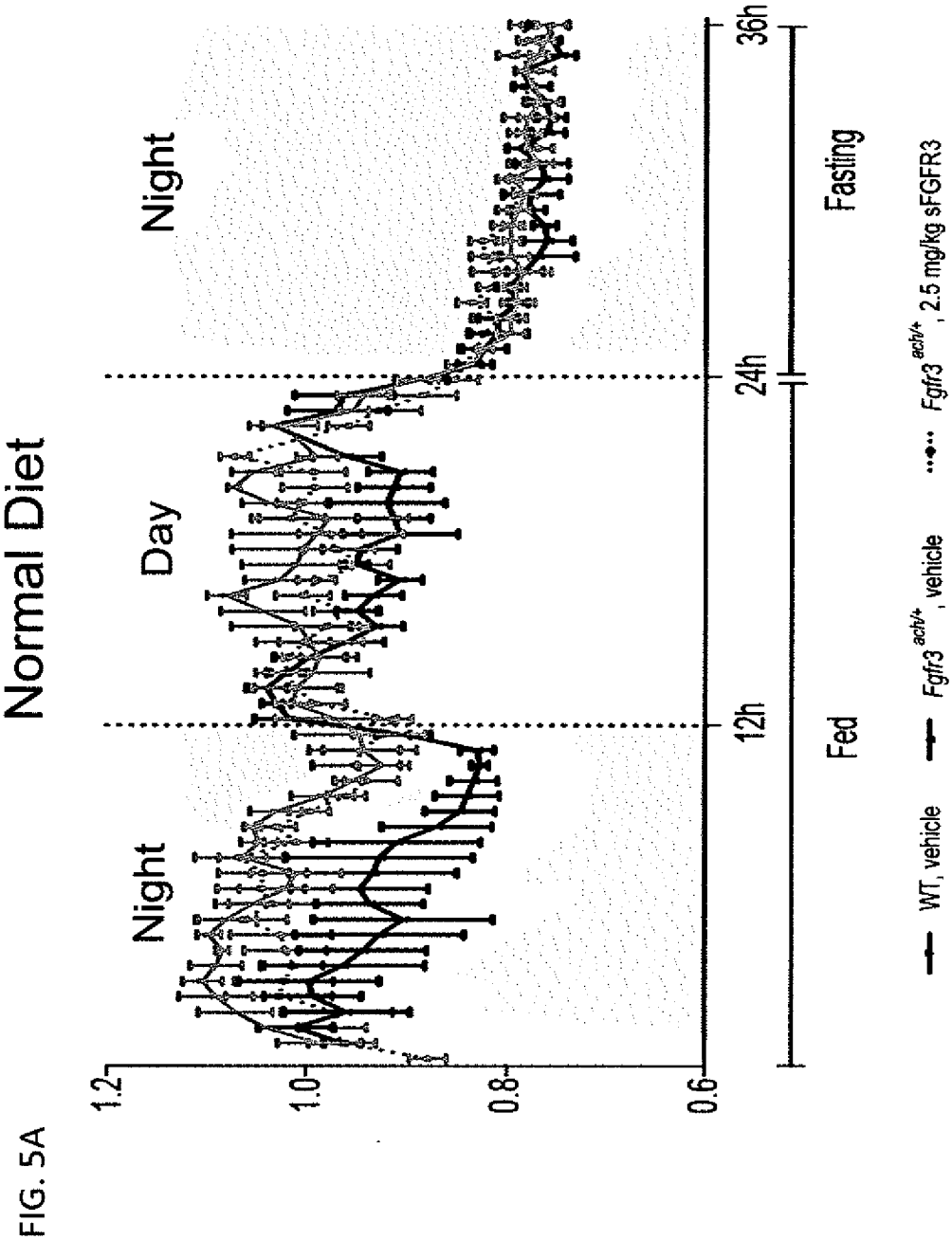

Normal Diet
Night
Day
Night
1.2
1.0
0.8
0.6
12h
24h
36h
Fed
Fasting
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 5A

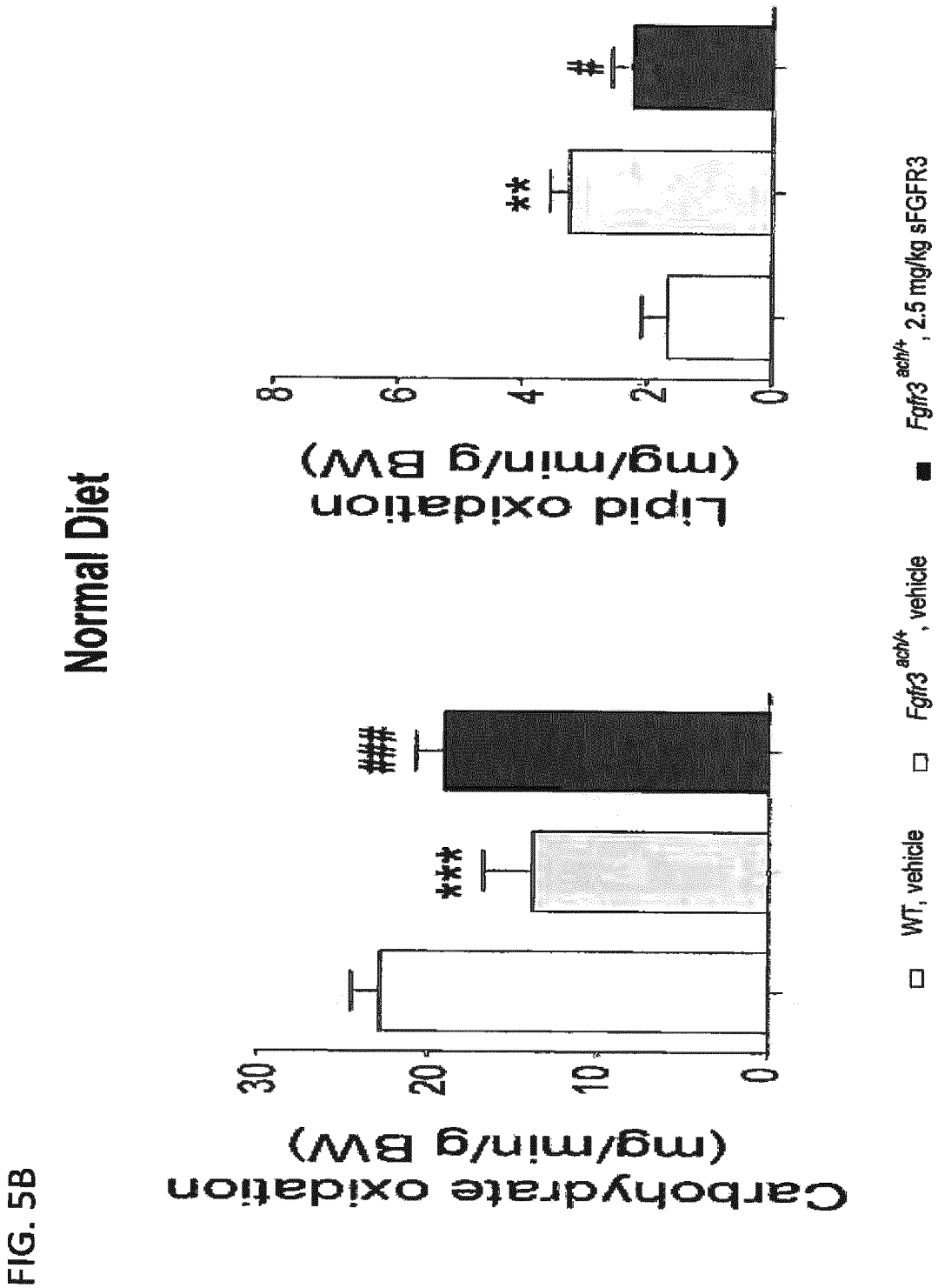

Normal Diet
Carbohydrate oxidation (mg/min/g BW)
Lipid oxidation (mg/min/g BW)
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 5B

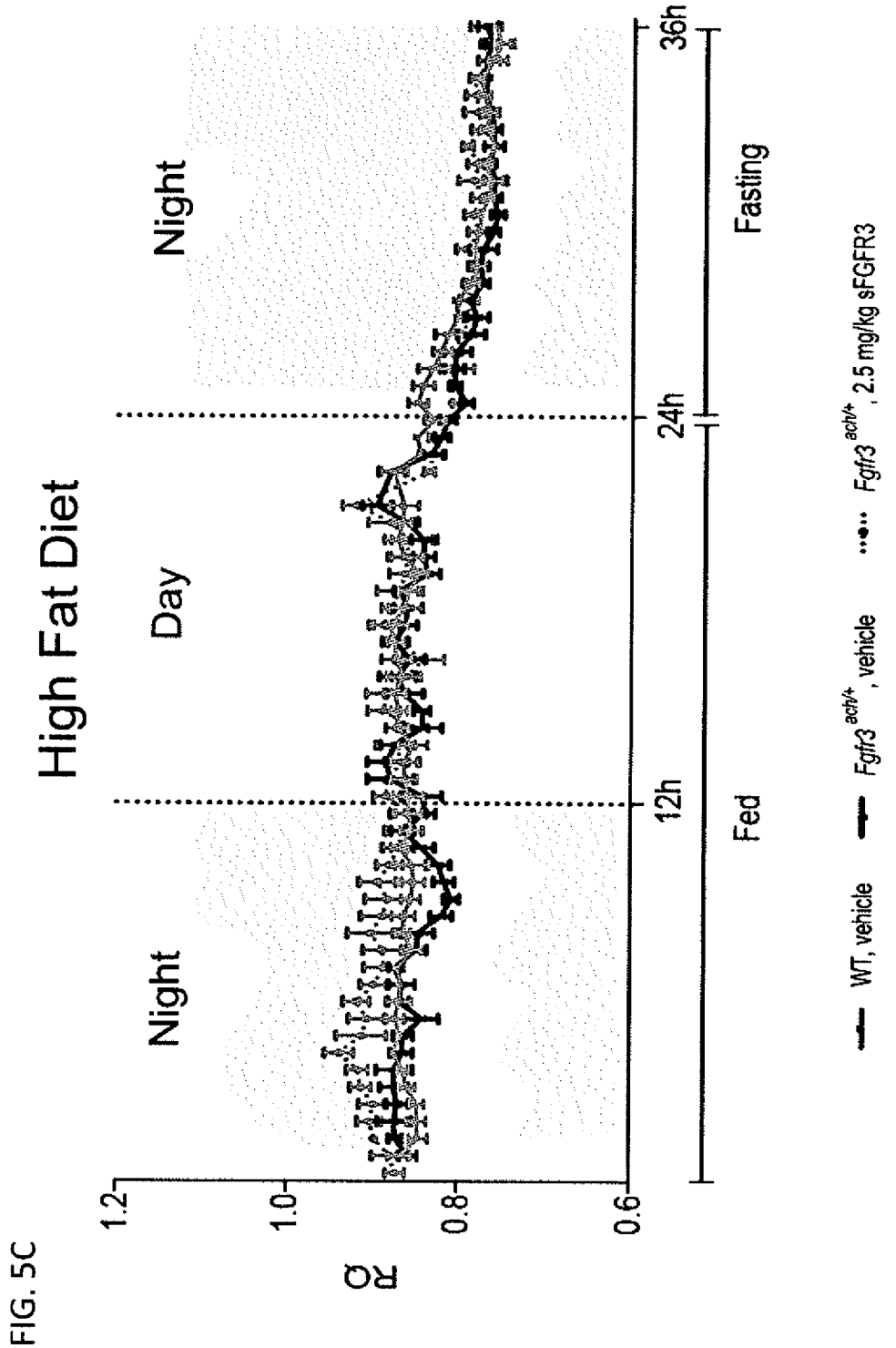

High Fat Diet
Night
Day
Night
RQ
1.2
1.0
0.8
0.6
12h
24h
36h
Fed
Fasting
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 5C

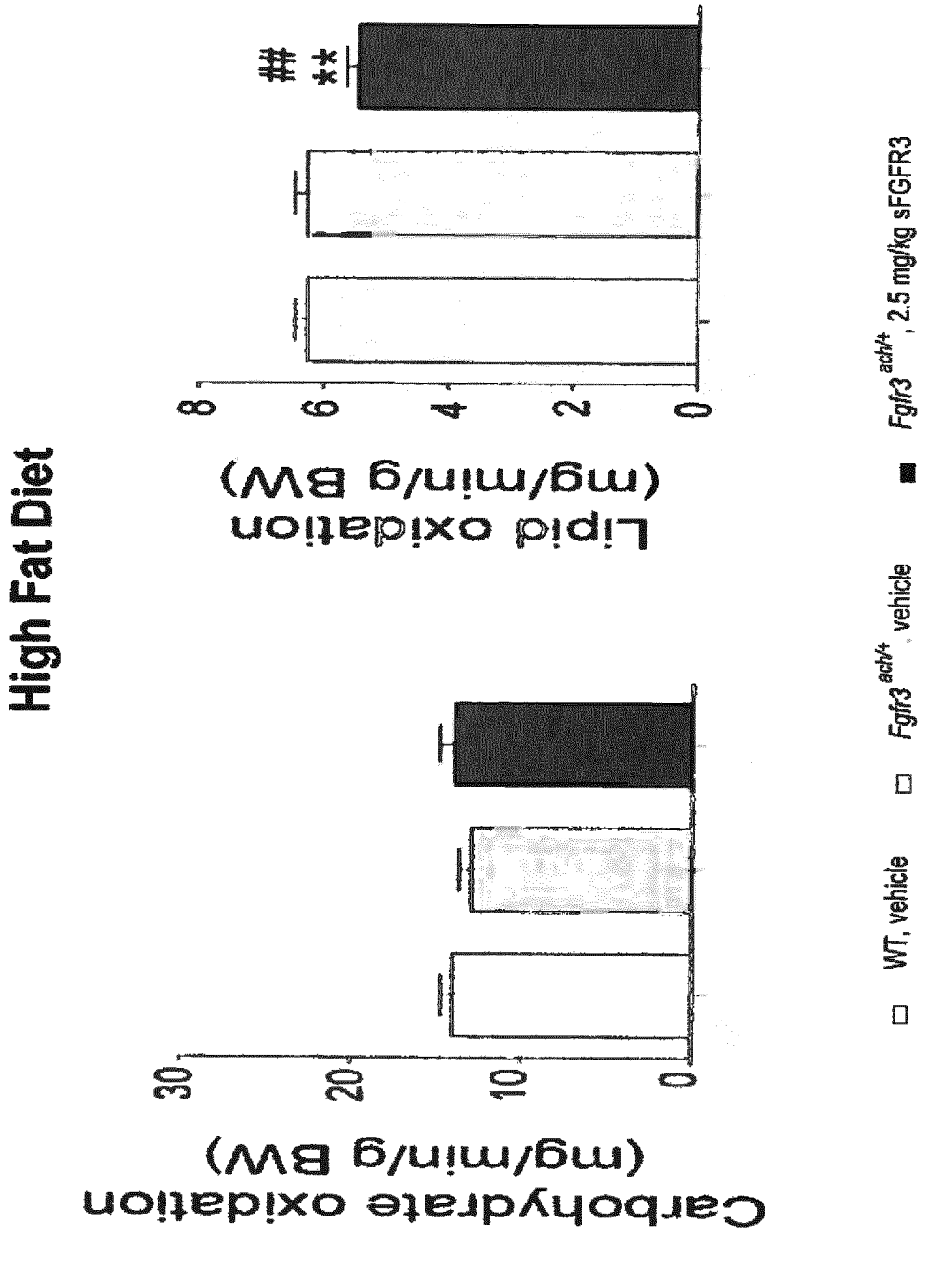
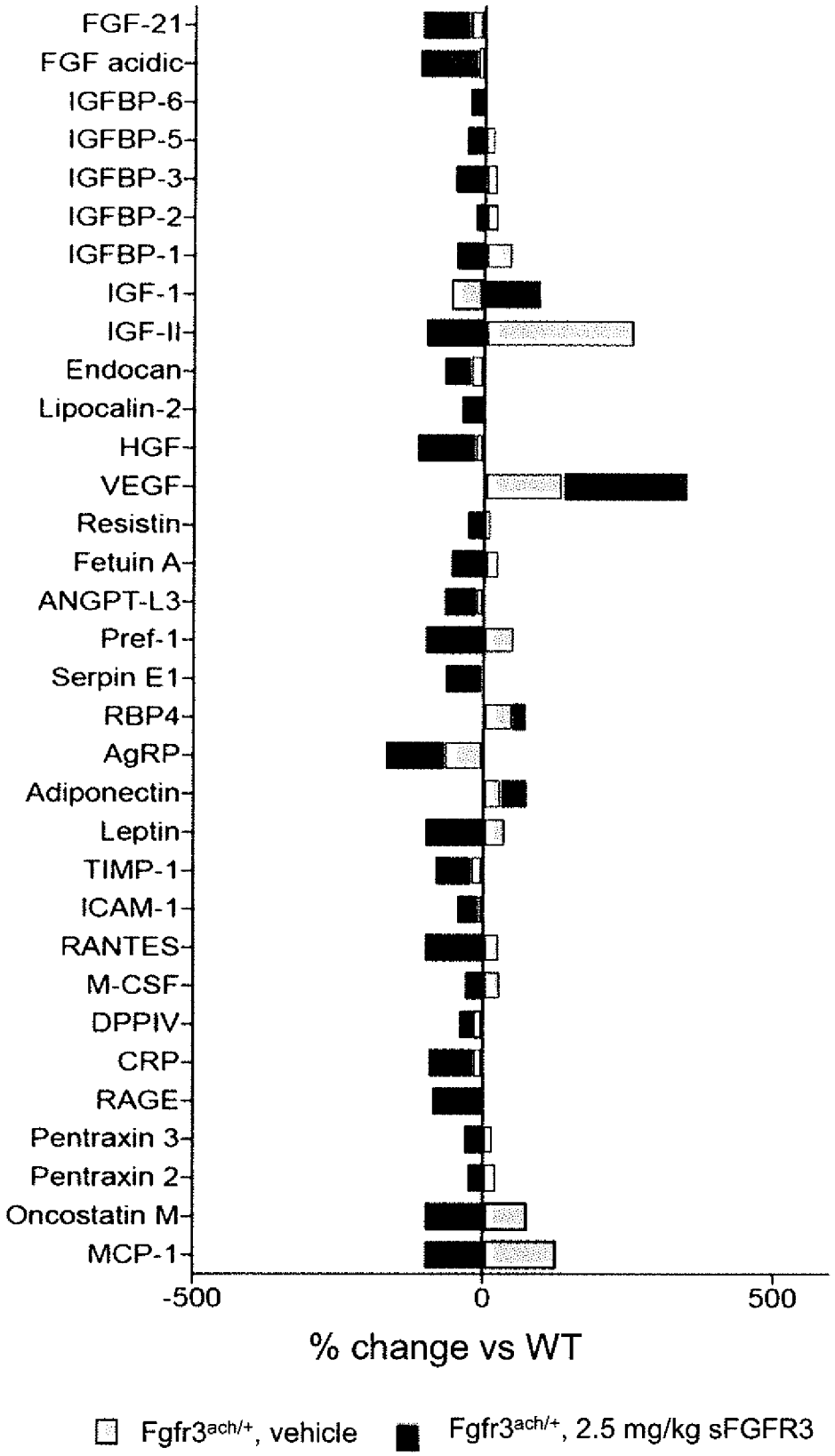

High Fat Diet
Carbohydrate oxidation (mg/min/g BW)
30
20
10
0
Lipid oxidation (mg/min/g BW)
8
6
4
2
0
##
**
WT, vehicle
Fgfr3 ach/+ vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 5D

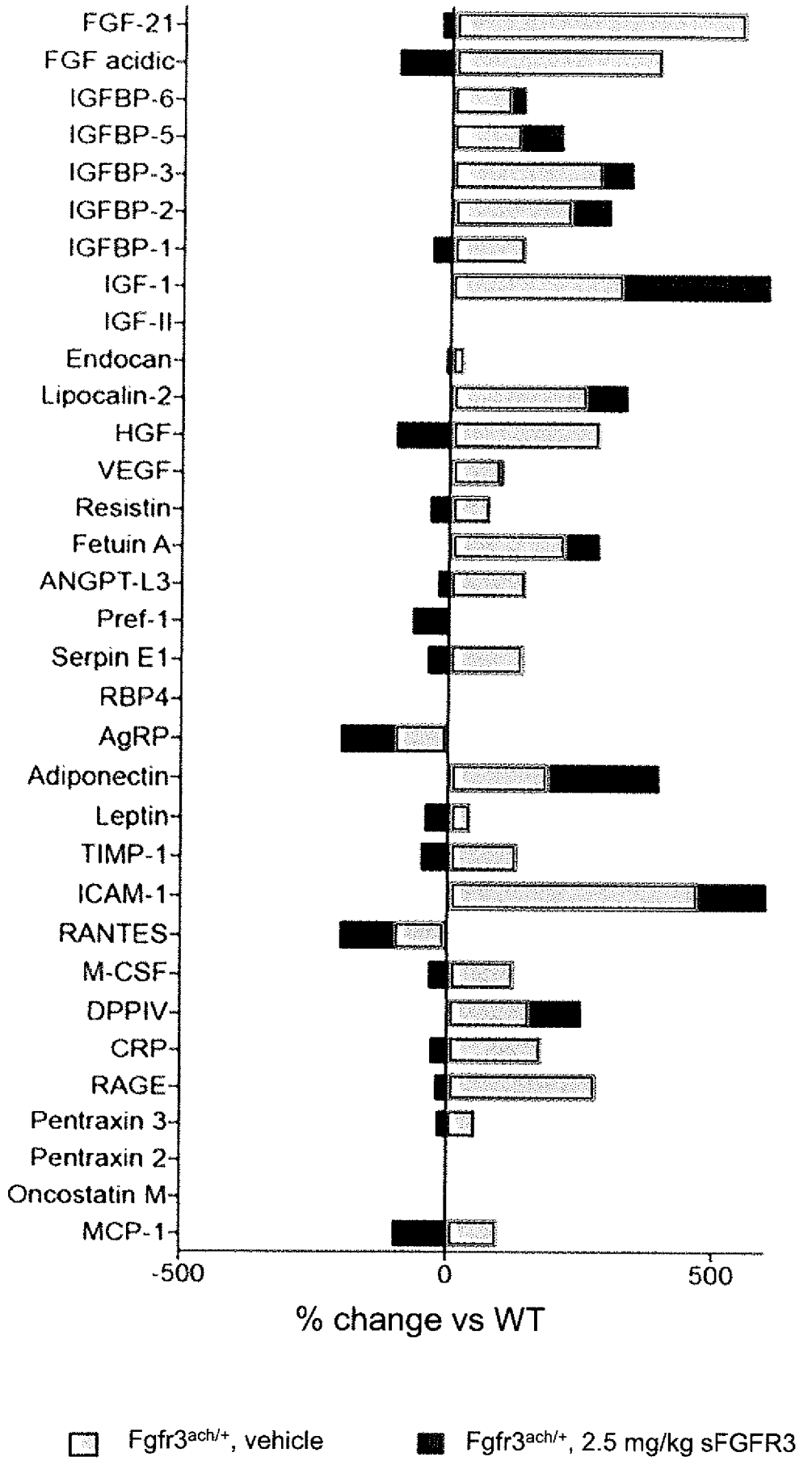
ND

FIG. 6A


FGF-21
FGF acidic
IGFBP-6
IGFBP-5
IGFBP-3
IGFBP-2
IGFBP-1
IGF-1
IGF-II
Endocan
Lipocalin-2
HGF
VEGF
Resistin
Fetuin A
ANGPT-L3
Pref-1
Serpin E1
RBP4
AgRP
Adiponectin
Leptin
TIMP-1
ICAM-1
RANTES
M-CSF
DPPIV
CRP
RAGE
Pentraxin 3
Pentraxin 2
Oncostatin M
MCP-1
-500
0
500
% change vs WT
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

HFD

FIG. 6B


FGF-21
FGF acidic
IGFBP-6
IGFBP-5
IGFBP-3
IGFBP-2
IGFBP-1
IGF-1
IGF-II
Endocan
Lipocalin-2
HGF
VEGF
Resistin
Fetuin A
ANGPT-L3
Pref-1
Serpin E1
RBP4
AgRP
Adiponectin
Leptin
TIMP-1
ICAM-1
RANTES
M-CSF
DPPIV
CRP
RAGE
Pentraxin 3
Pentraxin 2
Oncostatin M
MCP-1
-500
0
500
% change vs WT
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

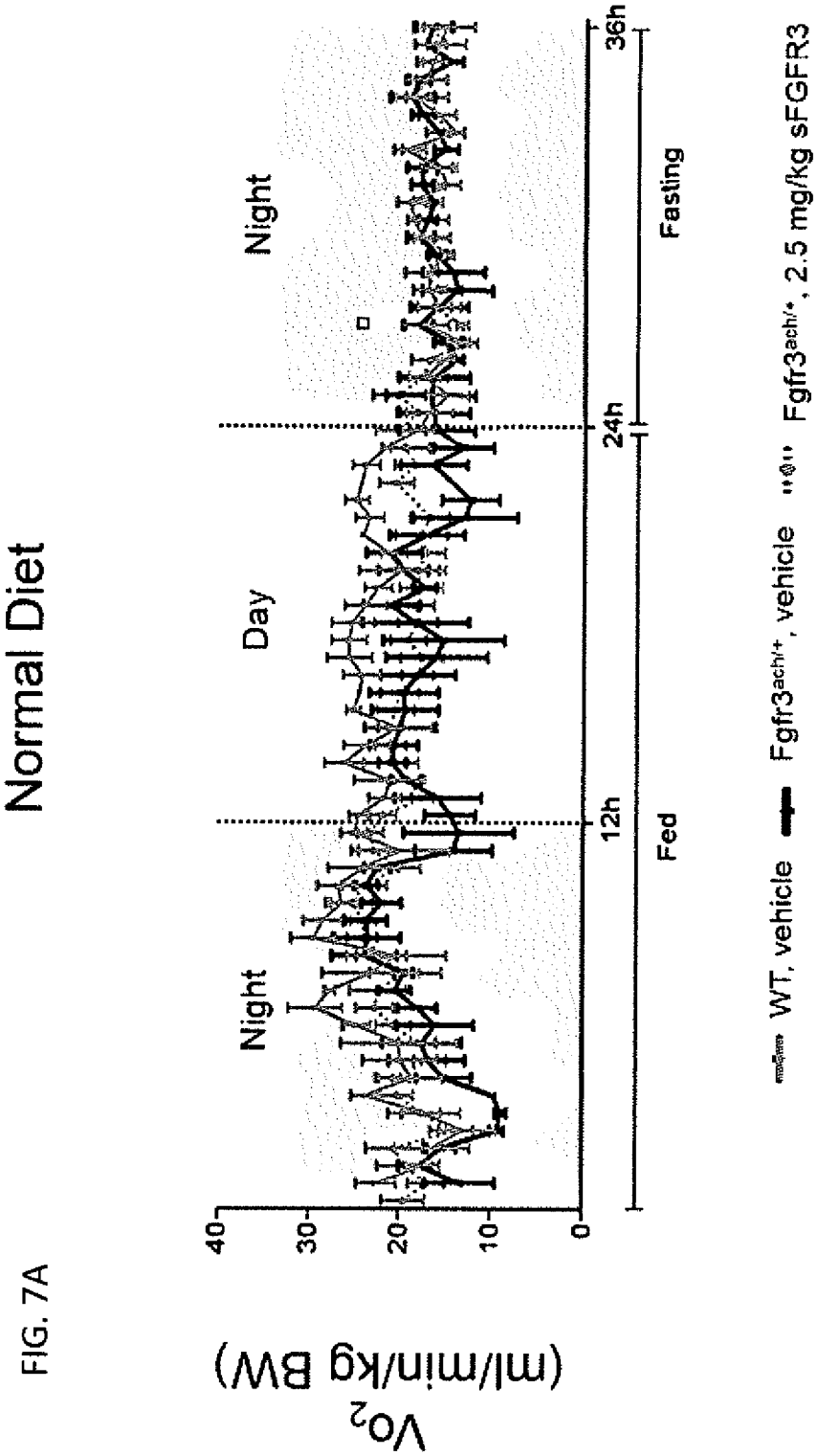

Normal Diet
Night
Day
Night
12h
24h
36h
Fed
Fasting
40
30
20
10
0
VO2
(ml/min/kg BW)
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7A

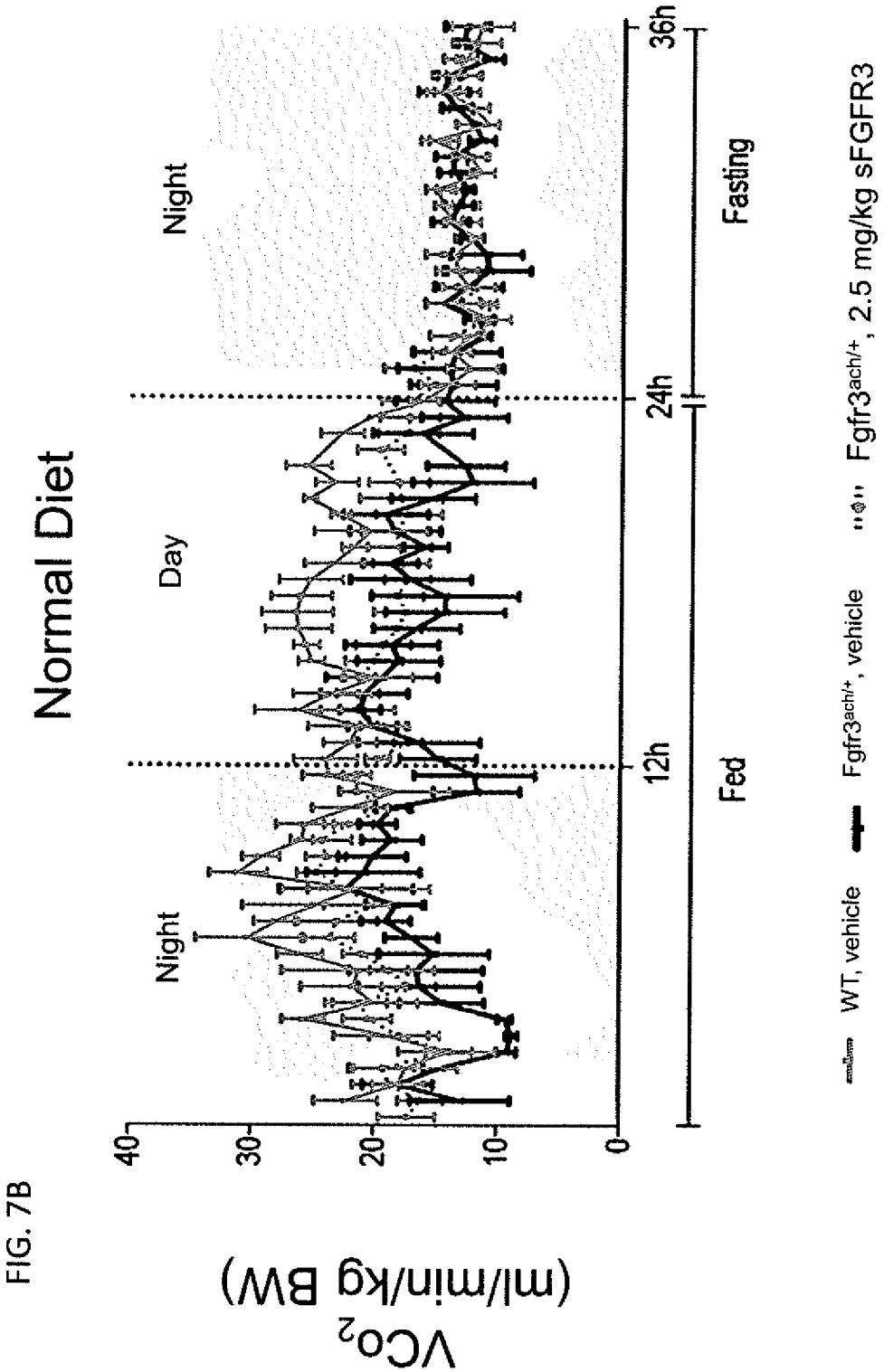

Normal Diet
Night
Day
Night
Fed
Fasting
12h
24h
36h
0
10
20
30
40
VCo2
(ml/min/kg BW)
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7B

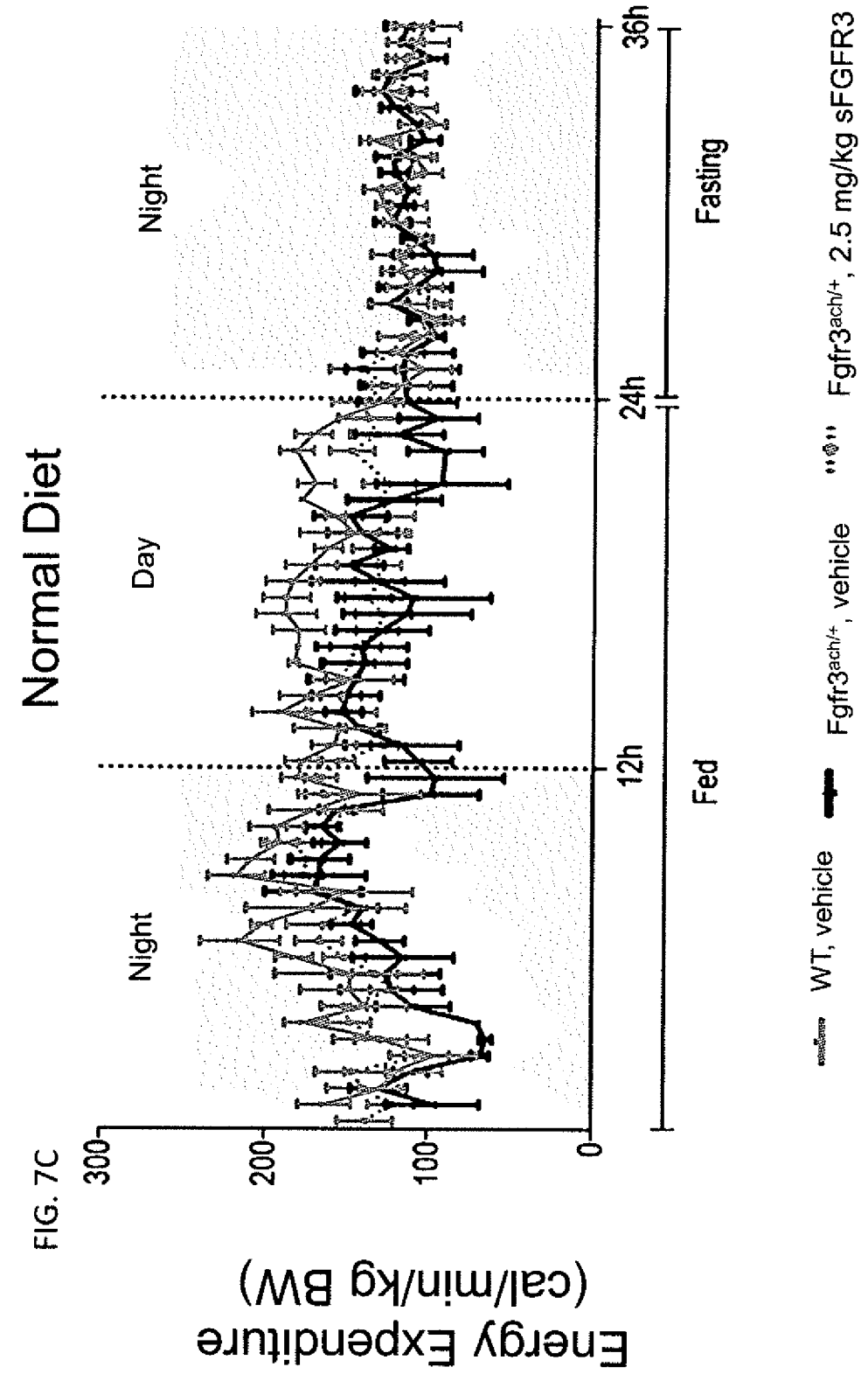

Normal Diet
Night
Day
Night
Fed
Fasting
12h
24h
36h
Energy Expenditure
(cal/min/kg BW)
300
200
100
0
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7C

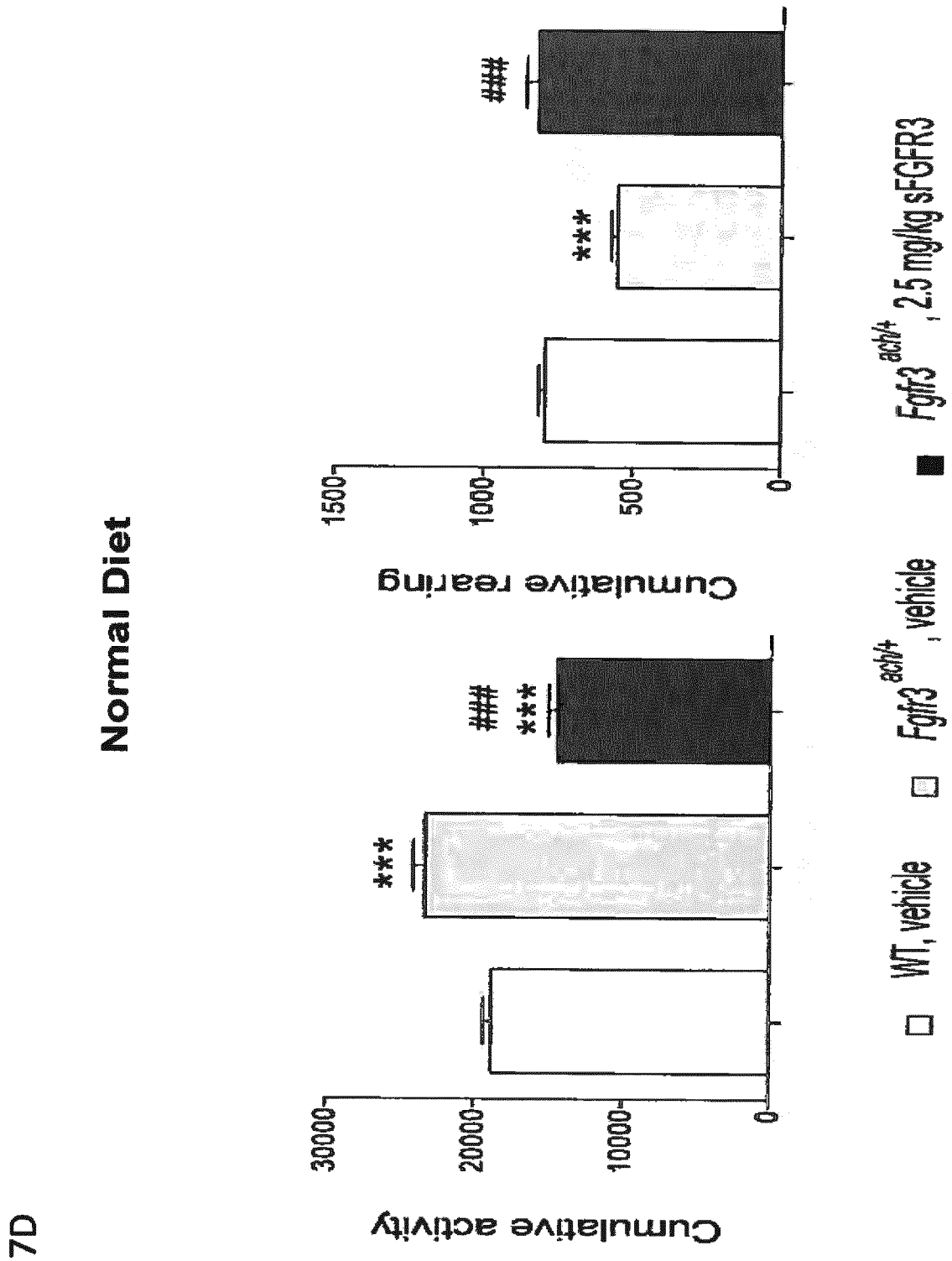

Normal Diet
Cumulative activity
30000
20000
10000
0
***
###
***
Cumulative rearing
1500
1000
500
0
***
###
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 7D

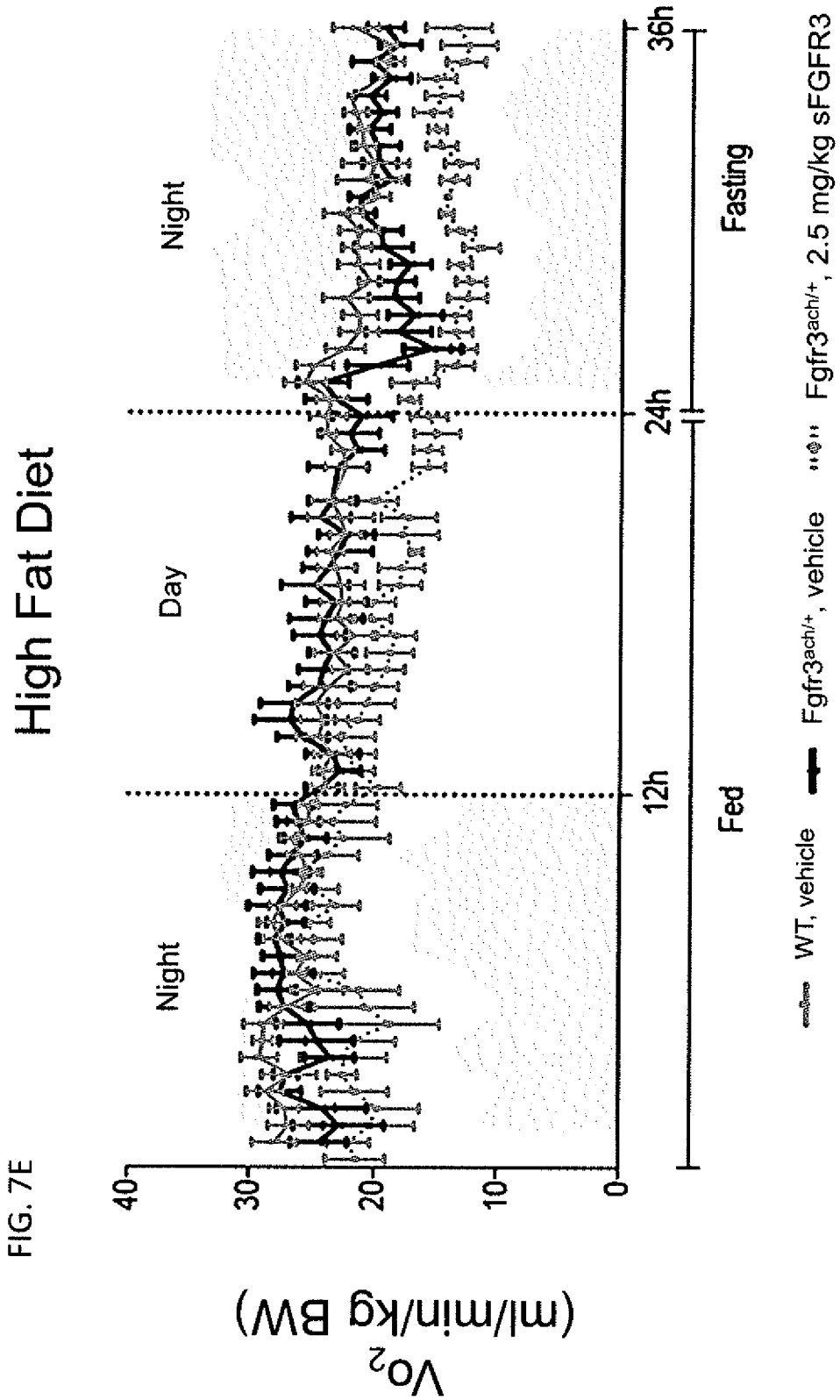

High Fat Diet
Night
Day
Night
Fed
Fasting
12h
24h
36h
40
30
20
10
0
VO2
(ml/min/kg BW)
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7E

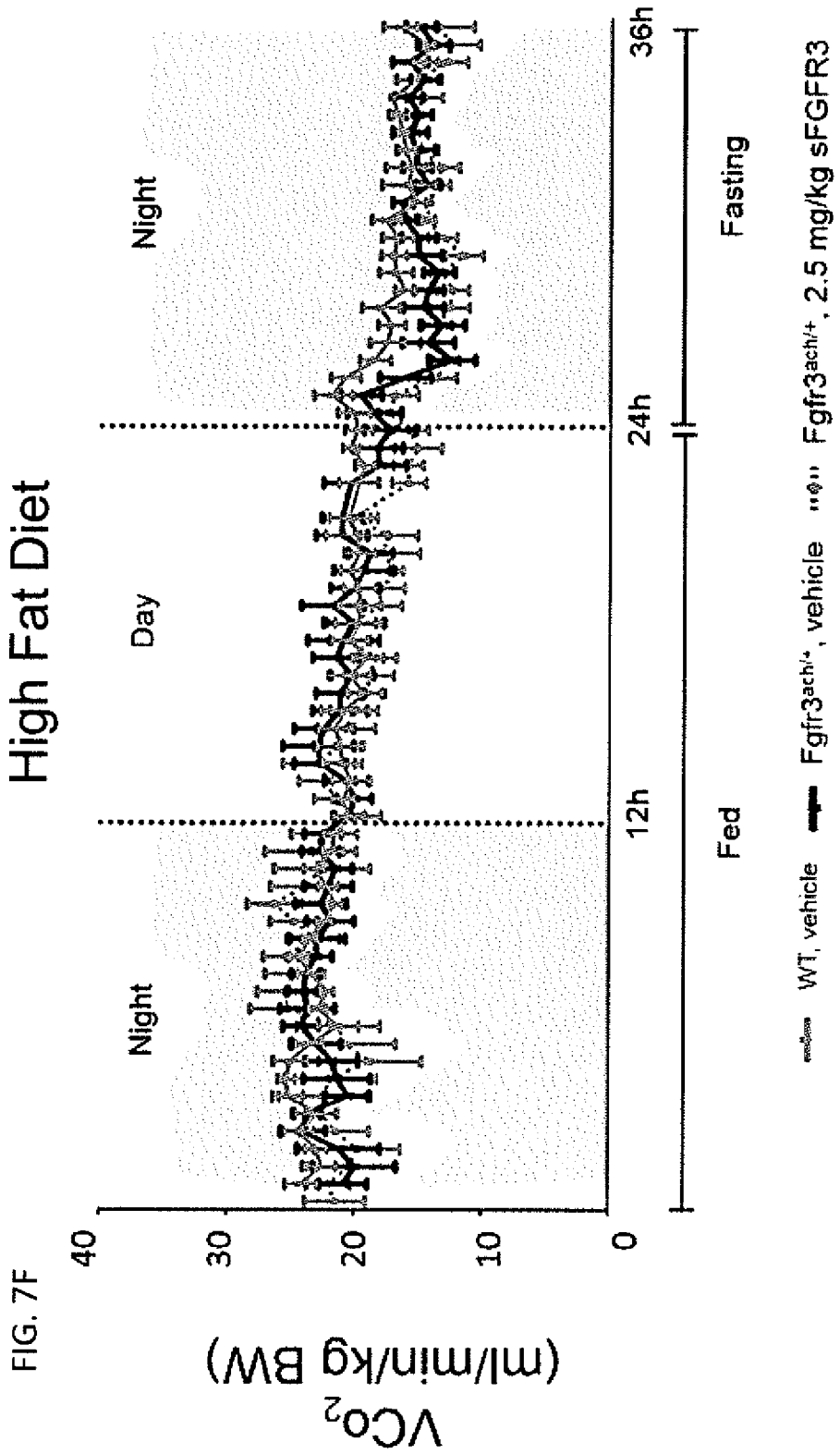

High Fat Diet
Night
Day
Night
12h
24h
36h
Fed
Fasting
VCo2 (ml/min/kg BW)
40
30
20
10
0
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7F

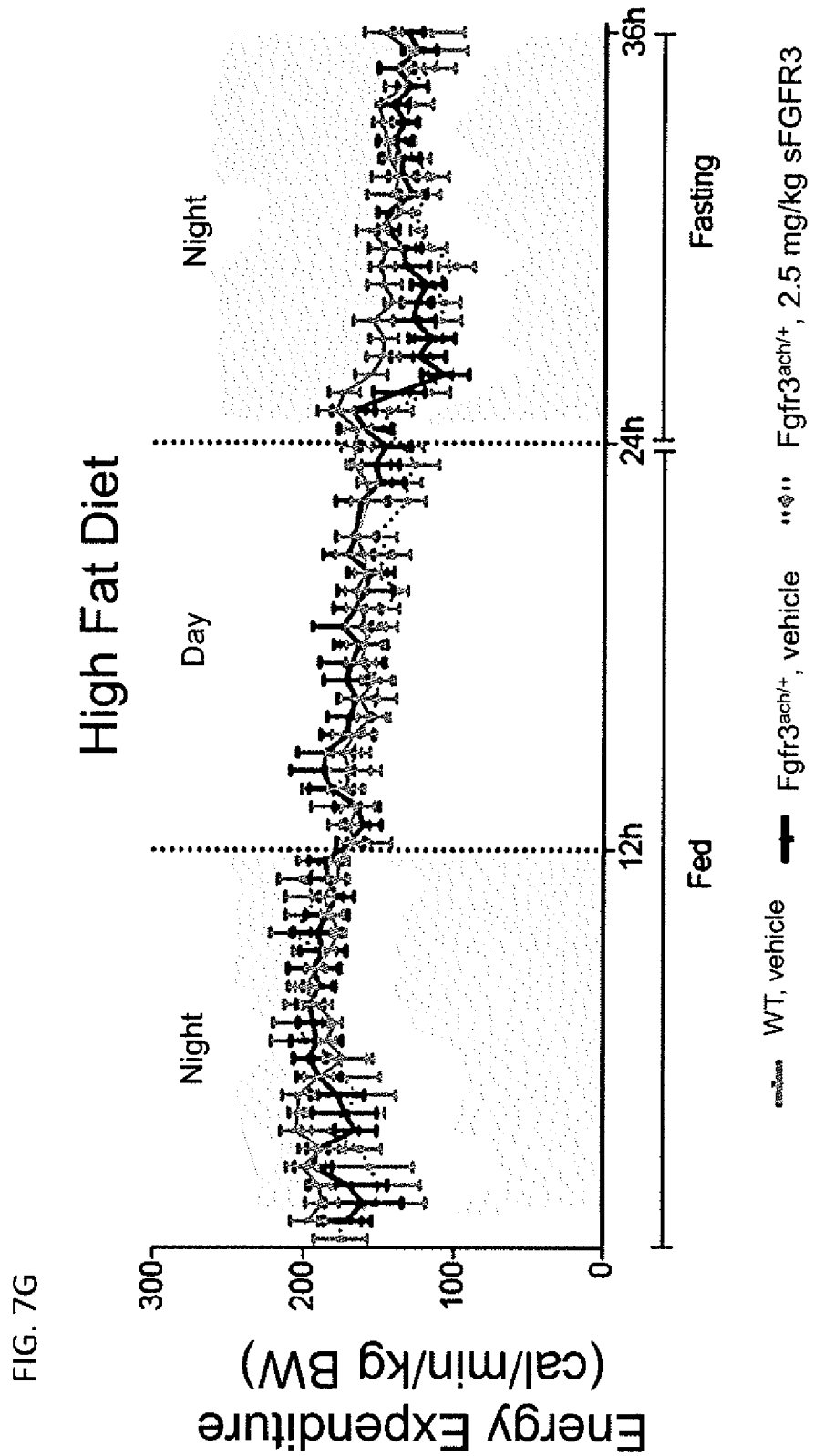

High Fat Diet
Night
Day
Night
Energy Expenditure
(cal/min/kg BW)
300
200
100
0
12h
24h
36h
Fed
Fasting
WT, vehicle
Fgfr3ach/+, vehicle
Fgfr3ach/+, 2.5 mg/kg sFGFR3

FIG. 7G

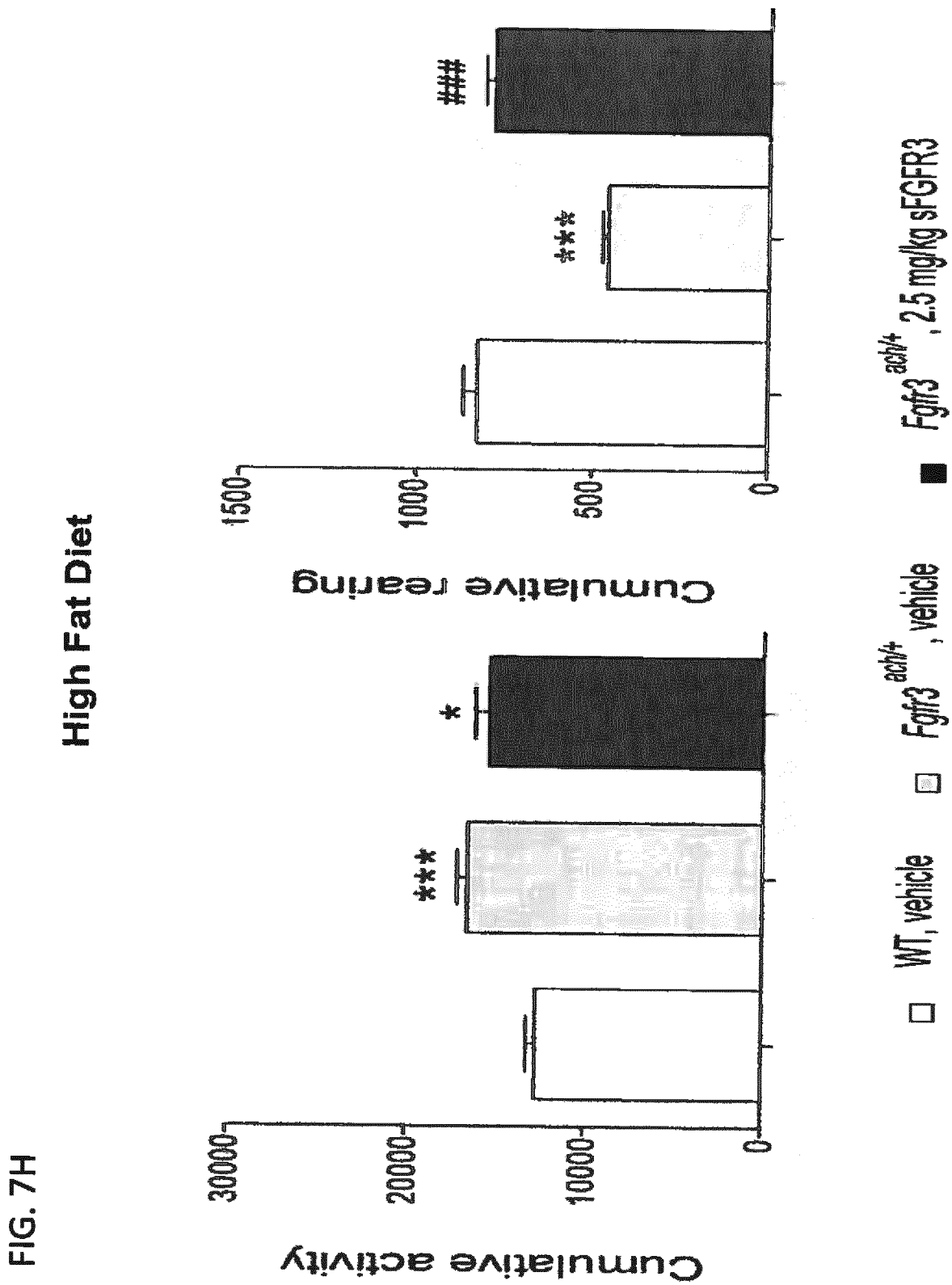

High Fat Diet
Cumulative activity
30000
20000
10000
0
*
***
Cumulative rearing
1500
1000
500
0
***
###
WT, vehicle
Fgfr3 ach/+, vehicle
Fgfr3 ach/+, 2.5 mg/kg sFGFR3

FIG. 7H

SEQUENCE LISTING

<110> THERACHON
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)

<120> TREATMENT OF ABNORMAL VISCERAL FAT DEPOSITION USING SOLUBLE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (SFGFR3) POLYPEPTIDES

<130> 51088-011WO2

<150> US 61/561,140
<151> 2017-09-20

<160> 53

<170> PatentIn version 3.5

<210> 1
<211> 672
<212> PRT
<213> Homo sapiens

<400> 1

```
Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                   10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95
```

```
Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110


Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125


Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140


Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160


Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175


His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190


Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205


Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220


Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240


Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255


Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270


Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285
```

```
Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
    290                 295                 300

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
305                 310                 315                 320

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
                325                 330                 335

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
            340                 345                 350

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
        355                 360                 365

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
    370                 375                 380

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
385                 390                 395                 400

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
                405                 410                 415

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
            420                 425                 430

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
        435                 440                 445

Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
    450                 455                 460

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
465                 470                 475                 480
```

```
His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
                485                 490                 495


Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
            500                 505                 510


Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
        515                 520                 525


Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
    530                 535                 540


Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
545                 550                 555                 560


Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
                565                 570                 575


His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr Met Ile
            580                 585                 590


Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
        595                 600                 605


Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser Thr Asp
    610                 615                 620


Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu Gln Tyr Ser Pro Gly Gly
625                 630                 635                 640


Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Ala
                645                 650                 655


His Asp Leu Leu Pro Pro Ala Pro Pro Ser Ser Gly Gly Ser Arg Thr
            660                 665                 670
```

<210> 2
<211> 526
<212> PRT
<213> Artificial Sequence

<220>
<223> sFGFR3

<400> 2

```
Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                  10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95


Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110


Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125


Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140


Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
```

```
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
    290                 295                 300

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
305                 310                 315                 320

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
                325                 330                 335

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
```

340 345 350

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
355 360 365

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
370 375 380

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
385 390 395 400

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
405 410 415

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
420 425 430

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
435 440 445

Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
450 455 460

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
465 470 475 480

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
485 490 495

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
500 505 510

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp
515 520 525

<210> 3

<211> 418
<212> PRT
<213> Artificial Sequence

<220>
<223> sFGFR3

<400> 3

```
Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                  10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95


Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110


Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125


Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140


Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160
```

```
Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
    290                 295                 300

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
305                 310                 315                 320

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
                325                 330                 335

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
            340                 345                 350
```

```
Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
        355                 360                 365


Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
    370                 375                 380


Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
385                 390                 395                 400


His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
                405                 410                 415


Leu Tyr



<210>  4
<211>  301
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  4

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                   10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
```

```
65                  70                  75                  80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
```

260 265 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
275 280 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr
290 295 300

<210> 5
<211> 349
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 5

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1 5 10 15

Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
20 25 30

Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
35 40 45

Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
50 55 60

Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65 70 75 80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
85 90 95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
100 105 110

```
Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu Ser Leu
    290                 295                 300
```

```
His Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
305                 310                 315                 320


Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro
                325                 330                 335


Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr
            340                 345


<210>  6
<211>  301
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  6

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                   10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95


Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
```

```
            100                 105                 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Ser Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr
```

290 295 300

<210> 7
<211> 512
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 7

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1 5 10 15

Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
20 25 30

Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
35 40 45

Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
50 55 60

Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65 70 75 80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
85 90 95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
100 105 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
115 120 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
130 135 140

```
Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Ser Gly Ser
    290                 295                 300

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Val Phe Pro
305                 310                 315                 320

Tyr Phe Pro Arg Leu Gly Arg Tyr Asn Leu Asn Phe His Glu Ala Gln
                325                 330                 335
```

```
Gln Ala Cys Leu Asp Gln Asp Ala Val Ile Ala Ser Phe Asp Gln Leu
            340                 345                 350

Tyr Asp Ala Trp Arg Gly Gly Leu Asp Trp Cys Asn Ala Gly Trp Leu
        355                 360                 365

Ser Asp Gly Ser Val Gln Tyr Pro Ile Thr Lys Pro Arg Glu Pro Cys
    370                 375                 380

Gly Gly Gln Asn Thr Val Pro Gly Val Arg Asn Tyr Gly Phe Trp Asp
385                 390                 395                 400

Lys Asp Lys Ser Arg Tyr Asp Val Phe Cys Phe Thr Ser Asn Phe Asn
                405                 410                 415

Gly Arg Phe Tyr Tyr Leu Ile His Pro Thr Lys Leu Thr Tyr Asp Glu
            420                 425                 430

Ala Val Gln Ala Cys Leu Asn Asp Gly Ala Gln Ile Ala Lys Val Gly
        435                 440                 445

Gln Ile Phe Ala Ala Trp Lys Ile Leu Gly Tyr Asp Arg Cys Asp Ala
    450                 455                 460

Gly Trp Leu Ala Asp Gly Ser Val Arg Tyr Pro Ile Ser Arg Pro Arg
465                 470                 475                 480

Arg Arg Cys Ser Pro Thr Glu Ala Ala Val Arg Phe Val Gly Phe Pro
                485                 490                 495

Asp Lys Lys His Lys Leu Tyr Gly Val Tyr Cys Phe Arg Ala Tyr Asn
            500                 505                 510
```

<210> 8
<211> 784
<212> PRT

<213> Homo sapiens

<400> 8

```
Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                  10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95


Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110


Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125


Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140


Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160


Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175
```

```
His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu Ser Leu
    290                 295                 300

His Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
305                 310                 315                 320

Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro
                325                 330                 335

Ala Glu Glu Glu Leu Val Glu Ala Asp Glu Ala Gly Ser Val Tyr Ala
            340                 345                 350

Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe Leu Phe Ile Leu Val Val
        355                 360                 365
```

```
Ala Ala Val Thr Leu Cys Arg Leu Arg Ser Pro Pro Lys Lys Gly Leu
    370                 375                 380

Gly Ser Pro Thr Val His Lys Ile Ser Arg Phe Pro Leu Lys Arg Gln
385                 390                 395                 400

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
                405                 410                 415

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
            420                 425                 430

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
        435                 440                 445

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
    450                 455                 460

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
465                 470                 475                 480

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
                485                 490                 495

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
            500                 505                 510

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
        515                 520                 525

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
    530                 535                 540

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
545                 550                 555                 560
```

```
Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
               565                 570                 575

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
            580                 585                 590

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
        595                 600                 605

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
    610                 615                 620

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
625                 630                 635                 640

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
               645                 650                 655

Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
            660                 665                 670

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
        675                 680                 685

His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr Met Ile
    690                 695                 700

Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
705                 710                 715                 720

Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser Thr Asp
               725                 730                 735

Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu Gln Tyr Ser Pro Gly Gly
            740                 745                 750
```

Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Ala
        755   760   765

His Asp Leu Leu Pro Pro Ala Pro Pro Ser Ser Gly Gly Ser Arg Thr
    770   775   780

<210> 9
<211> 784
<212> PRT
<213> Homo sapiens

<400> 9

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1   5   10   15

Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20   25   30

Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35   40   45

Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50   55   60

Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65   70   75   80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85   90   95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100   105   110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115   120   125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val

```
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu Ser Leu
    290                 295                 300

His Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
305                 310                 315                 320

Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro
```

```
                325                 330                 335

Ala Glu Glu Glu Leu Val Glu Ala Asp Glu Ala Gly Ser Val Tyr Ala
            340                 345                 350

Gly Ile Leu Ser Tyr Arg Val Gly Phe Phe Leu Phe Ile Leu Val Val
        355                 360                 365

Ala Ala Val Thr Leu Cys Arg Leu Arg Ser Pro Pro Lys Lys Gly Leu
    370                 375                 380

Gly Ser Pro Thr Val His Lys Ile Ser Arg Phe Pro Leu Lys Arg Gln
385                 390                 395                 400

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
                405                 410                 415

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
            420                 425                 430

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
        435                 440                 445

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
    450                 455                 460

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
465                 470                 475                 480

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
                485                 490                 495

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
            500                 505                 510

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
```

```
        515                 520                 525

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
    530                 535                 540

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
545                 550                 555                 560

Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
                565                 570                 575

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
            580                 585                 590

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
        595                 600                 605

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
    610                 615                 620

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
625                 630                 635                 640

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
                645                 650                 655

Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
            660                 665                 670

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
        675                 680                 685

His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr Met Ile
    690                 695                 700

Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
```

705 710 715 720

Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser Thr Asp
725 730 735

Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu Gln Tyr Ser Pro Gly Gly
740 745 750

Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Ala
755 760 765

His Asp Leu Leu Pro Pro Ala Pro Pro Ser Ser Gly Gly Ser Arg Thr
770 775 780

<210> 10
<211> 2016
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 10
gagtccttgg ggacggagca gcgcgtcgtg gggcgagcgg cagaagtccc gggcccagag 60

cccggccagc aggagcagtt ggtcttcggc agcggggatg ctgtggagct gagctgtccc 120

ccgcccgggg gtggtcccat ggggcccact gtctgggtca aggatggcac agggctggtg 180

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<213> Artificial Sequence

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<223> Synthetic construct

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<220>
<223> Synthetic construct

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<220>
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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

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<220>
<223> Synthetic construct

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<220>
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<212> DNA
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<220>
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<400> 19
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ttcggccagg tggtcatggc ggaggccatc ggcattgaca aggaccgggc cgccaagcct 1440

gtcaccgtag ccgtgaagat gctgaaagac gatgccactg acaaggacct gtcggacctg 1500

gtgtctgaga tggagatgat gaagatgatc gggaaacaca aaaacatcat caacctgctg 1560

ggcgcctgca cgcagggcgg gcccctgtac gtgctggtgg agtacgcggc caagggtaac 1620

ctgcgggagt ttctgcgggc gcggcggccc ccgggcctgg actactcctt cgacacctgc 1680

aagccgcccg aggagcagct caccttcaag gacctggtgt cctgtgccta ccaggtggcc 1740

cggggcatgg agtacttggc ctcccagaag tgcatccaca gggacctggc tgcccgcaat 1800

gtgctggtga ccgaggacaa cgtgatgaag atcgcagact tcgggctggc ccgggacgtg 1860

cacaacctcg actactacaa gaagacaacc aacggccggc tgcccgtgaa gtggatggcg 1920

cctgaggcct tgtttgaccg agtctacact caccagagtg acgtctggtc ctttggggtc 1980

ctgctctggg agatcttcac gctgggggc tccccgtacc ccggcatccc tgtggaggag 2040

ctcttcaagc tgctgaagga gggccaccgc atggacaagc ccgccaactg cacacacgac 2100

ctgtacatga tcatgcggga gtgctggcat gccgcgccct cccagaggcc caccttcaag 2160

cagctggtgg aggacctgga ccgtgtcctt accgtgacgt ccaccgacga gtacctggac 2220

ctgtcggcgc ctttcgagca gtactccccg ggtggccagg acacccccag ctccagctcc 2280

tcaggggacg actccgtgtt tgcccacgac ctgctgcccc cggccccacc cagcagtggg 2340

ggctcgcgga cgtga 2355

<210> 20
<211> 2355
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1073)..(1073)
<223> N is a or c

<400> 20
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cccggccagc aggagcagtt ggtcttcggc agcggggatg ctgtggagct gagctgtccc 120

ccgcccgggg gtggtcccat ggggcccact gtctgggtca aggatggcac agggctggtg 180

ccctcggagc gtgtcctggt ggggccccag cggctgcagg tgctgaatgc ctcccacgag 240

gactccgggg cctacagctg ccggcagcgg ctcacgcagc gcgtactgtg ccacttcagt 300

gtgcgggtga cagacgctcc atcctcggga gatgacgaag acggggagga cgaggctgag 360

gacacaggtg tggacacagg ggcccttac tggacacggc ccgagcggat ggacaagaag 420

ctgctggccg tgccggccgc caacaccgtc cgcttccgct gcccagccgc tggcaacccc 480

actccctcca tctcctggct gaagaacggc agggagttcc gcggcgagca ccgcattgga 540

ggcatcaagc tgcggcatca gcagtggagc ctggtcatgg aaagcgtggt gccctcggac 600

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cgcggcaact acacctgcgt cgtggagaac aagtttggca gcatccggca gacgtacacg      660

ctggacgtgc tggagcgctc cccgcaccgg cccatcctgc aggcggggct gccggccaac      720

cagacggcgg tgctgggcag cgacgtggag ttccactgca aggtgtacag tgacgcacag      780

ccccacatcc agtggctcaa gcacgtggag gtgaatggca gcaaggtggg cccggacggc      840

acaccctacg ttaccgtgct caagacggcg ggcgctaaca ccaccgacaa ggagctagag      900

gttctctcct tgcacaacgt cacctttgag gacgccgggg agtacacctg cctggcgggc      960

aattctattg ggttttctca tcactctgcg tggctggtgg tgctgccagc cgaggaggag     1020

ctggtggagg ctgacgaggc gggcagtgtg tatgcaggca tcctcagcta cgnggtgggc     1080

ttcttcctgt tcatcctggt ggtggcggct gtgacgctct gccgcctgcg cagccccccc     1140

aagaaaggcc tgggctcccc caccgtgcac aagatctccc gcttcccgct caagcgacag     1200

gtgtccctgg agtccaacgc gtccatgagc tccaacacac cactggtgcg catcgcaagg     1260

ctgtcctcag gggagggccc cacgctggcc aatgtctccg agctcgagct gcctgccgac     1320

cccaaatggg agctgtctcg ggcccggctg accctgggca agccccttgg ggagggctgc     1380

ttcggccagg tggtcatggc ggaggccatc ggcattgaca aggaccgggc cgccaagcct     1440

gtcaccgtag ccgtgaagat gctgaaagac gatgccactg acaaggacct gtcggacctg     1500

gtgtctgaga tggagatgat gaagatgatc gggaaacaca aaaacatcat caacctgctg     1560

ggcgcctgca cgcagggcgg gcccctgtac gtgctggtgg agtacgcggc caagggtaac     1620

ctgcgggagt ttctgcgggc gcggcggccc ccgggcctgg actactcctt cgacacctgc     1680

aagccgcccg aggagcagct caccttcaag gacctggtgt cctgtgccta ccaggtggcc     1740

cggggcatgg agtacttggc ctcccagaag tgcatccaca gggacctggc tgcccgcaat     1800

gtgctggtga ccgaggacaa cgtgatgaag atcgcagact tcgggctggc ccgggacgtg     1860

cacaacctcg actactacaa gaagacaacc aacggccggc tgcccgtgaa gtggatggcg     1920

cctgaggcct tgtttgaccg agtctacact caccagagtg acgtctggtc ctttggggtc     1980

ctgctctggg agatcttcac gctgggggggc tccccgtacc ccggcatccc tgtggaggag     2040
```

ctcttcaagc tgctgaagga gggccaccgc atggacaagc ccgccaactg cacacacgac 2100

ctgtacatga tcatgcggga gtgctggcat gccgcgccct cccagaggcc caccttcaag 2160

cagctggtgg aggacctgga ccgtgtcctt accgtgacgt ccaccgacga gtacctggac 2220

ctgtcggcgc ctttcgagca gtactccccg ggtggccagg acacccccag ctccagctcc 2280

tcaggggacg actccgtgtt tgcccacgac ctgctgcccc cggccccacc cagcagtggg 2340

ggctcgcgga cgtga 2355

<210> 21
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 21

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1 5 10 15

Val Ala Gly Ala Ser Ser
20

<210> 22
<211> 672
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 22

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1 5 10 15

Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
20 25 30

```
Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45

Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60

Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220
```

```
Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Ser Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
    290                 295                 300

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
305                 310                 315                 320

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
                325                 330                 335

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
            340                 345                 350

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
        355                 360                 365

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
    370                 375                 380

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
385                 390                 395                 400

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
                405                 410                 415
```

```
Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
            420                 425                 430

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
        435                 440                 445

Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
    450                 455                 460

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
465                 470                 475                 480

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
                485                 490                 495

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
            500                 505                 510

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
        515                 520                 525

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
    530                 535                 540

Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
545                 550                 555                 560

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
                565                 570                 575

His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr Met Ile
            580                 585                 590

Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
        595                 600                 605
```

```
Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser Thr Asp
    610                 615                 620


Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu Gln Tyr Ser Pro Gly Gly
625                 630                 635                 640


Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Ala
                645                 650                 655


His Asp Leu Leu Pro Pro Ala Pro Pro Ser Ser Gly Gly Ser Arg Thr
            660                 665                 670


<210>  23
<211>  720
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  23

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                   10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
```

```
                85                  90                  95

Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
```

```
        275                 280                 285

Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu Ser Leu
    290                 295                 300

His Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
305                 310                 315                 320

Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro
                325                 330                 335

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Pro Leu Val
            340                 345                 350

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala Asn Val
        355                 360                 365

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Ala
    370                 375                 380

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
385                 390                 395                 400

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala Lys Pro
                405                 410                 415

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
            420                 425                 430

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
        435                 440                 445

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Gly Pro
    450                 455                 460

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
```

```
465                 470                 475                 480

Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys
                485                 490                 495

Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser Cys Ala
            500                 505                 510

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
        515                 520                 525

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
    530                 535                 540

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
545                 550                 555                 560

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
                565                 570                 575

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
            580                 585                 590

Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
        595                 600                 605

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
    610                 615                 620

His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr Met Ile
625                 630                 635                 640

Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
                645                 650                 655

Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser Thr Asp
```

660 665 670

Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu Gln Tyr Ser Pro Gly Gly
675 680 685

Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Ala
690 695 700

His Asp Leu Leu Pro Pro Ala Pro Pro Ser Ser Gly Gly Ser Arg Thr
705 710 715 720

<210> 24
<211> 512
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 24

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1 5 10 15

Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
20 25 30

Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
35 40 45

Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
50 55 60

Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65 70 75 80

Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
85 90 95

```
Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110

Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Ser Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285
```

```
Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Ser Gly Ser
    290                 295                 300

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Val Phe Pro
305                 310                 315                 320

Tyr Phe Pro Arg Leu Gly Arg Tyr Asn Leu Asn Phe His Glu Ala Gln
                325                 330                 335

Gln Ala Cys Leu Asp Gln Asp Ala Val Ile Ala Ser Phe Asp Gln Leu
            340                 345                 350

Tyr Asp Ala Trp Arg Gly Gly Leu Asp Trp Cys Asn Ala Gly Trp Leu
        355                 360                 365

Ser Asp Gly Ser Val Gln Tyr Pro Ile Thr Lys Pro Arg Glu Pro Cys
    370                 375                 380

Gly Gly Gln Asn Thr Val Pro Gly Val Arg Asn Tyr Gly Phe Trp Asp
385                 390                 395                 400

Lys Asp Lys Ser Arg Tyr Asp Val Phe Cys Phe Thr Ser Asn Phe Asn
                405                 410                 415

Gly Arg Phe Tyr Tyr Leu Ile His Pro Thr Lys Leu Thr Tyr Asp Glu
            420                 425                 430

Ala Val Gln Ala Cys Leu Asn Asp Gly Ala Gln Ile Ala Lys Val Gly
        435                 440                 445

Gln Ile Phe Ala Ala Trp Lys Ile Leu Gly Tyr Asp Arg Cys Asp Ala
    450                 455                 460

Gly Trp Leu Ala Asp Gly Ser Val Arg Tyr Pro Ile Ser Arg Pro Arg
465                 470                 475                 480
```

```
Arg Arg Cys Ser Pro Thr Glu Ala Ala Val Arg Phe Val Gly Phe Pro
                485                 490                 495


Asp Lys Lys His Lys Leu Tyr Gly Val Tyr Cys Phe Arg Ala Tyr Asn
            500                 505                 510


<210>  25
<211>  560
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  25

Glu Ser Leu Gly Thr Glu Gln Arg Val Val Gly Arg Ala Ala Glu Val
1               5                   10                  15


Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln Leu Val Phe Gly Ser Gly
            20                  25                  30


Asp Ala Val Glu Leu Ser Cys Pro Pro Pro Gly Gly Gly Pro Met Gly
        35                  40                  45


Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg
    50                  55                  60


Val Leu Val Gly Pro Gln Arg Leu Gln Val Leu Asn Ala Ser His Glu
65                  70                  75                  80


Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu
                85                  90                  95


Cys His Phe Ser Val Arg Val Thr Asp Ala Pro Ser Ser Gly Asp Asp
            100                 105                 110


Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr Gly Val Asp Thr Gly Ala
```

```
        115                 120                 125

Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp Lys Lys Leu Leu Ala Val
    130                 135                 140

Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro Ala Ala Gly Asn Pro
145                 150                 155                 160

Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly Arg Glu Phe Arg Gly Glu
                165                 170                 175

His Arg Ile Gly Gly Ile Lys Leu Arg His Gln Gln Trp Ser Leu Val
            180                 185                 190

Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys Val Val
        195                 200                 205

Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr Tyr Thr Leu Asp Val Leu
    210                 215                 220

Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn
225                 230                 235                 240

Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr
                245                 250                 255

Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu Val Asn
            260                 265                 270

Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys
        275                 280                 285

Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu Ser Leu
    290                 295                 300

His Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
```

```
305                 310                 315                 320

Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro
                325                 330                 335

Val Ser Leu Glu Ser Asn Ala Ser Met Ser Ser Asn Thr Ser Gly Ser
            340                 345                 350

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Val Phe Pro
        355                 360                 365

Tyr Phe Pro Arg Leu Gly Arg Tyr Asn Leu Asn Phe His Glu Ala Gln
    370                 375                 380

Gln Ala Cys Leu Asp Gln Asp Ala Val Ile Ala Ser Phe Asp Gln Leu
385                 390                 395                 400

Tyr Asp Ala Trp Arg Gly Gly Leu Asp Trp Cys Asn Ala Gly Trp Leu
                405                 410                 415

Ser Asp Gly Ser Val Gln Tyr Pro Ile Thr Lys Pro Arg Glu Pro Cys
            420                 425                 430

Gly Gly Gln Asn Thr Val Pro Gly Val Arg Asn Tyr Gly Phe Trp Asp
        435                 440                 445

Lys Asp Lys Ser Arg Tyr Asp Val Phe Cys Phe Thr Ser Asn Phe Asn
    450                 455                 460

Gly Arg Phe Tyr Tyr Leu Ile His Pro Thr Lys Leu Thr Tyr Asp Glu
465                 470                 475                 480

Ala Val Gln Ala Cys Leu Asn Asp Gly Ala Gln Ile Ala Lys Val Gly
                485                 490                 495

Gln Ile Phe Ala Ala Trp Lys Ile Leu Gly Tyr Asp Arg Cys Asp Ala
```

500 505 510

Gly Trp Leu Ala Asp Gly Ser Val Arg Tyr Pro Ile Ser Arg Pro Arg
515 520 525

Arg Arg Cys Ser Pro Thr Glu Ala Ala Val Arg Phe Val Gly Phe Pro
530 535 540

Asp Lys Lys His Lys Leu Tyr Gly Val Tyr Cys Phe Arg Ala Tyr Asn
545 550 555 560

<210> 26
<211> 155
<212> PRT
<213> Homo sapiens

<400> 26

Met Ala Glu Gly Glu Ile Thr Thr Phe Thr Ala Leu Thr Glu Lys Phe
1 5 10 15

Asn Leu Pro Pro Gly Asn Tyr Lys Lys Pro Lys Leu Leu Tyr Cys Ser
20 25 30

Asn Gly Gly His Phe Leu Arg Ile Leu Pro Asp Gly Thr Val Asp Gly
35 40 45

Thr Arg Asp Arg Ser Asp Gln His Ile Gln Leu Gln Leu Ser Ala Glu
50 55 60

Ser Val Gly Glu Val Tyr Ile Lys Ser Thr Glu Thr Gly Gln Tyr Leu
65 70 75 80

Ala Met Asp Thr Asp Gly Leu Leu Tyr Gly Ser Gln Thr Pro Asn Glu
85 90 95

Glu Cys Leu Phe Leu Glu Arg Leu Glu Glu Asn His Tyr Asn Thr Tyr
100 105 110

```
Ile Ser Lys Lys His Ala Glu Lys Asn Trp Phe Val Gly Leu Lys Lys
        115                 120                 125


Asn Gly Ser Cys Lys Arg Gly Pro Arg Thr His Tyr Gly Gln Lys Ala
    130                 135                 140


Ile Leu Phe Leu Pro Leu Pro Val Ser Ser Asp
145                 150                 155


<210>  27
<211>  288
<212>  PRT
<213>  Homo sapiens

<400>  27

Met Val Gly Val Gly Gly Gly Asp Val Glu Asp Val Thr Pro Arg Pro
1               5                   10                  15


Gly Gly Cys Gln Ile Ser Gly Arg Gly Ala Arg Gly Cys Asn Gly Ile
            20                  25                  30


Pro Gly Ala Ala Ala Trp Glu Ala Ala Leu Pro Arg Arg Arg Pro Arg
        35                  40                  45


Arg His Pro Ser Val Asn Pro Arg Ser Arg Ala Ala Gly Ser Pro Arg
    50                  55                  60


Thr Arg Gly Arg Arg Thr Glu Glu Arg Pro Ser Gly Ser Arg Leu Gly
65                  70                  75                  80


Asp Arg Gly Arg Gly Arg Ala Leu Pro Gly Gly Arg Leu Gly Gly Arg
                85                  90                  95


Gly Arg Gly Arg Ala Pro Glu Arg Val Gly Gly Arg Gly Arg Gly Arg
            100                 105                 110
```

```
Gly Thr Ala Ala Pro Arg Ala Ala Pro Ala Ala Arg Gly Ser Arg Pro
        115                 120                 125

Gly Pro Ala Gly Thr Met Ala Ala Gly Ser Ile Thr Thr Leu Pro Ala
    130                 135                 140

Leu Pro Glu Asp Gly Gly Ser Gly Ala Phe Pro Pro Gly His Phe Lys
145                 150                 155                 160

Asp Pro Lys Arg Leu Tyr Cys Lys Asn Gly Gly Phe Phe Leu Arg Ile
                165                 170                 175

His Pro Asp Gly Arg Val Asp Gly Val Arg Glu Lys Ser Asp Pro His
            180                 185                 190

Ile Lys Leu Gln Leu Gln Ala Glu Glu Arg Gly Val Val Ser Ile Lys
        195                 200                 205

Gly Val Cys Ala Asn Arg Tyr Leu Ala Met Lys Glu Asp Gly Arg Leu
    210                 215                 220

Leu Ala Ser Lys Cys Val Thr Asp Glu Cys Phe Phe Phe Glu Arg Leu
225                 230                 235                 240

Glu Ser Asn Asn Tyr Asn Thr Tyr Arg Ser Arg Lys Tyr Thr Ser Trp
                245                 250                 255

Tyr Val Ala Leu Lys Arg Thr Gly Gln Tyr Lys Leu Gly Ser Lys Thr
            260                 265                 270

Gly Pro Gly Gln Lys Ala Ile Leu Phe Leu Pro Met Ser Ala Lys Ser
        275                 280                 285
```

<210> 28
<211> 208
<212> PRT

<213> Homo sapiens

<400> 28

```
Met Ala Pro Leu Gly Glu Val Gly Asn Tyr Phe Gly Val Gln Asp Ala
1               5                  10                  15

Val Pro Phe Gly Asn Val Pro Val Leu Pro Val Asp Ser Pro Val Leu
            20                  25                  30

Leu Ser Asp His Leu Gly Gln Ser Glu Ala Gly Gly Leu Pro Arg Gly
        35                  40                  45

Pro Ala Val Thr Asp Leu Asp His Leu Lys Gly Ile Leu Arg Arg Arg
    50                  55                  60

Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Glu Ile Phe Pro Asn Gly
65                  70                  75                  80

Thr Ile Gln Gly Thr Arg Lys Asp His Ser Arg Phe Gly Ile Leu Glu
                85                  90                  95

Phe Ile Ser Ile Ala Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser
            100                 105                 110

Gly Leu Tyr Leu Gly Met Asn Glu Lys Gly Glu Leu Tyr Gly Ser Glu
        115                 120                 125

Lys Leu Thr Gln Glu Cys Val Phe Arg Glu Gln Phe Glu Glu Asn Trp
    130                 135                 140

Tyr Asn Thr Tyr Ser Ser Asn Leu Tyr Lys His Val Asp Thr Gly Arg
145                 150                 155                 160

Arg Tyr Tyr Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Glu Gly Thr
                165                 170                 175
```

```
Arg Thr Lys Arg His Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val
            180                 185                 190


Asp Pro Asp Lys Val Pro Glu Leu Tyr Lys Asp Ile Leu Ser Gln Ser
        195                 200                 205


<210>  29
<211>  207
<212>  PRT
<213>  Homo sapiens

<400>  29

Met Tyr Ser Ala Pro Ser Ala Cys Thr Cys Leu Cys Leu His Phe Leu
1               5                   10                  15


Leu Leu Cys Phe Gln Val Gln Val Leu Val Ala Glu Glu Asn Val Asp
            20                  25                  30


Phe Arg Ile His Val Glu Asn Gln Thr Arg Ala Arg Asp Asp Val Ser
        35                  40                  45


Arg Lys Gln Leu Arg Leu Tyr Gln Leu Tyr Ser Arg Thr Ser Gly Lys
    50                  55                  60


His Ile Gln Val Leu Gly Arg Arg Ile Ser Ala Arg Gly Glu Asp Gly
65                  70                  75                  80


Asp Lys Tyr Ala Gln Leu Leu Val Glu Thr Asp Thr Phe Gly Ser Gln
                85                  90                  95


Val Arg Ile Lys Gly Lys Glu Thr Glu Phe Tyr Leu Cys Met Asn Arg
            100                 105                 110


Lys Gly Lys Leu Val Gly Lys Pro Asp Gly Thr Ser Lys Glu Cys Val
        115                 120                 125


Phe Ile Glu Lys Val Leu Glu Asn Asn Tyr Thr Ala Leu Met Ser Ala
```

130 135 140

Lys Tyr Ser Gly Trp Tyr Val Gly Phe Thr Lys Lys Gly Arg Pro Arg
145 150 155 160

Lys Gly Pro Lys Thr Arg Glu Asn Gln Gln Asp Val His Phe Met Lys
165 170 175

Arg Tyr Pro Lys Gly Gln Pro Glu Leu Gln Lys Pro Phe Lys Tyr Thr
180 185 190

Thr Val Thr Lys Arg Ser Arg Arg Ile Arg Pro Thr His Pro Ala
195 200 205

<210> 30
<211> 216
<212> PRT
<213> Homo sapiens

<400> 30

Met Arg Ser Gly Cys Val Val Val His Val Trp Ile Leu Ala Gly Leu
1 5 10 15

Trp Leu Ala Val Ala Gly Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro
20 25 30

His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr
35 40 45

Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala
50 55 60

Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu
65 70 75 80

Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His
85 90 95

```
Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu
            100                 105                 110


Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro
        115                 120                 125


Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser
    130                 135                 140


Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu
145                 150                 155                 160


Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro
                165                 170                 175


Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu
            180                 185                 190


Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala
        195                 200                 205


Val Arg Ser Pro Ser Phe Glu Lys
    210                 215


<210>  31
<211>  209
<212>  PRT
<213>  Homo sapiens

<400>  31

Met Asp Ser Asp Glu Thr Gly Phe Glu His Ser Gly Leu Trp Val Ser
1               5                   10                  15


Val Leu Ala Gly Leu Leu Leu Gly Ala Cys Gln Ala His Pro Ile Pro
            20                  25                  30
```

```
Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Gln Arg Tyr
        35                  40                  45

Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His Leu Glu Ile Arg
    50                  55                  60

Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser Pro Glu Ser Leu
65                  70                  75                  80

Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln Ile Leu Gly Val
                85                  90                  95

Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly Ala Leu Tyr Gly
            100                 105                 110

Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg Glu Leu Leu Leu
        115                 120                 125

Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His Gly Leu Pro Leu
    130                 135                 140

His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro Ala Pro Arg Gly
145                 150                 155                 160

Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro Ala Leu Pro Glu
                165                 170                 175

Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val Gly Ser Ser Asp
            180                 185                 190

Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser Pro Ser Tyr Ala
        195                 200                 205

Ser
```

<210> 32
<211> 2019
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 32
atggagtctc tgggcacaga gcagagagtc gtgggcagag ccgctgaagt gcctggacct 60

gagcctggcc agcaggaaca gctggtcttt ggctctggcg acgccgtgga actgagctgt 120

cctccacctg gcggaggccc tatgggacct accgtgtggg tcaaggatgg caccggactg 180

gtgcctagcg agagggtgct cgtgggacct cagagactgc aggtcctgaa cgccagccac 240

gaggatagcg gcgcctacag ctgcagacag agactgaccc agcgggtgct gtgccacttc 300

agcgtcagag tgaccgatgc ccccagcagc ggagatgacg aggatggcga ggatgaggcc 360

gaggatacag gcgtggacac aggcgcccct tactggacca gacccgagcg gatggacaag 420

aaactgctgg ccgtgcctgc cgccaacacc gtgcggttta gatgccctgc cgccggaaac 480

cccaccccca gcatctcttg gctgaagaac ggcagagagt tccggggcga gcaccggatc 540

ggcggcatta agctgagaca ccagcagtgg tccctggtca tggaaagcgt ggtgcccagc 600

gaccggggca actacacctg tgtggtggaa aacaagttcg gcagcatccg gcagacctac 660

accctggacg tgctggaaag aagcccccac agacctatcc tgcaggccgg actgcctgcc 720

aatcagacag ccgtgctggg cagcgacgtg gaatttcaca gcaaggtgta cagcgacgcc 780

cagccccaca tccagtggct gaagcacgtg gaagtgaacg gcagcaaagt gggccccgac 840

ggcacccctt acgtgaccgt gctgaaagtg tccctggaaa gcaacgccag catgagcagc 900

aacacccccc tcgtgcggat cgccagactg tctagcggag agggccctac cctggccaac 960

gtgtccgaac tggaactgcc cgccgacccc aagtgggagc tgagcagagc tagactgacc 1020

ctgggcaagc ctctgggcga gggctgtttt ggacaggtgg tcatggccga ggccatcggc 1080

atcgacaagg acagagccgc caagcctgtg accgtggccg tgaagatgct gaaggacgac 1140

gccaccgaca aggacctgag cgacctggtg tccgagatgg aaatgatgaa gatgatcggc 1200

aagcacaaga acatcatcaa cctgctgggc gcctgcaccc agggcggacc tctgtacgtg 1260

ctggtggaat acgccgccaa gggcaacctg agagagttcc tgagagccag aaggcccccc 1320

ggcctggact acagcttcga tacctgcaag ccccccgaag aacagctgac cttcaaggat 1380

ctggtgtcct gcgcctatca ggtggccaga ggcatggaat acctggccag ccagaagtgc 1440

atccaccggg atctggccgc cagaaacgtg ctggtcaccg aggacaacgt gatgaagatc 1500

gccgacttcg gcctggcccg ggacgtgcac aacctggact actacaagaa aaccaccaac 1560

ggccggctgc ccgtgaagtg gatggccccc gaggccctgt tcgacagagt gtacacccac 1620

cagagcgacg tgtggtcctt cggcgtgctg ctgtgggaga tctttaccct gggcggcagc 1680

ccttaccccg gcatccctgt ggaagaactg ttcaagctgc tgaaagaggg ccacagaatg 1740

gacaagcccg ccaactgcac ccacgacctg tacatgatca tgagagagtg ctggcacgcc 1800

gctcccagcc agaggcctac ctttaagcag ctggtggaag atctggaccg ggtgctgacc 1860

gtgaccagca ccgacgagta cctggatctg agcgcccccc tcgagcagta ctctcctggc 1920

ggccaggata cccctagcag cagctctagc ggcgacgaca gcgtgttcgc ccacgatctg 1980

ctgcctccag cccctcctag ctctggcggc tctagaacc 2019

<210> 33
<211> 1491
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 33
atggagagcc tgggcacaga acagagagtc gtgggcagag ccgccgaagt gcctggacct 60

gaacctggcc agcaggaaca gctggtcttt ggctctggcg acgccgtgga actgagctgt 120

cctccacctg gcggaggccc tatgggacct accgtgtggg tcaaggatgg caccggactg 180

gtgcctagcg agagggtgct cgtgggacct cagagactgc aggtcctgaa cgccagccac 240

gaggatagcg gcgcctacag ctgcagacag agactgaccc agcgggtgct gtgccacttc 300

agcgtcagag tgaccgatgc ccccagcagc ggagatgacg aggatggcga ggatgaggcc 360

gaggatacag gcgtggacac aggcgcccct tactggacca gacccgagcg gatggacaag 420

aaactgctgg ccgtgcctgc cgccaacacc gtgcggttta gatgccctgc cgccggaaac 480

cccaccccca gcatctcttg gctgaagaac ggcagagagt tccggggcga gcaccggatc 540

ggcggcatta agctgagaca ccagcagtgg tccctggtca tggaaagcgt ggtgcccagc 600

gaccggggca actacacctg tgtggtggaa aacaagttcg gcagcatccg gcagacctac 660

accctggacg tgctggaaag aagcccccac agacctatcc tgcaggccgg actgcctgcc 720

aatcagacag ccgtgctggg cagcgacgtg gaatttcact gcaaggtgta cagcgacgcc 780

cagccccaca tccagtggct gaagcacgtg gaagtgaacg gcagcaaagt gggccccgac 840

ggcacccctt acgtgaccgt gctgaaagtg tccctggaaa gcaacgccag catgagcagc 900

aacaccagcg gcagcggctc tggcagcgga tctggttctg gctccggcag cgtggtgttc 960

ccctacttcc cccggctggg ccggtacaac ctgaactttc atgaggccca gcaggcctgc 1020

ctggaccagg atgccgtgat cgccagcttc gaccagctgt acgatgcttg gagaggcggc 1080

ctggactggt gcaatgccgg ctggctgtct gacggcagcg tgcagtaccc catcaccaag 1140

cccagagagc cctgcggcgg acagaatacc gtgcccggcg tgcggaacta cggcttctgg 1200

gacaaggaca agagcagata cgacgtgttc tgcttcacca gcaacttcaa cggccggttc 1260

tactacctga tccaccccac caagctgacc tacgacgagg ccgtgcaggc ctgtctgaac 1320

gatggcgccc agatcgccaa agtgggacag atcttcgccg cctggaagat cctgggctac 1380

gacagatgtg acgccggatg gctggccgac ggctccgtgc ggtatcccat cagccggcct 1440

agaagaagat gcagccctac cgaggccgcc gtcagattcg tgggcttccc c 1491

<210> 34
<211> 1710
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 34
atgggagcac cagcttgtgc cctggctctg tgtgtggccg tggctattgt ggctggcgcc 60

tctagcgaga gcctgggcac agaacagaga gtcgtgggca gagccgccga agtgcctgga 120

cctgaacctg gccagcagga acagctggtc tttggctctg gcgacgccgt ggaactgagc 180

tgtcctccac ctggcggagg ccctatggga cctaccgtgt gggtcaagga tggcaccgga 240

ctggtgccta gcgagagggt gctcgtggga cctcagagac tgcaggtcct gaacgccagc 300

cacgaggata gcggcgccta cagctgcaga cagagactga cccagcgggt gctgtgccac 360

ttcagcgtca gagtgaccga tgcccccagc agcggagatg acgaggatgg cgaggatgag 420

gccgaggata caggcgtgga cacaggcgcc ccttactgga ccagacccga gcggatggac 480

aagaaactgc tggccgtgcc tgccgccaac accgtgcggt ttagatgccc tgccgccgga 540

aaccccaccc ccagcatctc ttggctgaag aacggcagag agttccgggg cgagcaccgg 600

atcggcggca ttaagctgag acaccagcag tggtccctgg tcatggaaag cgtggtgccc 660

agcgaccggg gcaactacac ctgtgtggtg gaaaacaagt tcggcagcat ccggcagacc 720

tacaccctgg acgtgctgga aagaagcccc cacagaccta tcctgcaggc cggactgcct 780

gccaatcaga cagccgtgct gggcagcgac gtggaatttc actgcaaggt gtacagcgac 840

gcccagcccc acatccagtg gctgaagcac gtggaagtga acggcagcaa agtgggcccc 900

gacggcaccc cttacgtgac cgtgctgaaa accgctggcg ccaacaccac cgacaaagaa 960

ctggaagtgc tgagcctgca caacgtgacc ttcgaggacg ccggcgagta cacctgtctg 1020

gccggcaata gcatcggctt cagccaccac tctgcctggc tggtggtgct gccaggcgga 1080

ggctctgtgt ccctggaaag caacgccagc atgagcagca acaccagcgg cagcggctct 1140

ggcagcggat ctggttctgg ctccggcagc gtggtgttcc cctacttccc ccggctgggc 1200

cggtacaacc tgaactttca tgaggcccag caggcctgcc tggaccagga tgccgtgatc 1260

gccagcttcg accagctgta cgatgcttgg agaggcggcc tggactggtg caatgccggc 1320

tggctgtctg acggcagcgt gcagtacccc atcaccaagc ccagagagcc ctgcggcgga 1380

cagaataccg tgcccggcgt gcggaactac ggcttctggg acaaggacaa gagcagatac 1440

gacgtgttct gcttcaccag caacttcaac ggccggttct actacctgat ccaccccacc 1500

aagctgacct acgacgaggc cgtgcaggcc tgtctgaacg atggcgccca gatcgccaaa 1560

gtgggacaga tcttcgccgc ctggaagatc ctgggctacg acagatgtga cgccggatgg 1620

ctggccgacg gctccgtgcg gtatcccatc agccggccta gaagaagatg cagccctacc 1680

gaggccgccg tcagattcgt gggcttcccc 1710

<210> 35
<211> 236
<212> PRT
<213> Homo sapiens

<400> 35

Gly Gly Gly Gly Ala Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
1 5 10 15

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
20 25 30

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
35 40 45

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
50 55 60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

```
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
        115                 120                 125


Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130                 135                 140


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


Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
                165                 170                 175


Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
            180                 185                 190


Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
        195                 200                 205


Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
    210                 215                 220


Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225                 230                 235


<210>  36
<211>  236
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  36

Gly Gly Gly Gly Ala Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
1               5                   10                  15
```

```
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
            20                  25                  30

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
        35                  40                  45

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
    50                  55                  60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65                  70                  75                  80

Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
                85                  90                  95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100                 105                 110

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
        115                 120                 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130                 135                 140

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

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
                165                 170                 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
            180                 185                 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
        195                 200                 205
```

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
    210   215   220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225   230   235

<210> 37
<211> 585
<212> PRT
<213> Homo sapiens

<400> 37

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1   5   10   15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20   25   30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35   40   45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50   55   60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65   70   75   80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85   90   95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100   105   110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115   120   125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg

```
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
```

```
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

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

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
```

515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 38
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 38

Gly Gly Gly Gly Ala Gly Gly Gly Gly
1 5

<210> 39
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct

<400> 39

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 40

<211> 208
<212> PRT
<213> Homo sapiens

<400> 40

```
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
1               5                  10                  15


Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30


Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45


Ala Thr Asn Ser Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
    50                  55                  60


Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
65                  70                  75                  80


Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
                85                  90                  95


Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110


Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125


Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140


Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160


Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175
```

```
Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190


Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205


<210>  41
<211>  251
<212>  PRT
<213>  Homo sapiens

<400>  41

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1               5                   10                  15


Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30


Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45


Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60


Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80


Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95


Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110


Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125
```

```
Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140


Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160


Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175


His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190


Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205


Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220


Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240


Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250


<210>  42
<211>  806
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic construct

<400>  42

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1               5                   10                  15


Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
```

```
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Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
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Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
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Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65                  70                  75                  80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
                85                  90                  95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
            100                 105                 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
        115                 120                 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
    130                 135                 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145                 150                 155                 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
                165                 170                 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
            180                 185                 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
        195                 200                 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
```

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    210                 215                 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
225                 230                 235                 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
                245                 250                 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
            260                 265                 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
        275                 280                 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
    290                 295                 300

Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
305                 310                 315                 320

Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
                325                 330                 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
            340                 345                 350

Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
        355                 360                 365

Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
    370                 375                 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
385                 390                 395                 400

Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
```

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                405                 410                 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
            420                 425                 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
        435                 440                 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
    450                 455                 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
465                 470                 475                 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
                485                 490                 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
            500                 505                 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
        515                 520                 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
    530                 535                 540

Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
545                 550                 555                 560

Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
                565                 570                 575

Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
            580                 585                 590

Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
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        595                 600                 605

Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
    610                 615                 620

Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
625                 630                 635                 640

Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
                645                 650                 655

Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
            660                 665                 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                 680                 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
    690                 695                 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                 710                 715                 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
                725                 730                 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
            740                 745                 750

Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu
        755                 760                 765

Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly
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Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro Pro Ser
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Thr Gln Ala

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