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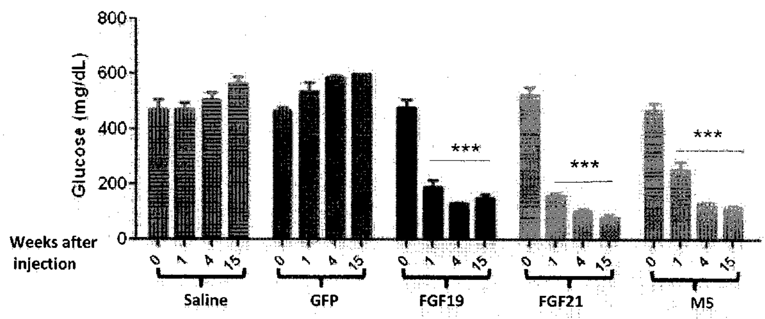
Figure 3A



(57) Abstract: The invention relates to variants and fusions of fibroblast growth factor 19 (FGF19), variants and fusions of fibroblast growth factor 21 (FGF21), fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21), and variants or fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) proteins and peptide sequences (and peptidomimetics), having one or more activities, such as glucose lowering activity, and methods for and uses in treatment of hyperglycemia and other disorders.

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Compositions, Uses and Methods for Treatment of Metabolic Disorders and Diseases

Related Applications

[0001] This application claims the benefit of priority of application serial no. 61/504,128, filed July 1, 2011, and application serial no. 61/515,126, filed August 4, 2011, both of which applications are expressly incorporated herein by reference in their entirety.

Field of the Invention

[0002] The invention relates to variants of fibroblast growth factor 19 (FGF19) proteins and peptide sequences (and peptidomimetics) and fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) proteins and peptide sequences (and peptidomimetics), and variants of fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) proteins and peptide sequences (and peptidomimetics) having glucose lowering activity, and methods for and uses in treatment of hyperglycemia and other disorders.

Introduction

[0003] Diabetes mellitus is a debilitating metabolic disease caused by absent insulin production (type 1) or insulin resistance or insufficient insulin production (type 2) from pancreatic β-cells . β-cells are specialized endocrine cells that manufacture and store insulin for release following a meal. Insulin is a hormone that facilitates the transfer of glucose from the blood into tissues where it is needed. Patients with diabetes must frequently monitor blood glucose levels and many require multiple daily insulin injections to survive. However, such patients rarely attain ideal glucose levels by insulin injection (Turner, R.C. *et al. JAMA* 281:2005(1999)). Furthermore, prolonged elevation of insulin levels can result in detrimental side effects such as hypoglycemic shock and desensitization of the body's response to insulin. Consequently, diabetic patients still develop long-term complications, such as cardiovascular diseases, kidney disease, blindness, nerve damage and wound healing disorders (UK Prospective Diabetes Study (UKPDS) Group, *Lancet* 352:837 (1998)).

[0004] Bariatric surgery has been proposed as a potential treatment for diabetes. It has been postulated that changes in gut hormone secretion after the surgery are responsible for the resolution of diabetic conditions. The underlying molecular mechanism has yet to be elucidated, although glucagon-like peptide 1 (GLP-1) has been speculated as a possible candidate (Rubino, F. Diabetes Care 32 Suppl 2:S368(2009)). FGF19 is highly expressed in the distal small intestine and transgenic over-expression of FGF19 improves glucose homeostasis (Tomlinson, E.

Endocrinology 143(5):1741-7(2002)). Serum levels of FGF19 in humans are elevated following gastric bypass surgery. Augmented expression and secretion of FGF19 could at least partially explain the diabetes remission experienced following surgery.

[0005] Accordingly, there is a need for alternative treatments of hyperglycemic conditions such as diabetes, prediabetes, insulin resistance, hyperinsulinemia, glucose intolerance or metabolic syndrome, and other disorders and diseases associated with elevated glucose levels, in humans. The invention satisfies this need and provides related advantages.

Summary

[0006] The invention is based, in part, on variants of fibroblast growth factor 19 (FGF19) peptide sequences, fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) peptide sequences and variants of fusions (chimeras) of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) peptide sequences having one or more activities, such as glucose lowering activity. Such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences include sequences that do not increase or induce hepatocellular carcinoma (HCC) formation or HCC tumorigenesis. Such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences also include sequences that do not induce a substantial elevation or increase in lipid profile.

[0007] In one embodiment, a chimeric peptide sequence includes or consists of: an N-terminal region having at least seven amino acid residues, the N-terminal region having a first amino acid position and a last amino acid position, where the N-terminal region has a DSSPL or DASPH sequence; and a C-terminal region having a portion of FGF19, where the C-terminal region has a first amino acid position and a last amino acid position, where the C-terminal region includes amino acid residues 16-29 of FGF19 (WGDPIRLRHLYTSG), and where the W residue corresponds to the first amino acid position of the C-terminal region.

[0008] In another embodiment, a chimeric peptide sequence includes or consists of: an N-terminal region having a portion of FGF21, where the N-terminal region has a first amino acid position and a last amino acid position, where the N-terminal region has a GQV sequence, and where the V residue corresponds to the last amino acid position of the N-terminal region; and a C-terminal region including a portion of FGF19, the C-terminal region having a first amino acid position and a last amino acid position, where the C-terminal region includes amino acid residues 21-29 of FGF19 (RLRHLYTSG), and where the R residue corresponds to the first position of the C-terminal region.

[0009] In a further embodiment, a chimeric peptide sequence includes or consists of any of: an N-terminal region comprising a portion of SEQ ID NO:100 [FGF21], the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises at least 5 (or more) contiguous amino acids of SEQ ID NO:100 [FGF21] including the amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region; and a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 [FGF19], RLRHLYTSG, and wherein the R residue corresponds to the first position of the C-terminal region. In particular aspects, the N-terminal region comprises at least 6 contiguous amino acids (or more, e.g., 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 20-25, 25-30, 30-40, 40-50, 50-75, 75-100 contiguous amino acids) of SEQ ID NO:100 [FGF21] including the amino acid residues GQV.

[0010] In an additional embodiment, a peptide sequence includes or consists of any of: a fibroblast growth factor 19 (FGF19) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19; a fibroblast growth factor 21 (FGF21) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21; a portion of an FGF19 sequence fused to a portion of an FGF21 sequence; or a portion of an FGF19 sequence fused to a portion of an FGF21 sequence, wherein the FGF19 and/or FGF21 sequence portion(s) have one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19 and/or FGF21.

[0011] In still further embodiments, a peptide sequence or a chimeric peptide sequence includes or consists of amino-terminal amino acids 1-16 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 21-194 of SEQ ID NO:99 [FGF19], or the peptide sequence has amino-terminal amino acids 1-147 of SEQ ID NO:99 [FGF19] fused to carboxy-terminal amino acids 147-181 of SEQ ID NO:100 [FGF21] (M41), or the peptide sequence has amino-terminal amino acids 1-20 of SEQ ID NO:99 [FGF19] fused to carboxy-terminal amino acids 17-181 of SEQ ID NO:100 [FGF21] (M44), or the peptide sequence has amino-terminal amino acids 1-146 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 [FGF19] (M45), or the peptide sequence has amino-terminal amino acids 1-20 of SEQ ID NO:99 [FGF19] fused to internal amino acids17-146 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 [FGF19] (M46).

[0012] In yet additional embodiments, a peptide sequence or a chimeric peptide sequence has a WGDPI sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of SEQ ID NO:99 [FGF19], or has a substituted, mutated or absent WGDPI sequence motif corresponding to FGF19 WGDPI sequence of amino acids 16-20 of FGF19, or the WGDPI sequence motif has one or more amino acids substituted, mutated or absent; or is distinct from an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the FGF19 WGDPI sequence at amino acids 16-20.

[0013] In yet further embodiments, a peptide sequence or a chimeric peptide sequence has an N-terminal region that includes or consists of amino acid residues VHYG, where the N-terminal region comprises amino acid residues DASPHVHYG, or where the N-terminal region comprises amino acid residues DSSPLVHYG, or where the N-terminal region comprises amino acid residues DSSPLLQ, or where the N-terminal region comprises amino acid residues DSSPLLQFGGQV. In particular aspects, the G corresponds to the last position of the N-terminal region, or the Q residue is the last amino acid position of the N-terminal region, or the V residue corresponds to the last position of the N-terminal region..

[0014] In still additional embodiments, a peptide sequence or a chimeric peptide sequence has an N-terminal region that includes or consists of RHPIP, where R is the first amino acid position of the N-terminal region; or HPIP (e.g., where HPIP are the first 4 amino acid residues of the N-terminal region), where H is the first amino acid position of the N-terminal region; or RPLAF, where R is the first amino acid position of the N-terminal region; or PLAF, where P is the first amino acid position of the N-terminal region; or R, where R is the first amino acid position of the N-terminal region, or has at the N-terminal region any one of the following sequences: MDSSPL, MSDSSPL, SDSSPL, MSSPL or SSPL.

[0015] In other embodiments, a peptide sequence or a chimeric peptide sequence has, at the first position of the N-terminal region, an "M" residue, an "R" residue, a "S" residue, a "H" residue, a "P" residue, a "L" residue or an "D" residue. In alternative embodiments, a peptide sequence or a chimeric peptide sequence does not have a "M" residue or an "R" residue at the first amino acid position of the N-terminal region.

[0016] In still other embodiments, a peptide sequence or a chimeric peptide sequence has at the first and second positions of the N-terminal region an MR sequence, or at the first and second positions of the N-terminal region an RM sequence, or at the first and second positions of the N-terminal region an RD sequence, or at the first and second positions of the N-terminal region an DS sequence, or at the first and second positions of the N-terminal region an MD sequence, or at the first and second positions of the N-terminal region an MS sequence, or at the first through third positions of the N-terminal region an MDS sequence, or at the first through third positions of the N-terminal region an RDS sequence, or at the first through third positions of the N-terminal region an MSD sequence, or at the first through third positions of the N-terminal region an MSS sequence, or at the first through third positions of the N-terminal region an DSS sequence, or at the first through fourth positions of the N-terminal region an RDSS sequence, or at the first through fourth positions of the N-terminal region an MDSS sequence, or at the first through fifth positions of the N-terminal region an MRDSS sequence, or at the first through fifth positions of the N-terminal region an MSSPL sequence, or at the first through sixth positions of the N-terminal region an MDSSPL sequence, or at the first through seventh positions of the N-terminal region an MSDSSPL sequence.

[0017] In still other embodiments, a peptide sequence or a chimeric peptide sequence an addition of amino acid residues 30-194 of SEQ ID NO:99 [FGF19] at the C-terminus, resulting in a chimeric polypeptide having at the last position of the C-terminal region that corresponds to about residue 194 of SEQ ID NO:99 [FGF19]. In further other embodiments, a chimeric peptide sequence or peptide sequence comprises all or a portion of an FGF19 sequence (e.g., SEQ ID NO:99), positioned at the C-terminus of the peptide, or where the amino terminal "R" residue is deleted from the peptide. I

[0018] In more particular embodiments, a chimeric peptide sequence or peptide sequence includes or consists of any of M1-M98 variant peptide sequences, or a subsequence or fragment of any of the M1-M98 variant peptide sequences.

[0019] In additional particular embodiments, a chimeric peptide sequence or peptide sequence has an N-terminal or a C-terminal region from about 20 to about 200 amino acid residues in length. In further particular embodiments, a chimeric peptide sequence or peptide sequence has at least one amino acid deletion. In still further particular embodiments, a chimeric peptide sequence or peptide sequence, or a subsequence or fragment thereof, has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally. In a particular non-limiting aspect, the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI).

[0020] In more particular embodiments, a chimeric peptide sequence or peptide sequence includes or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids. In more particular embodiments, a chimeric peptide sequence or peptide sequence includes or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids of FGF19 or FGF21.

[0021] In further particular embodiments, chimeric peptide sequences and peptide sequences have particular functions or activities. In one aspect, a chimeric peptide sequence or peptide sequence maintains or increases an FGFR4 mediated activity. In additional aspects, a chimeric peptide sequence or peptide sequence binds to fibroblast growth factor receptor 4 (FGFR4) or activates FGFR4, or does not detectably bind to fibroblast growth factor receptor 4 (FGFR4) or activate FGFR4, or binds to FGFR4 with an affinity less than, comparable to or greater than FGF19 binding affinity for FGFR4, or activates FGFR4 to an extent or amount less than, comparable to or greater than FGF19 activates FGFR4. In further aspects, a chimeric peptide sequence or peptide sequence has reduced hepatocellular carcinoma (HCC) formation compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19, and/or has greater glucose lowering activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19, and/or has less lipid increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19, and/or has less triglyceride, cholesterol, non-HDL or HDL increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19, and/or has less lean mass reducing activity compared to FGF21. Such functions and activities can be ascertained in vitro or in vivo, for example, in a *db/db* mouse.

[0022] In still additional embodiments, chimeric peptide sequences and peptide sequences isolated or purified, and/or chimeric peptide sequences and peptide sequences can be included in compositions. In one embodiment, a chimeric peptide sequence or peptide sequence is included in a pharmaceutical composition. Such compositions include combinations of inactive or other active ingredients. In one embodiment, a compositions, such as a pharmaceutical composition includes chimeric peptide sequence or peptide sequence and a glucose lowering agent.

[0023] In yet further embodiments, nucleic acid molecules encoding the chimeric peptide sequence or peptide sequence are provided. Such molecules can further include an expression control element in operable linkage that confers expression of the nucleic acid molecule encoding the peptide in vitro, in a cell or in vivo, or a vector comprising the nucleic acid molecule (e.g., a viral vector). Transformed and host cells that express the chimeric peptide sequences and peptide sequences are also provided.

[0024] Uses and methods of treatment that include administration or delivery of any chimeric peptide sequence or peptide sequence are also provided. In particular embodiments, a use or method of treatment of a subject includes administering an invention chimeric peptide or peptide sequence to a subject, such as a subject having, or at risk of having, a disease or disorder treatable by an invention peptide sequence, in an amount effective for treating the disease or disorder. In a further embodiment, a method includes administering an invention chimeric peptide or peptide sequence to a subject, such as a subject having a hyperglycemic condition (e.g., diabetes, such as insulin-dependent (type I) diabetes, type II diabetes, or gestational diabetes), insulin resistance, hyperinsulinemia, glucose intolerance or metabolic syndrome, or is obese or has an undesirable body mass.

[0025] In particular aspects of the methods and uses, a chimeric peptide sequence or peptide sequence is administered to a subject in an amount effective to improve glucose metabolism in the subject. In more particular aspects, a subject has a fasting plasma glucose level greater than 100 mg/dl or has a hemoglobin A1c (HbA1c) level above 6%, prior to administration.

[0026] In further embodiments, a use or method of treatment of a subject is intended to or results in reduced glucose levels, increased insulin sensitivity, reduced insulin resistance, reduced glucagon, an improvement in glucose tolerance, or glucose metabolism or homeostasis, improved pancreatic function, or reduced triglyceride, cholesterol, IDL, LDL or VLDL levels, or a decrease in blood pressure, a decrease in intimal thickening of the blood vessel, or a decrease in body mass or weight gain.

[0027] Methods of analyzing and/or identifying a chimeric peptide sequence or peptide sequence are also provided, such as chimeric peptide sequences and peptide sequences that have glucose lowering activity without substantial hepatocellular carcinoma (HCC) activity. In one embodiment, a method includes: a) providing a candidate chimeric peptide sequence or peptide sequence; b) administering the candidate peptide sequence to a test animal (e.g., a db/db mouse); c) measuring glucose levels of the animal after administration of the candidate peptide sequence, to determine if the candidate peptide sequence reduces glucose levels. In a particular aspect, the chimeric peptide sequence or peptide sequence is also analyzed for induction of HCC in the animal (e.g., assessing a hepatic tissue sample from the test animal), or expression of a marker correlating with HCC activity, wherein a candidate peptide having glucose lowering activity and not substantial HCC activity. Such methods identify the candidate as having glucose lowering activity, optionally also without substantial hepatocellular carcinoma (HCC) activity.

Description of Drawings

[0028] **FIG. 1** shows FGF19 and FGF21 protein sequences, and representative variant sequences, namely variant M5, variant M1, variant M2, variant M69, variant M3, variant M48, variant M49, variant M50, variant M51, variant M52, variant M53 and variant M70 peptide sequences. 3 additional allelic (polymorphic) forms of FGF21, namely M71, M72 and M73 are also shown.

[0029] **FIG. 2** shows representative domain exchanges between FGF21 (no shading) and FGF19 (grey shading) protein sequences, and the resultant fusion (chimeric) sequences. The amino acid regions from each of FGF21 and FGF19 present in the fusion (chimera) are indicated by the numbers. Glucose lowering and lipid elevation are shown for each of the chimeric sequences.

[0030] **FIG. 3A-3I** show glucose lowering and body weight data. A) variant M5; B) variant M1; C) variant M2 and variant M69; D) variant M3; E) variant M48 and variant M49; F) variant M51 and variant M50; G) variant M52 peptide; H) variant M53 peptide; and I) variant M70 peptide sequences all have glucose lowering (i.e., anti-diabetic) activity in *db/db* mice. Mice were injected with AAV vector expressing FGF19, FGF21, the selected variants, and saline and GFP are negative controls.

[0031] **FIG. 4A-4I** show serum lipid profile (triglyceride, total cholesterol, HDL and non-HDL) of *db/db* mice injected with AAV vector expressing FGF19, FGF21 or A) variant M5; B) variant M1; C) variant M2 and variant M69; D) variant M3; E) variant M48 and variant M49; F) variant M51 and variant M50; G) variant M52 peptide; H) variant M53 peptide; and I) variant M70 peptide sequences. Variant M5 peptide sequence did not increase or elevate lipids, in contrast to FGF19, M1, M2 and M69 which increases and elevates lipids. Serum levels of all variants were comparable. Saline and GFP are negative controls.

[0032] **FIG. 5A-5I** show hepatocellular carcinoma (HCC) – related data for A) variant M5; B) variant M1; C) variant M2 and variant M69; D) variant M3; E) variant M48 and variant M49; F) variant M51 and variant M50; G) variant M52; H) variant M53 peptide; and I) variant M70 peptide sequences. All variants did not significantly increase or induce hepatocellular carcinoma (HCC) formation or HCC tumorigenesis, in contrast to FGF19. HCC score is recorded as the number of HCC nodules on the surface of the entire liver from variants-injected mice divided by the number of HCC nodules from wild type FGF19-injected mice.

[0033] **FIG. 6A-6I** show lean mass or fat mass data for A) variant M5; B) variant M1; C) variant M2 and variant M69; D) variant M3; E) variant M48 and variant M49; F) variant M51 and variant M50; G) variant M52; H) variant M53 peptide; and I) variant M70 peptide sequences. Except for M2, M5 and M69, the variant peptide sequences reduce lean mass or fat mass, in contrast to FGF21.

[0034] **FIG. 7A-7B** show graphical data demonstrating that injection of the recombinant A) variant M5; and B) variant M69 polypeptides reduce blood glucose in *ob/ob* mice.

[0035] **FIG. 8** shows data indicating that liver expression of aldo-keto reductase family 1, member C18 (Akr1C18) and solute carrier family 1, member 2 (slc1a2) appears to correlate with HCC activity.

Detailed Description

[0036] The invention provides chimeric and peptide sequences that are able to lower or reduce levels of glucose. In one embodiment, a chimeric peptide sequence includes or consists of an N-terminal region having at least seven amino acid residues and the N-terminal region having a first amino acid position and a last amino acid position, where the N-terminal region has a DSSPL or DASPH sequence; and a C-terminal region having a portion of FGF19 and the C-terminal region having a first amino acid position and a last amino acid position, where the C-terminal region includes amino acid residues 16-29 of FGF19 (WGDPIRLRHLYTSG) and the W residue corresponds to the first amino acid position of the C-terminal region.

[0037] In another embodiment, a chimeric peptide sequence includes or consists of an N-terminal region having a portion of FGF21 and the N-terminal region having a first amino acid position and a last amino acid position, where the N-terminal region has a GQV sequence and the V residue corresponds to the last amino acid position of the N-terminal region; and a C-terminal region having a portion of FGF19 and the C-terminal region having a first amino acid position and a last amino acid position where the C-terminal region includes amino acid residues 21-29 of FGF19 (RLRHLYTSG) and the R residue corresponds to the first position of the C-terminal region.

[0038] In further embodiments, a peptide sequence includes or consists of a fibroblast growth factor 19 (FGF19) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19. In additional embodiments, a peptide sequence includes or consists of a fibroblast growth factor 21 (FGF21) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21. In yet additional embodiments, a peptide sequence includes or consists of a portion of an FGF19 sequence fused to a portion of an FGF21 sequence. In still additional embodiments, a peptide sequence includes or consists of a portion of an FGF19 sequence fused to a portion of an FGF21 sequence, where the FGF19 and/or FGF21 sequence portion(s) have one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19 and/or FGF21.

[0039] The invention also provides methods and uses of treating a subject having or at risk of having a metabolic disorder treatable using variants and fusions of fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) peptide sequences. In one embodiment, a method includes contacting or administering to a subject one or more variant or fusion fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) peptide sequences in an amount effective for treating the disorder. In another embodiment, a method includes contacting or administering to a subject one or more nucleic acid molecules encoding a variant or fusion fibroblast growth factor 19 (FGF19) and/or fibroblast growth factor 21 (FGF21) peptide sequence (for example, an expression control element in operable linkage with the nucleic acid encoding the peptide sequence, optionally including a vector), in an amount effective for treating the disorder.

[0040] Although an understanding of the underlying mechanism of action of the invention peptides is not required in order to practice the invention, without being bound to any particular theory or hypothesis, it is believed that invention peptides mimic, at least in part, the effect that bariatric surgery has on, for example, glucose homeostasis and weight loss. Changes in gastrointestinal hormone secretion (e.g., glucagon-like peptide 1 (GLP-1)) after bariatric surgery are believed responsible for the resolution of, for example, diabetic conditions. FGF19 is highly expressed in the distal small intestine, and transgenic over-expression of FGF19 improves glucose homeostasis. Because levels of FGF19 in humans are also elevated following gastric bypass surgery, the elevated FGF19 might be involved with the remission of diabetes observed following bariatric surgery.

[0041] A representative reference or wild type FGF19 sequence is set forth as:
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHR
LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPF
GLVTGLEAVRSPSFEK (SEQ ID NO:99).

[0042] A representative reference or wild type FGF21 sequence is set forth as:
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKP
GVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPG
NKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS
(SEQ ID NO:100). FGF21 allelic variants are illustrated in Figure 1 (e.g., M70, M71 and M72).

[0043] The terms "peptide," "protein," and "polypeptide" sequence are used interchangeably herein to refer to two or more amino acids, or "residues," including chemical modifications and derivatives of amino acids, covalently linked by an amide bond or equivalent. The amino acids forming all or a part of a peptide may be from among the known 21 naturally occurring amino acids, which are referred to by both their single letter abbreviation or common three-letter abbreviation. In the peptide sequences of the invention, conventional amino acid residues have their conventional meaning. Thus, "Leu" is leucine, "Ile" is isoleucine, "Nle" is norleucine, and so on.

[0044] Exemplified herein are peptide sequences, distinct from reference FGF19 and FGF21 polypeptides set forth herein, that reduce or lower glucose, *in vivo* (Tables 1-8 and Figure 1). Non-limiting particular examples are a peptide sequence with amino-terminal amino acids 1-16 of FGF21 fused to carboxy-terminal amino acids 21-194 of FGF19; a peptide sequence with amino-terminal amino acids 1-147 of FGF19 fused to carboxy-terminal amino acids 147-181 of FGF21; a peptide sequence with amino-terminal amino acids 1-20 of FGF19 fused to carboxy-terminal amino acids 17-181 of FGF21; a peptide sequence with amino-terminal amino acids 1-146 of FGF21 fused to carboxy-terminal amino acids 148-194 of FGF19; and a peptide sequence with amino-terminal amino acids 1-20 of FGF19 fused to internal amino acids 17-146 of FGF21 fused to carboxy-terminal amino acids 148-194 of FGF19.

[0045] Additional particular peptides sequences have a WGDPI sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of FGF19, lack a WGDPI sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of FGF19, or have a substituted (i.e., mutated) WGDPI sequence motif corresponding to FGF19 WGDPI sequence of amino acids 16-20 of FGF19.

[0046] Particular peptide sequences of the invention also include sequences distinct from FGF19 and FGF21 (e.g., as set forth herein), and FGF 19 variant sequences having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for FGF19 WGDPI sequence at amino acids 16-20. Accordingly, the wild-type FGF19 and FGF21 (e.g., as set forth herein as SEQ ID NOS:99 and 100, respectively) may be excluded sequences, and FGF19 having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19 may also be excluded. This exclusion, however, does not apply to where a sequence has, for example, 3 FGF21 residues fused to FGF19 having, for example, any of GQV, GQV, GDI, or GPI, or 2 FGF21 residues fused to any of WGPI, WGDI, GDPI, WDPI, WGDI, or WGDP.

[0047] Particular non-limiting examples of peptide sequences include or consist of all or a part of a sequence variant specified herein as M1-M98 (SEQ ID NOs:1-98). More particular non-limiting examples of peptide sequences include or consist of all or a part of a sequence set forth as:

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL
RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS

SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL EAVRSPSFEK (FGF21 sequences can also include an "R" residue at the amino terminus), or a subsequence or fragment thereof; or

DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTV AIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAV RSPSFEK, or a subsequence or fragment thereof; or

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHR LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPF GLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; or

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRL PVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFG LVTGLEAVRSPSFEK, or a subsequence or fragment thereof; or

DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE AVRSPSFEK, or a subsequence or fragment thereof; or

RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL EAVRSPSFEK (M69), or a subsequence or fragment thereof; or

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA VRSPSFEK (M52), or a subsequence or fragment thereof; or

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL EAVRSPSFEK (M5), or a subsequence or fragment thereof;

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKP GVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLPG NKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M71), or a subsequence or fragment thereof; or

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M72), or a subsequence or fragment thereof; or

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGGEGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE (M73), or a subsequence or fragment thereof; or

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M1), or a subsequence or fragment thereof; or

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M2), or a subsequence or fragment thereof; or

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M3), or a subsequence or fragment thereof; or

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M48), or a subsequence or fragment thereof; or

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M49), or a subsequence or fragment thereof; or

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M50), or a subsequence or fragment thereof; or

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL

SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M51), or a subsequence or fragment thereof; or MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M53), or a subsequence or fragment thereof; and MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M70), or a subsequence or fragment thereof, or for any of the foregoing peptide sequences the R terminal residue may be deleted.

[0048] Further particular non-limiting examples of peptide sequences include or consist of: HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; or DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof.

[0049] Additional particular non-limiting examples of peptide sequences, having at the N-terminus, a peptide sequence including or consisting of all or a part of any of: HPIPDSSPLLQFGGQVRLRHLYTSG (M5); DSSPLLQFGGQVRLRHLYTSG (M6);

RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7); HPIPDSSPLLQWGDPIRLRHLYTSG (M8); HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9); HPIPDSSPHVHYGWGDPI RLRHLYTSG (M10); RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11); RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12); RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13); HPIPDSSPHVHYGGQVRLRHLYTSG (M14); RPLAFSDAGPHVHWGDPIRLRHLYTSG (M15); RPLAFSDAGPHVHWGDPI RLRHLYTSG (M16); RPLAFSDAGPHVGWGDPI RLRHLYTSG (M17); RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18); RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19); RPLAFSDAGPVHGWGDPI RLRHLYTSG (M20); RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21); RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22); RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23); RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24); RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25); RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26); RPLAFSDSSPHVHWGDPIRLRHLYTSG (M22); RPLAFSDAGPHVWGDPIRLRHLYTSG (M28); RPLAFSDAGPHVHYWGDPI RLRHLYTSG (M29); RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30); RHPIPDSSPLLQFGAQVRLRHLYTSG (M31); RHPIPDSSPLLQFGDQVRLRHLYTSG (M32); RHPIPDSSPLLQFGPQVRLRHLYTSG (M33); RHPIPDSSPLLQFGGAVRLRHLYTSG (M34); RHPIPDSSPLLQFGGEVRLRHLYTSG (M35); RHPIPDSSPLLQFGGNVRLRHLYTSG (M36); RHPIPDSSPLLQFGGQARLRHLYTSG (M37); RHPIPDSSPLLQFGGQI RLRHLYTSG (M38); RHPIPDSSPLLQFGGQTRLRHLYTSG (M39); RHPIPDSSPLLQFGWGQPVRLRHLYTSG (M40); DAGPHVHYGWGDPIRLRHLYTSG (M74); VHYGWGDPIRLRHLYTSG (M75); RLRHLYTSG (M77); RHPIPDSSPLLQFGWGDPIRLRHLYTSG; RHPIPDSSPLLQWGDPIRLRHLYTSG; RPLAFSDAGPLLQFGWGDPI RLRHLYTSG; RHPIPDSSPHVHYGWGDPIRLRHLYTSG; RPLAFSDAGPLLQFGGQVRLRHLYTSG; RHPIPDSSPHVHYGGQVRLRHLYTSG; RPLAFSDAGPHVHYGGDIRLRHLYTSG; RDSSPLLQFGGQVRLRHLYTSG; RPLAFSDSSPLLQFGGQVRLRHLYTSG; RHPIPDSSPLLQFGAQVRLRHLYTSG; RHPIPDSSPLLQFGDQVRLRHLYTSG; RHPIPDSSPLLQFGPQVRLRHLYTSG; RHPIPDSSPLLQFGGAVRLRHLYTSG; RHPIPDSSPLLQFGGEVRLRHLYTSG; RHPIPDSSPLLQFGGNVRLRHLYTSG; RHPIPDSSPLLQFGGQARLRHLYTSG; RHPIPDSSPLLQFGGQIRLRHLYTSG; RHPIPDSSPLLQFGGQTRLRHLYTSG; RHPIPDSSPLLQFGWGQPVRLRHLYTSG; and for any of the foregoing peptide sequences the amino terminal R residue may be deleted.

[0050] Peptide sequences of the invention additionally include those with reduced or absent induction or formation of hepatocellular carcinoma (HCC) compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19. Peptide sequences of the invention also include those with greater glucose lowering activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19. Peptide sequences of the invention moreover include those with less lipid (e.g., triglyceride, cholesterol, non-HDL or HDL) increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

[0051] Typically, the number of amino acids or residues in an invention peptide sequence will total less than about 250 (e.g., amino acids or mimetics thereof). In various particular embodiments, the number of residues comprise from about 20 up to about 200 residues (e.g., amino acids or mimetics thereof). In additional embodiments, the number of residues comprise from about 50 up to about 200 residues (e.g., amino acids or mimetics thereof). In further embodiments, the number of residues comprise from about 100 up to about 195 residues (e.g., amino acids or mimetics thereof) in length.

[0052] Amino acids or residues can be linked by amide or by non-natural and non-amide chemical bonds including, for example, those formed with glutaraldehyde, N-hydroxysuccinimide esters, bifunctional maleimides, or N, N'-dicyclohexylcarbodiimide (DCC). Non-amide bonds include, for example, ketomethylene, aminomethylene, olefin, ether, thioether and the like (see, *e.g.,* Spatola in Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Vol. 7, pp 267-357 (1983), "Peptide and Backbone Modifications," Marcel Decker, NY). Thus, when a peptide of the invention includes a portion of an FGF19 sequence and a portion of an FG21 sequence, the two portions need not be joined to each other by an amide bond, but can be joined by any other chemical moiety or conjugated together via a linker moiety.

[0053] The invention also includes subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-8 and Figure 1, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1), so long as the foregoing retains at least a detectable or measureable activity or function. For example, certain exemplified variant peptides have FGF19 C-terminal sequence, PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKM

QGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPML PMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK at the C-terminal portion, e.g., following the "TSG" amino acid residues of the variant.

[0054] Also, certain exemplified variant peptides, for example, those having all or a portion of FGF21 sequence at the amino-terminus, have an "R" residue positioned at the N-terminus, which can be omitted. Similarly, certain exemplified variant peptides, include an "M" residue positioned at the N-terminus, which can be appended to or further substituted for an omitted residue, such as an "R" residue. More particularly, in various embodiments peptide sequences at the N-terminus include any of: RDSS, DSS, MDSS or MRDSS. Furthermore, in cells when a "M" residue is adjacent to a "S" residue, the "M" residue may be cleaved such that the "M" residue is deleted from the peptide sequence, whereas when the "M" residue is adjacent to a "D" residue, the "M" residue may not be cleaved. Thus, by way of example, in various embodiments peptide sequences include those with the following residues at the N-terminus: MDSSPL, MSDSSPL (cleaved to SDSSPL) and MSSPL (cleaved to SSPL).

[0055] Accordingly, the "peptide," "polypeptide," and "protein" sequences of the invention include subsequences, variants and modified forms of the FGF19 and FGF21 variants and subsequences listed in Tables 1-8 and Figure 1, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1, so long as the subsequence, variant or modified form (e.g., fusion or chimera) retains at least a detectable activity or function.

[0056] As used herein, the term "modify" and grammatical variations thereof, means that the composition deviates relative to a reference composition, such as a peptide sequence. Such modified peptide sequences, nucleic acids and other compositions may have greater or less activity or function, or have a distinct function or activity compared with a reference unmodified peptide sequence, nucleic acid, or other composition, or may have a property desirable in a protein formulated for therapy (e.g. serum half-life), to elicit antibody for use in a detection assay, and/or for protein purification. For example, a peptide sequence of the invention can be modified to increase serum half-life, to increase in vitro and/or in vivo stability of the protein, etc.

[0057] Particular examples of such subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., a peptide sequence listed in Tables 1-8 and Figure 1) include substitutions, deletions and/or insertions/additions of one or more amino acids, to or from the amino terminus, the carboxy-terminus or internally. One example is a substitution of an amino acid residue for another amino acid residue within the peptide sequence. Another is a deletion of one or more amino acid residues from the peptide sequence, or an insertion or addition of one or more amino acid residues into the peptide sequence.

[0058] The number of residues substituted, deleted or inserted/added are one or more amino acids (e.g., 1-3, 3-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250, or more) of a peptide sequence. Thus, an FGF19 or FGF21 sequence can have few or many amino acids substituted, deleted or inserted/added (e.g., 1-3, 3-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250, or more). In addition, an FGF19 amino acid sequence can include or consist of an amino acid sequence of about 1-3, 3-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250, or more amino acids from FGF21; or an FGF21 amino acid or sequence can include or consist of an amino acid sequence of about 1-3, 3-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250, or more amino acids from FGF19.

[0059] Specific examples of substitutions include substituting a D residue for an L-residue. Accordingly, although residues are listed in the L-isomer configuration D-amino acids at any particular or all positions of the peptide sequences of the invention are included, unless a D-isomer leads to a sequence that has no detectable or measurable function.

[0060] Additional specific examples are non-conservative and conservative substitutions. A "conservative substitution" is a replacement of one amino acid by a biologically, chemically or structurally similar residue. Biologically similar means that the substitution is compatible with a biological activity, e.g., glucose lowering activity. Structurally similar means that the amino acids have side chains with similar length, such as alanine, glycine and serine, or having similar size, or the structure of a first, second or additional peptide sequence is maintained. Chemical similarity means that the residues have the same charge or are both hydrophilic and hydrophobic. Particular examples include the substitution of one hydrophobic residue, such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, serine for threonine, etc. Routine assays can be used to determine whether a subsequence, variant or modified form has activity, e.g., glucose lowering activity.

[0061] Particular examples of subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., a peptide sequence listed in Tables 1-8 and Figure 1) have 50%-60%, 60%-70%, 70%-75%, 75%-80%, 80%-85%, 85%-90%, 90%-95%, or 96%, 97%, 98%, or 99% identity to a reference peptide sequence (for example, a peptide sequence in any of Tables 1-8 and Figure 1). The term "identity" and "homology" and grammatical variations thereof mean that two or more referenced entities are the same. Thus, where two amino acid sequences are identical, they have the identical amino acid sequence. "Areas, regions or domains of identity" mean that a portion of two or more referenced entities are the same. Thus, where two amino acid sequences are identical or homologous over one or more sequence regions, they share identity in these regions.

[0062] The extent of identity between two sequences can be ascertained using a computer program and mathematical algorithm known in the art. Such algorithms that calculate percent sequence identity (homology) generally account for sequence gaps and mismatches over the comparison region. For example, a BLAST (e.g., BLAST 2.0) search algorithm (see, e.g., Altschul et al., *J. Mol. Biol.* 215:403 (1990), publicly available through NCBI) has exemplary search parameters as follows: Mismatch -2; gap open 5; gap extension 2. For peptide sequence comparisons, a BLASTP algorithm is typically used in combination with a scoring matrix, such as PAM100, PAM 250, BLOSUM 62 or BLOSUM 50. FASTA (e.g., FASTA2 and FASTA3) and SSEARCH sequence comparison programs are also used to quantitate the extent of identity (Pearson et al., *Proc. Natl. Acad. Sci. USA* 85:2444 (1988); Pearson, *Methods Mol Biol.* 132:185 (2000); and Smith et al., *J. Mol. Biol.* 147:195 (1981)). Programs for quantitating protein structural similarity using Delaunay-based topological mapping have also been developed (Bostick et al., *Biochem Biophys Res Commun.* 304:320 (2003)).

[0063] In the invention peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-8 and Figure 1) an "amino acid" or "residue" includes conventional alpha-amino acids as well as beta-amino acids, alpha, alpha disubstituted amino acids and N-substituted amino acids wherein at least one side chain is an amino acid side chain moiety as defined herein. An "amino acid" further includes N-alkyl alpha-amino acids, wherein the N-terminus amino group has a C_1 to C_6 linear or branched alkyl substituent. The term "amino acid" therefore includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids (e.g., by glycosylation, phosphorylation, ester or amide cleavage, etc.), enzymatically modified or synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, amino acids with a side chain moiety modified, derivatized from naturally occurring moieties, or synthetic, or not naturally occurring, etc. Modified and unusual amino acids are included in the peptide sequences of the invention (see, for example, in Synthetic Peptides: A User's Guide; Hruby et al., *Biochem. J.* 268:249 (1990); and Toniolo C., *Int. J. Peptide Protein Res.* 35:287 (1990)).

[0064] In addition, protecting and modifying groups of amino acids are included. The term "amino acid side chain moiety" as used herein includes any side chain of any amino acid, as the term "amino acid" is defined herein. This therefore includes the side chain moiety in naturally occurring amino acids. It further includes side chain moieties in modified naturally occurring amino acids as set forth herein and known to one of skill in the art, such as side chain moieties in stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically modified or synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, etc. For example, the side chain moiety of any amino acid disclosed herein or known to one of skill in the art is included within the definition.

[0065] A "derivative of an amino acid side chain moiety" is included within the definition of an amino acid side chain moiety. Non-limiting examples of derivatized amino acid side chain moieties include, for example: (a) adding one or more saturated or unsaturated carbon atoms to an existing alkyl, aryl, or aralkyl chain; (b) substituting a carbon in the side chain with another atom, preferably oxygen or nitrogen; (c) adding a terminal group to a carbon atom of the side chain, including methyl (--CH_3), methoxy (--OCH_3), nitro (--NO_2), hydroxyl (--OH), or cyano (--C=N); (d) for side chain moieties including a hydroxy, thiol or amino groups, adding a suitable hydroxy, thiol or amino protecting group; or (e) for side chain moieties including a ring structure, adding one or more ring substituents, including hydroxyl, halogen, alkyl, or aryl groups attached directly or through an ether linkage. For amino groups, suitable protecting groups are known to the skilled artisan. Provided such derivatization provides a desired activity in the final peptide sequence (e.g., glucose lowering, improved glucose or lipid metabolism, anti-diabetic activity, absence of substantial HCC formation or tumorigenesis, absence of substantial modulation of lean or fat mass, etc.).

[0066] An "amino acid side chain moiety" includes all such derivatization, and particular non-limiting examples include: gamma-amino butyric acid, 12-amino dodecanoic acid, alpha-aminoisobutyric acid, 6-amino hexanoic acid, 4-(aminomethyl)-cyclohexane carboxylic acid, 8-amino octanoic acid, biphenylalanine, Boc--t-butoxycarbonyl, benzyl, benzoyl, citrulline, diaminobutyric acid, pyrrollysine, diaminopropionic acid, 3,3-diphenylalanine, orthonine, citrulline, 1,3-dihydro-2H-isoindolecarboxylic acid, ethyl, Fmoc—fluorenylmethoxycarbonyl, heptanoyl (CH3--(CH2).sub.5--C(=O)--), hexanoyl (CH3--(CH2)4--C(=O)--), homoarginine, homocysteine, homolysine, homophenylalanine, homoserine, methyl, methionine sulfoxide, methionine sulfone, norvaline (NVA), phenylglycine, propyl, isopropyl, sarcosine (SAR), tert-butylalanine, and benzyloxycarbonyl.

[0067] A single amino acid, including stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, non-naturally occurring amino acids including derivatized amino acids, an alpha, alpha disubstituted amino acid derived from any of the foregoing (i.e., an alpha, alpha disubstituted amino acid, wherein at least one side chain is the same as that of the residue from which it is derived), a beta-amino acid derived from any of the foregoing (i.e., a beta-amino acid which other than for the presence of a beta-carbon is otherwise the same as the residue from which it is derived) etc., including all of the foregoing can be referred to herein as a "residue." Suitable substituents, in addition to the side chain moiety of the alpha-amino acid, include C1 to C6 linear or branched alkyl. Aib is an example of an alpha, alpha disubstituted amino acid. While alpha, alpha disubstituted amino acids can be referred to using conventional L- and D-isomeric references, it is to be understood that such references are for convenience, and that where the substituents at the alpha-position are different, such amino acid can interchangeably be referred to as an alpha, alpha disubstituted amino acid derived from the L- or D-isomer, as appropriate, of a residue with the designated amino acid side chain moiety. Thus (S)-2-Amino-2-methyl-hexanoic acid can be referred to as either an alpha, alpha disubstituted amino acid derived from L-Nle (norleucine) or as an alpha, alpha disubstituted amino acid derived from D-Ala. Similarly, Aib can be referred to as an alpha, alpha disubstituted amino acid derived from Ala. Whenever an alpha, alpha disubstituted amino acid is provided, it is to be understood as including all (R) and (S) configurations thereof.

[0068] An "N-substituted amino acid" includes any amino acid wherein an amino acid side chain moiety is covalently bonded to the backbone amino group, optionally where there are no substituents other than H in the alpha-carbon position. Sarcosine is an example of an N-substituted amino acid. By way of example, sarcosine can be referred to as an N-substituted amino acid derivative of Ala, in that the amino acid side chain moiety of sarcosine and Ala is the same, i.e., methyl.

[0069] Covalent modifications of the invention peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-8 and Figure 1), are included in the invention. One type of covalent modification includes reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the peptide. Derivatization with bifunctional agents is useful, for instance, for cross linking peptide to a water-insoluble support matrix or surface for use in the method for purifying anti-peptide antibodies, and vice-versa. Commonly used cross linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

[0070] Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, amidation of any C-terminal carboxyl group, etc.

[0071] Exemplified peptide sequences, and subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-8 and Figure 1), can also include alterations of the backbone for stability, derivatives, and peptidomimetics. The term "peptidomimetic" includes a molecule that is a mimic of a residue (referred to as a "mimetic"), including but not limited to piperazine core molecules, keto-piperazine core molecules and diazepine core molecules. Unless otherwise specified, an amino acid mimetic of an invention peptide sequence includes both a carboxyl group and amino group, and a group corresponding to an amino acid side chain, or in the case of a mimetic of Glycine, no side chain other than hydrogen.

[0072] By way of example, these would include compounds that mimic the sterics, surface charge distribution, polarity, etc. of a naturally occurring amino acid, but need not be an amino acid, which would impart stability in the biological system. For example, Proline may be substituted by other lactams or lactones of suitable size and substitution; Leucine may be substituted by an alkyl ketone, N-substituted amide, as well as variations in amino acid side chain length using alkyl, alkenyl or other substituents, others may be apparent to the skilled artisan. The essential element of making such substitutions is to provide a molecule of roughly the same size and charge and configuration as the residue used to design the molecule. Refinement of these modifications will be made by analyzing the compounds in a functional (e.g., glucose lowering) or other assay, and comparing the structure activity relationship. Such methods are within the scope of the skilled artisan working in medicinal chemistry and drug development.

[0073] Another type of modification of the invention peptide sequences, including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-8 and Figure 1), is glycosylation. As used herein, "glycosylation" broadly refers to the presence, addition or attachment of one or more sugar (e.g., carbohydrate) moieties to proteins, lipids or other organic molecules. The use of the term "deglycosylation" herein is generally intended to mean the removal or deletion, of one or more sugar (e.g., carbohydrate) moieties. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins involving a change in the type and proportions (amount) of the various sugar (e.g., carbohydrate) moieties present.

[0074] Glycosylation can be achieved by modification of an amino acid residue, or by adding one or more glycosylation sites that may or may not be present in the native sequence. For example, a typically non-glycosylated residue can be substituted for a residue that may be glycosylated. Addition of glycosylation sites can be accomplished by altering the amino acid sequence. The alteration to the peptide sequence may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues (for O-linked glycosylation sites) or asparagine residues (for N-linked glycosylation sites). The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type may be different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (hereafter referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycoprotein.

[0075] Peptide sequences of the invention may optionally be altered through changes at the nucleotide (e.g., DNA) level, particularly by mutating the DNA encoding the peptide at preselected bases such that codons are generated that will translate into the desired amino acids. Another means of increasing the number of carbohydrate moieties on the peptide is by chemical or enzymatic coupling of glycosides to the polypeptide (see, for example, in WO 87/05330). De-glycosylation can be accomplished by removing the underlying glycosylation site, by deleting the glycosylation by chemical and/or enzymatic means, or by substitution of codons encoding amino acid residues that are glycosylated. Chemical deglycosylation techniques are known, and enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases.

[0076] Various cell lines can be used to produce proteins that are glycosylated. One non-limiting example is Dihydrofolate reductase (DHFR) - deficient Chinese Hamster Ovary (CHO) cells, which are a commonly used host cell for the production of recombinant glycoproteins. These cells do not express the enzyme beta-galactoside alpha-2,6-sialyltransferase and therefore do not add sialic acid in the alpha-2,6 linkage to N-linked oligosaccharides of glycoproteins produced in these cells.

[0077] Another type of modification is to conjugate (e.g., link) one or more additional components or molecules at the N- and/or C-terminus of an invention peptide sequence, such as another protein (e.g., a protein having an amino acid sequence heterologous to the subject protein), or a carrier molecule. Thus, an exemplary peptide sequence can be a conjugate with another component or molecule.

[0078] In certain embodiments, the amino- or carboxy- terminus of an invention peptide sequence can be fused with an immunoglobulin Fc region (e.g., human Fc) to form a fusion conjugate (or fusion molecule). Fc fusion conjugates can increase the systemic half-life of biopharmaceuticals, and thus the biopharmaceutical product may have prolonged activity or require less frequent administration. Fc binds to the neonatal Fc receptor (FcRn) in endothelial cells that line the blood vessels, and, upon binding, the Fc fusion molecule is protected from degradation and re-released into the circulation, keeping the molecule in circulation longer. This Fc binding is believed to be the mechanism by which endogenous IgG retains its long plasma half-life. Well-known and validated Fc-fusion drugs consist of two copies of a biopharmaceutical linked to the Fc region of an antibody to improve pharmacokinetics, solubility, and production efficiency. More recent Fc-fusion technology links a single copy of a biopharmaceutical to Fc region of an antibody to optimize the pharmacokinetic and pharmacodynamic properties of the biopharmaceutical as compared to traditional Fc-fusion conjugates.

[0079] A conjugate modification can be used to produce a peptide sequence that retains activity with an additional or complementary function or activity of the second molecule. For example, a peptide sequence may be conjugated to a molecule, e.g., to facilitate solubility, storage, *in vivo* or shelf half-life or stability, reduction in immunogenicity, delayed or controlled release *in vivo*, etc. Other functions or activities include a conjugate that reduces toxicity relative to an unconjugated peptide sequence, a conjugate that targets a type of cell or organ more efficiently than an unconjugated peptide sequence, or a drug to further counter the causes or effects associated with a disorder or disease as set forth herein (*e.g.*, diabetes).

[0080] Clinical effectiveness of protein therapeutics may be limited by short plasma half-life and susceptibility to degradation. Studies of various therapeutic proteins have shown that various modifications, including conjugating or linking the peptide sequence to any of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes (see, for example, typically via a linking moiety covalently bound to both the protein and the nonproteinaceous polymer (e.g., a PEG) can prolong half-life. Such PEG-conjugated biomolecules have been shown to possess clinically useful properties, including better physical and thermal stability, protection against susceptibility to enzymatic degradation, increased solubility, longer in vivo circulating half-life and decreased clearance, reduced immunogenicity and antigenicity, and reduced toxicity.

[0081] PEGs suitable for conjugation to an invention peptide sequence is generally soluble in water at room temperature, and have the general formula $R(O-CH_2-CH_2)_nO-R$, where R is hydrogen or a protective group such as an alkyl or an alkanol group, and where n is an integer from 1 to 1000. When R is a protective group, it generally has from 1 to 8 carbons. The PEG conjugated to the peptide sequence can be linear or branched. Branched PEG derivatives, "star-PEGs" and multi-armed PEGs are included in the invention. A molecular weight of the PEG used in the invention is not restricted to any particular range, but certain embodiments have a molecular weight between 500 and 20,000 while other embodiments have a molecular weight between 4,000 and 10,000.

[0082] The invention includes compositions of conjugates wherein the PEGs have different "n" values and thus the various different PEGs are present in specific ratios. For example, some compositions comprise a mixture of conjugates where n=1, 2, 3 and 4. In some compositions, the percentage of conjugates where n=1 is 18-25%, the percentage of conjugates where n=2 is 50-66%, the percentage of conjugates where n=3 is 12-16%, and the percentage of conjugates where n=4 is up to 5%. Such compositions can be produced by reaction conditions and purification methods know in the art.

[0083] PEG may directly or indirectly (e.g., through an intermediate) bind to the peptide sequences of the invention. For example, in one embodiment, PEG binds via a terminal reactive group (a "spacer"). The spacer, is, for example, a terminal reactive group which mediates a bond between the free amino or carboxyl groups of one or more of the peptide sequences and polyethylene glycol. The PEG having the spacer which may be bound to the free amino group includes N-hydroxysuccinylimide polyethylene glycol which may be prepared by activating succinic acid ester of polyethylene glycol with N-hydroxysuccinylimide. Another activated polyethylene glycol which may be bound to free amino group is 2,4-bis(O-methoxypolyethyleneglycol)-6-chloro-s-triazine which may be prepared by reacting polyethylene glycol monomethyl ether with cyanuric chloride. The activated polyethylene glycol which is bound to the free carboxyl group includes polyoxyethylenediamine.

[0084] Conjugation of one or more of invention peptide sequences to PEG having a spacer may be carried out by various conventional methods. For example, the conjugation reaction can be carried out in solution at a pH of from 5 to 10, at temperature from 4°C to room temperature, for 30 minutes to 20 hours, utilizing a molar ratio of reagent to protein of from 4:1 to 30:1. Reaction conditions may be selected to direct the reaction towards producing predominantly a desired degree of substitution. In general, low temperature, low pH (e.g., pH=5), and short reaction time tend to decrease the number of PEGs attached, whereas high temperature, neutral to high pH (e.g., pH≥7), and longer reaction time tend to increase the number of PEGs attached. Various methods known in the art may be used to terminate the reaction. In some embodiments the reaction is terminated by acidifying the reaction mixture and freezing at, e.g., -20°C.

[0085] Invention peptide sequences including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-8 and Figure 1), further include conjugation to large, slowly metabolized macromolecules such as proteins; polysaccharides, such as sepharose, agarose, cellulose, cellulose beads; polymeric amino acids such as polyglutamic acid, polylysine; amino acid copolymers; inactivated virus particles; inactivated bacterial toxins such as toxoid from diphtheria, tetanus, cholera, leukotoxin molecules; inactivated bacteria; and dendritic cells. Such conjugated forms, if desired, can be used to produce antibodies against peptide sequences of the invention.

[0086] Additional suitable components and molecules for conjugation include, for example, thyroglobulin; albumins such as human serum albumin (HSA); tetanus toxoid; Diphtheria toxoid; polyamino acids such as poly(D-lysine:D-glutamic acid); VP6 polypeptides of rotaviruses; influenza virus hemaglutinin, influenza virus nucleoprotein; Keyhole Limpet Hemocyanin (KLH); and hepatitis B virus core protein and surface antigen; or any combination of the foregoing.

[0087] Fusion of albumin to an invention peptide sequence can, for example, be achieved by genetic manipulation, such that the DNA coding for HSA (human serum albumin), or a fragment thereof, is joined to the DNA coding for a peptide sequence. Thereafter, a suitable host can be transformed or transfected with the fused nucleotide sequence in the form of, for example, a suitable plasmid, so as to express a fusion polypeptide. The expression may be effected *in vitro* from, for example, prokaryotic or eukaryotic cells, or in vivo from, for example, a transgenic organism. In some embodiments of the invention, the expression of the fusion protein is performed in mammalian cell lines, for example, CHO cell lines.

[0088] Further means for genetically fusing target proteins or peptides to albumin include a technology known as Albufuse® (Novozymes Biopharma A/S; Denmark), and the conjugated therapeutic peptide sequences frequently become much more effective with better uptake in the body. The technology has been utilized commercially to produce Albuferon® (Human Genome Sciences), a combination of albumin and interferon α-2B used to treat hepatitis C infection.

[0089] Another embodiment entails the use of one or more human domain antibodies (dAb). dAbs are the smallest functional binding units of human antibodies (IgGs) and have favorable stability and solubility characteristics. The technology entails a dAb(s) conjugated to HSA (thereby forming a "AlbudAb"; see, e.g., EP1517921B, WO2005/118642 and WO2006/051288) and a molecule of interest (e.g., a peptide sequence of the invention). AlbudAbs are often smaller and easier to manufacture in microbial expression systems, such as bacteria or yeast, than current technologies used for extending the serum half-life of peptides. As HSA has a half-life of about three weeks, the resulting conjugated molecule improves the half-life. Use of the dAb technology may also enhance the efficacy of the molecule of interest.

[0090] Additional suitable components and molecules for conjugation include those suitable for isolation or purification. Particular non-limiting examples include binding molecules, such as biotin (biotin-avidin specific binding pair), an antibody, a receptor, a ligand, a lectin, or molecules that comprise a solid support, including, for example, plastic or polystyrene beads, plates or beads, magnetic beads, test strips, and membranes.

[0091] Purification methods such as cation exchange chromatography may be used to separate conjugates by charge difference, which effectively separates conjugates into their various molecular weights. For example, the cation exchange column can be loaded and then washed with ~20 mM sodium acetate, pH ~4, and then eluted with a linear (0M to 0.5M) NaCl gradient buffered at a pH from 3 to 5.5, preferably at pH ~4.5. The content of the fractions obtained by cation exchange chromatography may be identified by molecular weight using conventional methods, for example, mass spectroscopy, SDS-PAGE, or other known methods for separating molecular entities by molecular weight. A fraction is then accordingly identified which contains the conjugate having the desired number of PEGs attached, purified free from unmodified protein sequences and from conjugates having other numbers of PEGs attached.

[0092] In still other embodiments, an invention peptide sequence is linked to a chemical agent (e.g., an immunotoxin or chemotherapeutic agent), including, but are not limited to, a cytotoxic agent, including taxol, cytochalasin B, gramicidin D, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, and analogs or homologs thereof. Other chemical agents include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6- thioguanine, cytarabine, 5-fluorouracil decarbazine); alkylating agents (e.g., mechlorethamine, carmustine and lomustine, cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisplatin); antibiotics (e.g., bleomycin); and anti-mitotic agents (e.g., vincristine and vinblastine). Cytotoxins can be conjugated to a peptide of the invention using linker technology known in the art and described herein.

[0093] Further suitable components and molecules for conjugation include those suitable for detection in an assay. Particular non-limiting examples include detectable labels, such as a radioisotope (e.g., ^{125}I; ^{35}S, ^{32}P; ^{33}P), an enzyme which generates a detectable product (e.g., luciferase, β-galactosidase, horse radish peroxidase and alkaline phosphatase), a fluorescent protein, a chromogenic protein, dye (e.g., fluorescein isothiocyanate); fluorescence emitting metals (e.g., ^{152}Eu); chemiluminescent compounds (e.g., luminol and acridinium salts); bioluminescent compounds (e.g., luciferin); and fluorescent proteins. Indirect labels include labeled or detectable antibodies that bind to a peptide sequence, where the antibody may be detected.

[0094] In certain embodiments, a peptide sequence of the invention is conjugated to a radioactive isotope to generate a cytotoxic radiopharmaceutical (radioimmunoconjugates) useful as a diagnostic or therapeutic agent. Examples of such radioactive isotopes include, but are not limited to, iodine ^{13} indium ^{11}', yttrium ^{90} and lutetium ^{177}. Methods for preparing radioimmunoconjugates are known to the skilled artisan. Examples of radioimmunoconjugates that are commercially available include ibritumomab, tiuxetan, and tositumomab.

[0095] Other means and methods included in the invention for prolonging the circulation half-life, increasing stability, reducing clearance, or altering immunogenicity or allergenicity of a peptide sequence of the invention involves modification of the peptide sequence by hesylation, which utilizes hydroxyethyl starch derivatives linked to other molecules in order to modify the molecule's characteristics. Various aspects of hesylation are described in, for example, U.S. Patent Appln. Nos. 2007/0134197 and 2006/0258607.

[0096] Any of the foregoing components and molecules used to modify peptide sequences of the invention may optionally be conjugated via a linker. Suitable linkers include "flexible linkers" which are generally of sufficient length to permit some movement between the modified peptide sequences and the linked components and molecules. The linker molecules are generally about 6-50 atoms long. The linker molecules may also be, for example, aryl acetylene, ethylene glycol oligomers containing 2-10 monomer units, diamines, diacids, amino acids, or combinations thereof. Suitable linkers can be readily selected and can be of any suitable length, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 10-20, 20-30, 30-50 amino acids (e.g., Gly).

[0097] Exemplary flexible linkers include glycine polymers $(G)_n$, glycine-serine polymers (for example, $(GS)_n$, $GSGGS_n$ and $GGGS_n$, where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Glycine and glycine-serine polymers are relatively unstructured, and therefore may serve as a neutral tether between components. Exemplary flexible linkers include, but are not limited to GGSG, GGSGG, GSGSG, GSGGG, GGGSG, and GSSSG.

[0098] Peptide sequences of the invention, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1, as well as subsequences, sequence variants and modified forms of the sequences listed in Tables 1-8 and Figure 1 have one or more activities as set forth herein. One example of an activity is glucose lowering activity. Another example of an activity is reduced stimulation or formation of hepatocellular carcinoma (HCC), for example, as compared to FGF19. An additional example of an activity is lower or reduced lipid (e.g., triglyceride, cholesterol, non-HDL) or HDL increasing activity, for example, as compared to FGF21. A further example of an activity is a lower or reduced lean muscle mass reducing activity, for example, as compared to FGF21. Yet another example of an activity is binding to fibroblast growth factor receptor-4 (FGFR4), or activating FGFR4, for example, peptide sequences that bind to FGFR4 with an affinity comparable to or greater than FGF19 binding affinity for FGFR4; and peptide sequences that activate FGFR4 to an extent or amount comparable to or greater than FGF19 activates FGFR4. Still further examples of activities include down-regulation or reduction of aldo-keto reductase gene expression, for example, compared to FGF19; up-regulation or increased Slc1a2 gene expression compared to FGF21.

[0099] More particularly, peptide sequences of the invention, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1, as well as subsequences, variants and modified forms of the sequences listed in Tables 1-8 and Figure 1 include those with the following activities: peptide sequences having reduced hepatocellular carcinoma (HCC) formation compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19; peptide sequences having greater glucose lowering activity compared to FGF19, or FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19; peptide sequences having less lipid increasing activity (e.g., less triglyceride, cholesterol, non-HDL) or more HDL increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19; and peptide sequences having less lean mass reducing activity as compared to FGF21.

[0100] More particularly, peptide sequences of the invention, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1, as well as subsequences, variants and modified forms of the sequences listed in Tables 1-8 and Figure 1 include those with the following activities: peptide sequences that bind to fibroblast growth factor receptor-4 (FGFR4), or activate FGFR4, such as peptide sequences that bind to FGFR4 with an affinity comparable to or greater than FGF19 binding affinity for FGFR4; peptide sequences that activate FGFR4 to an extent or amount comparable to or greater than FGF19 activates FGFR4; peptide sequences that down-regulate or reduce aldo-keto reductase gene expression, for example, compared to FGF19; and peptide sequences that up-regulate or increase solute carrier family 1, member 2 (Slc1a2) gene expression as compared to FGF21.

[0101] Activities such as, for example, hepatocellular carcinoma (HCC) formation or tumorigenesis, glucose lowering activity, lipid increasing activity, or lean mass reducing activity can be ascertained in an animal, such as a *db/db* mouse. Measurement of binding to FGFR4 or activation of FGFR4 can be ascertained by assays disclosed herein (see, for example, Example 1) or known to the skilled artisan.

[0102] The term "bind," or "binding," when used in reference to a peptide sequence, means that the peptide sequence interacts at the molecular level. Thus, a peptide sequence that binds to FGFR4 binds to all or a part of the FGFR4 sequence. Specific and selective binding can be distinguished from non-specific binding using assays known in the art (e.g., competition binding, immunoprecipitation, ELISA, flow cytometry, Western blotting).

[0103] Peptides and peptidomimetics can be produced and isolated using methods known in the art. Peptides can be synthesized, in whole or in part, using chemical methods (see, e.g., Caruthers (1980). *Nucleic Acids Res. Symp. Ser.* 215; Horn (1980); and Banga, A.K., Therapeutic Peptides and Proteins, Formulation, Processing and Delivery Systems (1995) Technomic Publishing Co., Lancaster, PA). Peptide synthesis can be performed using various solid-phase techniques (see, e.g., Roberge *Science* 269:202 (1995); Merrifield, *Methods Enzymol.* 289:3 (1997)) and automated synthesis may be achieved, e.g., using the ABI 431A Peptide Synthesizer (Perkin Elmer) in accordance with the manufacturer's instructions. Peptides and peptide mimetics can also be synthesized using combinatorial methodologies. Synthetic residues and polypeptides incorporating mimetics can be synthesized using a variety of procedures and methodologies known in the art (see, e.g., Organic Syntheses Collective Volumes, Gilman, *et al.* (Eds) John Wiley & Sons, Inc., NY). Modified peptides can be produced by chemical modification methods (see, for example, Belousov, *Nucleic Acids Res.* 25:3440 (1997); Frenkel, *Free Radic. Biol. Med.* 19:373 (1995); and Blommers, *Biochemistry* 33:7886 (1994)). Peptide sequence variations, derivatives, substitutions and modifications can also be made using methods such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR based mutagenesis. Site-directed mutagenesis (Carter et al., *Nucl. Acids Res.*, 13:4331 (1986); Zoller et al., *Nucl. Acids Res.* 10:6487 (1987)), cassette mutagenesis (Wells et al., *Gene* 34:315 (1985)), restriction selection mutagenesis (Wells et al., Philos. *Trans. R. Soc. London SerA* 317:415 (1986)) and other techniques can be performed on cloned DNA to produce invention peptide sequences, variants, fusions and chimeras, and variations, derivatives, substitutions and modifications thereof.

[0104] A "synthesized" or "manufactured" peptide sequence is a peptide made by any method involving manipulation by the hand of man. Such methods include but are not limited to the aforementioned, such as chemical synthesis, recombinant DNA technology, biochemical or enzymatic fragmentation of larger molecules, and combinations of the foregoing.

[0105] Peptide sequences of the invention including subsequences, sequence variants and modified forms of the exemplified peptide sequences (e.g., sequences listed in Tables 1-8 and Figure 1), can also be modified to form a chimeric molecule. In accordance with the invention, there are provided peptide sequences that include a heterologous domain. Such domains can be added to the amino-terminus or at the carboxyl-terminus of the peptide sequence. Heterologous domains can also be positioned within the peptide sequence, and/or alternatively flanked by FGF19 and/or FGF21 derived amino acid sequences.

[0106] The term "peptide" also includes dimers or multimers (oligomers) of peptides. In accordance with the invention, there are also provided dimers or multimers (oligomers) of the exemplified peptide sequences as well as subsequences, variants and modified forms of the exemplified peptide sequences (e.g., sequences listed in Tables 1-8 and Figure 1).

[0107] The invention further provides nucleic acid molecules encoding peptide sequences of the invention, including subsequences, sequence variants and modified forms of the sequences listed in Tables 1-8 and Figure 1, and vectors that include nucleic acid that encodes the peptide. Accordingly, "nucleic acids" include those that encode the exemplified peptide sequences disclosed herein, as well as those encoding functional subsequences, sequence variants and modified forms of the exemplified peptide sequences, so long as the foregoing retain at least detectable or measureable activity or function. For example, a subsequence, a variant or modified form of an exemplified peptide sequence disclosed herein (e.g., a sequence listed in Tables 1-8 and Figure 1) that retains some ability to lower or reduce glucose, provide normal glucose homeostasis, or reduce the histopathological conditions associated with chronic or acute hyperglycemia *in vivo*, etc.

[0108] Nucleic acid, which can also be referred to herein as a gene, polynucleotide, nucleotide sequence, primer, oligonucleotide or probe refers to natural or modified purine- and pyrimidine-containing polymers of any length, either polyribonucleotides or polydeoxyribonucleotides or mixed polyribo-polydeoxyribo nucleotides and α-anomeric forms thereof. The two or more purine- and pyrimidine-containing polymers are typically linked by a phosphoester bond or analog thereof. The terms can be used interchangeably to refer to all forms of nucleic acid, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The nucleic acids can be single strand, double, or triplex, linear or circular. Nucleic acids include genomic DNA and cDNA. RNA nucleic acid can be spliced or unspliced mRNA, rRNA, tRNA or antisense. Nucleic acids include naturally occurring, synthetic, as well as nucleotide analogues and derivatives.

[0109] As a result of the degeneracy of the genetic code, nucleic acid molecules include sequences degenerate with respect to nucleic acid molecules encoding the peptide sequences of the invention. Thus, degenerate nucleic acid sequences encoding peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-8 and Figure 1), are provided. The term "complementary," when used in reference to a nucleic acid sequence, means the referenced regions are 100% complementary, i.e., exhibit 100% base pairing with no mismatches.

[0110] Nucleic acid can be produced using any of a variety of known standard cloning and chemical synthesis methods, and can be altered intentionally by site-directed mutagenesis or other recombinant techniques known to one skilled in the art. Purity of polynucleotides can be determined through sequencing, gel electrophoresis, UV spectrometry.

[0111] Nucleic acids may be inserted into a nucleic acid construct in which expression of the nucleic acid is influenced or regulated by an "expression control element," referred to herein as an "expression cassette." The term "expression control element" refers to one or more nucleic acid sequence elements that regulate or influence expression of a nucleic acid sequence to which it is operatively linked. An expression control element can include, as appropriate, promoters, enhancers, transcription terminators, gene silencers, a start codon (*e.g.*, ATG) in front of a protein-encoding gene, etc.

[0112] An expression control element operatively linked to a nucleic acid sequence controls transcription and, as appropriate, translation of the nucleic acid sequence. The term "operatively linked" refers to a juxtaposition wherein the referenced components are in a relationship permitting them to function in their intended manner. Typically, expression control elements are juxtaposed at the 5' or the 3' ends of the genes but can also be intronic.

[0113] Expression control elements include elements that activate transcription constitutively, that are inducible (i.e., require an external signal or stimuli for activation), or derepressible (i.e., require a signal to turn transcription off; when the signal is no longer present, transcription is activated or "derepressed"). Also included in the expression cassettes of the invention are control elements sufficient to render gene expression controllable for specific cell-types or tissues (i.e., tissue-specific control elements). Typically, such elements are located upstream or downstream (i.e., 5' and 3') of the coding sequence. Promoters are generally positioned 5' of the coding sequence. Promoters, produced by recombinant DNA or synthetic techniques, can be used to provide for transcription of the polynucleotides of the invention. A "promoter" typically means a minimal sequence element sufficient to direct transcription.

[0114] Nucleic acids may be inserted into a plasmid for transformation into a host cell and for subsequent expression and/or genetic manipulation. A plasmid is a nucleic acid that can be stably propagated in a host cell; plasmids may optionally contain expression control elements in order to drive expression of the nucleic acid. For purposes of this invention, a vector is synonymous with a plasmid. Plasmids and vectors generally contain at least an origin of replication for propagation in a cell and a promoter. Plasmids and vectors may also include an expression control element for expression in a host cell, and are therefore useful for expression and/or genetic manipulation of nucleic acids encoding peptide sequences, expressing peptide sequences in host cells and organisms (e.g., a subject in need of treatment), or producing peptide sequences, for example.

[0115] As used herein, the term "transgene" means a polynucleotide that has been introduced into a cell or organism by artifice. For example, a cell having a transgene, the transgene has been introduced by genetic manipulation or "transformation" of the cell. A cell or progeny thereof into which the transgene has been introduced is referred to as a "transformed cell" or "transformant." Typically, the transgene is included in progeny of the transformant or becomes a part of the organism that develops from the cell. Transgenes may be inserted into the chromosomal DNA or maintained as a self-replicating plasmid, YAC, minichromosome, or the like.

[0116] Bacterial system promoters include T7 and inducible promoters such as pL of bacteriophage λ, plac, ptrp, ptac (ptrp-lac hybrid promoter) and tetracycline responsive promoters. Insect cell system promoters include constitutive or inducible promoters (e.g., ecdysone). Mammalian cell constitutive promoters include SV40, RSV, bovine papilloma virus (BPV) and other virus promoters, or inducible promoters derived from the genome of mammalian cells (e.g., metallothionein IIA promoter; heat shock promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the inducible mouse mammary tumor virus long terminal repeat). Alternatively, a retroviral genome can be genetically modified for introducing and directing expression of a peptide sequence in appropriate host cells.

[0117] As methods and uses of the invention include *in vivo* delivery, expression systems further include vectors designed for *in vivo* use. Particular non-limiting examples include adenoviral vectors (U.S. Patent Nos. 5,700,470 and 5,731,172), adeno-associated vectors (U.S. Patent No. 5,604,090), herpes simplex virus vectors (U.S. Patent No. 5,501,979), retroviral vectors (U.S. Patent Nos. 5,624,820, 5,693,508 and 5,674,703), BPV vectors (U.S. Patent No. 5,719,054), CMV vectors (U.S. Patent No. 5,561,063) and parvovirus, rotavirus, Norwalk virus and lentiviral vectors (see, *e.g.*, U.S. Patent No. 6,013,516). Vectors include those that deliver genes to cells of the intestinal tract, including the stem cells (Croyle *et al.*, *Gene Ther.* 5:645 (1998); S.J. Henning, *Adv. Drug Deliv. Rev.* 17:341 (1997), U.S. Patent Nos. 5,821,235 and 6,110,456). Many of these vectors have been approved for human studies.

[0118] Yeast vectors include constitutive and inducible promoters (see, e.g., Ausubel et al., In: Current Protocols in Molecular Biology, Vol. 2, Ch. 13, ed., Greene Publish. Assoc. & Wiley Interscience, 1988; Grant et al. *Methods in Enzymology*, 153:516 (1987), eds. Wu & Grossman; Bitter *Methods in Enzymology*, 152:673 (1987), eds. Berger & Kimmel, Acad. Press, N.Y.; and, Strathern et al., The Molecular Biology of the Yeast Saccharomyces (1982) eds. Cold Spring Harbor Press, Vols. I and II). A constitutive yeast promoter such as ADH or LEU2 or an inducible promoter such as GAL may be used (R. Rothstein In: DNA Cloning, A Practical Approach, Vol.11, Ch. 3, ed. D.M. Glover, IRL Press, Wash., D.C., 1986). Vectors that facilitate integration of foreign nucleic acid sequences into a yeast chromosome, via homologous recombination for example, are known in the art. Yeast artificial chromosomes (YAC) are typically used when the inserted polynucleotides are too large for more conventional vectors (e.g., greater than about 12 Kb).

[0119] Expression vectors also can contain a selectable marker conferring resistance to a selective pressure or identifiable marker (e.g., beta-galactosidase), thereby allowing cells having the vector to be selected for, grown and expanded. Alternatively, a selectable marker can be on a second vector that is co-transfected into a host cell with a first vector containing a nucleic acid encoding a peptide sequence. Selection systems include but are not limited to herpes simplex virus thymidine kinase gene (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase gene (Szybalska et al., *Proc. Natl. Acad. Sci. USA* 48:2026 (1962)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:817 (1980)) genes that can be employed in tk-, hgprt- or aprt- cells, respectively. Additionally, antimetabolite resistance can be used as the basis of selection for *dhfr*, which confers resistance to methotrexate (O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); the *gpt* gene, which confers resistance to mycophenolic acid (Mulligan et al., *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); *neomycin* gene, which confers resistance to aminoglycoside G-418 (Colberre-Garapin et al., *J. Mol. Biol.* 150:1(1981)); *puromycin*; and *hygromycin* gene, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Additional selectable genes include trpB, which allows cells to utilize indole in place of tryptophan; hisD, which allows cells to utilize histinol in place of histidine (Hartman et al., *Proc. Natl. Acad. Sci. USA* 85:8047 (1988)); and ODC (ornithine decarboxylase), which confers resistance to the ornithine decarboxylase inhibitor, 2-(difluoromethyl)-DL-ornithine, DFMO (McConlogue (1987) In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory).

[0120] In accordance with the invention, there are provided transformed cell(s) (*in vitro*, *ex vivo* and *in vivo*) and host cells that produce a variant or fusion of FGF19 and/or FGF21 as set forth herein, where expression of the variant or fusion of FGF19 and/or FGF21 is conferred by a nucleic acid encoding the variant or fusion of FGF19 and/or FGF21. Transformed and host cells that express invention peptide sequences typically include a nucleic acid that encodes the invention peptide sequence. In one embodiment, a transformed or host cell is a prokaryotic cell. In another embodiment, a transformed or host cell is a eukaryotic cell. In various aspects, the eukaryotic cell is a yeast or mammalian (e.g., human, primate, etc.) cell.

[0121] As used herein, a "transformed" or "host" cell is a cell into which a nucleic acid is introduced that can be propagated and/or transcribed for expression of an encoded peptide sequence. The term also includes any progeny or subclones of the host cell.

[0122] Transformed and host cells include but are not limited to microorganisms such as bacteria and yeast; and plant, insect and mammalian cells. For example, bacteria transformed with recombinant bacteriophage nucleic acid, plasmid nucleic acid or cosmid nucleic acid expression vectors; yeast transformed with recombinant yeast expression vectors; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid); insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus); and animal cell systems infected with recombinant virus expression vectors (e.g., retroviruses, adenovirus, vaccinia virus), or transformed animal cell systems engineered for transient or stable propagation or expression.

[0123] For gene therapy uses and methods, a transformed cell can be in a subject. A cell in a subject can be transformed with a nucleic acid that encodes an invention peptide sequence as set forth herein *in vivo*. Alternatively, a cell can be transformed *in vitro* with a transgene or polynucleotide, and then transplanted into a tissue of subject in order to effect treatment. Alternatively, a primary cell isolate or an established cell line can be transformed with a transgene or polynucleotide that encodes a variant of FGF19 and/or FGF21 or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, and then optionally transplanted into a tissue of a subject.

[0124] Non-limiting target cells for expression of peptide sequences, particularly for expression *in vivo*, include pancreas cells (islet cells), muscle cells, mucosal cells and endocrine cells. Such endocrine cells can provide inducible production (secretion) of a variant of FGF19 and/or FGF21, or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21. Additional cells to transform include stem cells or other multipotent or pluripotent cells, for example, progenitor cells that differentiate into the various pancreas cells (islet cells), muscle cells, mucosal cells and endocrine cells. Targeting stem cells provides longer term expression of peptide sequences of the invention.

[0125] As used herein, the term "cultured," when used in reference to a cell, means that the cell is grown *in vitro*. A particular example of such a cell is a cell isolated from a subject, and grown or adapted for growth in tissue culture. Another example is a cell genetically manipulated *in vitro*, and transplanted back into the same or a different subject.

[0126] The term "isolated," when used in reference to a cell, means a cell that is separated from its naturally occurring *in vivo* environment. "Cultured" and "isolated" cells may be manipulated by the hand of man, such as genetically transformed. These terms include any progeny of the cells, including progeny cells that may not be identical to the parental cell due to mutations that occur during cell division. The terms do not include an entire human being.

[0127] Nucleic acids encoding invention peptide sequences can be introduced for stable expression into cells of a whole organism. Such organisms including non-human transgenic animals are useful for studying the effect of peptide expression in a whole animal and therapeutic benefit. For example, as disclosed herein, production of a variant of FGF19 and/or FGF21 or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21 as set forth herein, in mice lowered glucose and is anti-diabetic.

[0128] Mice strains that develop or are susceptible to developing a particular disease (*e.g.*, diabetes, degenerative disorders, cancer, etc.) are also useful for introducing therapeutic proteins as described herein in order to study the effect of therapeutic protein expression in the disease susceptible mouse. Transgenic and genetic animal models that are susceptible to particular disease or physiological conditions, such as streptozotocin (STZ)-induced diabetic (STZ) mice, are appropriate targets for expressing variants of FGF19 and/or FGF21, fusions/chimeric sequences (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, as set forth herein. Thus, in accordance with the invention, there are provided non-human transgenic animals that produce a variant of FGF19 and/or FGF21, or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, the production of which is not naturally occurring in the animal which is conferred by a transgene present in somatic or germ cells of the animal.

[0129] The term "transgenic animal" refers to an animal whose somatic or germ line cells bear genetic information received, directly or indirectly, by deliberate genetic manipulation at the subcellular level, such as by microinjection or infection with recombinant virus. The term "transgenic" further includes cells or tissues (*i.e.*, "transgenic cell," "transgenic tissue") obtained from a transgenic animal genetically manipulated as described herein. In the present context, a "transgenic animal" does not encompass animals produced by classical crossbreeding or *in vitro* fertilization, but rather denotes animals in which one or more cells receive a nucleic acid molecule. Invention transgenic animals can be either heterozygous or homozygous with respect to the transgene. Methods for producing transgenic animals, including mice, sheep, pigs and frogs, are well known in the art (see, *e.g.*, U.S. Patent Nos. 5,721,367, 5,695,977, 5,650,298, and 5,614,396) and, as such, are additionally included.

[0130] Peptide sequences, nucleic acids encoding peptide sequences, vectors and transformed host cells expressing peptide sequences include isolated and purified forms. The term "isolated," when used as a modifier of an invention composition, means that the composition is separated, substantially completely or at least in part, from one or more components in an environment. Generally, compositions that exist in nature, when isolated, are substantially free of one or more materials with which they normally associate with in nature, for example, one or more protein, nucleic acid, lipid, carbohydrate or cell membrane. The term "isolated" does not exclude alternative physical forms of the composition, such as variants, modifications or derivatized forms, fusions and chimeras, multimers/oligomers, etc., or forms expressed in host cells. The term "isolated" also does not exclude forms (e.g., pharmaceutical compositions, combination compositions, etc.) in which there are combinations therein, any one of which is produced by the hand of man.

[0131] An "isolated" composition can also be "purified" when free of some, a substantial number of, or most or all of one or more other materials, such as a contaminant or an undesired substance or material. Peptide sequences of the invention are generally not known or believed to exist in nature. However, for a composition that does exist in nature, an isolated composition will generally be free of some, a substantial number of, or most or all other materials with which it typically associates with in nature. Thus, an isolated peptide sequence that also occurs in nature does not include polypeptides or polynucleotides present among millions of other sequences, such as proteins of a protein library or nucleic acids in a genomic or cDNA library, for example. A "purified" composition includes combinations with one or more other inactive or active molecules. For example, a peptide sequence of the invention combined with another drug or agent, such as a glucose lowering drug or therapeutic agent, for example.

[0132] As used herein, the term "recombinant," when used as a modifier of peptide sequences, nucleic acids encoding peptide sequences, etc., means that the compositions have been manipulated (*i.e.*, engineered) in a fashion that generally does not occur in nature (*e.g.*, *in vitro*). A particular example of a recombinant peptide would be where a peptide sequence of the invention is expressed by a cell transfected with a nucleic acid encoding the peptide sequence. A particular example of a recombinant nucleic acid would be where a nucleic acid (*e.g.*, genomic or cDNA) encoding a peptide sequence cloned into a plasmid, with or without 5', 3' or intron regions that the gene is normally contiguous with in the genome of the organism. Another example of a recombinant peptide or nucleic acid is a hybrid or fusion sequence, such as a chimeric peptide sequence comprising a portion of FGF19 and a portion of FGF21.

[0133] In accordance with the invention, there are provided compositions and mixtures of invention peptide sequences, including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-8 and Figure 1, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1). In one embodiment, a mixture includes one or more peptide sequences and a pharmaceutically acceptable carrier or excipient. In another embodiment, a mixture includes one or more peptide sequences and an adjunct drug or therapeutic agent, such as an anti-diabetic, or glucose lowering, drug or therapeutic agent. Examples of drugs and therapeutic agents are set forth hereafter. Combinations, such as one or more peptide sequences in a pharmaceutically acceptable carrier or excipient, with one or more of an anti-diabetic, or glucose lowering drug or therapeutic agent are also provided. Such combinations of peptide sequence of the invention with another drug or agent, such as a glucose lowering drug or therapeutic agent, for example are useful in accordance with the invention methods and uses, for example, for treatment of a subject.

[0134] Combinations also include incorporation of peptide sequences or nucleic acids of the invention into particles or a polymeric substances, such as polyesters, carbohydrates, polyamine acids, hydrogel, polyvinyl pyrrolidone, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers; entrapment in microcapsules prepared by coacervation techniques or by interfacial polymerization, for example, by the use of hydroxymethylcellulose or gelatin-microcapsules, or poly (methylmethacrolate) microcapsules, respectively; incorporation in colloid drug delivery and dispersion systems such as macromolecule complexes, nano-capsules, microspheres, beads, and lipid-based systems (e.g., N-fatty acyl groups such as N-lauroyl, N-oleoyl, fatty amines such as dodecyl amine, oleoyl amine, etc., see US Patent No. 6,638,513), including oil-in-water emulsions, micelles, mixed micelles, and liposomes, for example.

[0135] Invention peptides including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-8 and Figure 1, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1) as set forth herein can be used to modulate glucose metabolism and facilitate transport of glucose from the blood to key metabolic organs such as muscle, liver and fat. Such peptide sequences can be produced in amounts sufficient or effective to restore glucose tolerance and/or to improve or provide normal glucose homeostasis.

[0136] As disclosed herein, administration of various FGF19 and/ FGF21 variants and fusion peptide sequences to mice successfully reduced glucose levels. Furthermore, in contrast to FGF19, certain peptide sequences did not stimulate or induce HCC formation or tumorigenesis in mice. Thus, administration of invention peptides, including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-8 and Figure 1, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-8 and Figure 1), into an animal, either by direct or indirect *in vivo* or by *ex vivo* methods (*e.g.*, administering the variant or fusion peptide, a nucleic acid encoding the variant or fusion peptide, or a transformed cell or gene therapy vector expressing the variant or fusion peptide), can be used to treat various disorders.

[0137] Accordingly, the invention includes *in vitro*, *ex vivo* and *in vivo* (e.g., on or in a subject) methods and uses. Such methods and uses can be practiced with any of the peptide sequences of the invention set forth herein.

[0138] In accordance with the invention, there are provided methods of treating a subject having, or at risk of having, a disorder. In various embodiments, a method includes administering a peptide sequence, such as an FGF19 or FGF21 variant, fusion or chimera listed in Tables 1-8 and Figure 1, or a subsequence, a variant or modified form of an FGF19 or FGF21 variant, fusion or chimera listed in Tables 1-8 and Figure 1, to a subject in an amount effective for treating the disorder.

[0139] Exemplary disorders treatable, preventable, and the like with invention peptides, and methods and uses, include metabolic diseases and disorders. Non limiting examples of diseases and disorders include: 1. Glucose utilization disorders and the sequelae associated therewith, including diabetes mellitus (Type I and Type-2), gestational diabetes, hyperglycemia, insulin resistance, abnormal glucose metabolism, "pre-diabetes" (Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT)), and other physiological disorders associated with, or that result from, the hyperglycemic condition, including, for example, histopathological changes such as pancreatic β-cell destruction. For treatment, invention peptide sequences can be administered to subjects having a fasting plasma glucose (FPG) level greater than about 100 mg/dl. Peptide sequences of the invention may also be useful in other hyperglycemic-related disorders, including kidney damage (e.g., tubule damage or nephropathy), liver degeneration, eye damage (e.g., diabetic retinopathy or cataracts), and diabetic foot disorders; 2. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary artery disease, cerebrovascular disorders and the like; 3. Other conditions which may be associated with the metabolic syndrome, such as obesity and elevated body mass (including the co-morbid conditions thereof such as, but not limited to, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and polycystic ovarian syndrome (PCOS)), and also include thromboses, hypercoagulable and prothrombotic states (arterial and venous), hypertension, cardiovascular disease, stroke and heart failure; 4. Disorders or conditions in which inflammatory reactions are involved, including atherosclerosis, chronic inflammatory bowel diseases (e.g., Crohn's disease and ulcerative colitis), asthma, lupus erythematosus, arthritis, or other inflammatory rheumatic disorders; 5. Disorders of cell cycle or cell differentiation processes such as adipose cell tumors, lipomatous carcinomas including, for example, liposarcomas, solid tumors, and neoplasms; 6. Neurodegenerative diseases and/or demyelinating disorders of the central and peripheral nervous systems and/or neurological diseases involving neuroinflammatory processes and/or other peripheral neuropathies, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, progressive multifocal leukoencephalopathy and Guillian-Barre syndrome; 7. Skin and dermatological disorders and/or disorders of wound healing processes, including erythemato-squamous dermatoses; and 8. Other disorders such as syndrome X, osteoarthritis, and acute respiratory distress syndrome.

[0140] As used herein, the term "hyperglycemic" or "hyperglycemia," when used in reference to a condition of a subject means a transient or chronic abnormally high level of glucose present in the blood of a subject. The condition can be caused by a delay in glucose metabolism or absorption such that the subject exhibits glucose intolerance or a state of elevated glucose not typically found in normal subjects (*e.g.*, in glucose-intolerant pre-diabetic subjects at risk of developing diabetes, or in diabetic subjects). Fasting plasma glucose (FPG) levels for normoglycemia are less than about 100 mg/dl, for impaired glucose metabolism, between about 100 and 126 mg/dl, and for diabetics greater than about 126 mg/dl.

[0141] As disclosed herein, the invention includes methods of preventing (e.g., in subjects predisposed to having a particular disorder(s)), delaying, slowing or inhibiting progression of, the onset of, or treating (e.g., ameliorating) obesity or an undesirable body mass (e.g., a greater than normal body mass index, or "BMI" relative to an appropriate matched subject of comparable age, gender, race, etc.). Thus, in various embodiments, a method of the invention for, for example, treating obesity or an undesirable body mass (including the co-morbid conditions of obesity, e.g., obstructive sleep apnea, arthritis, cancer (e.g., breast, endometrial, and colon), gallstones or hyperglycemia, includes contacting or administering a peptide of the invention as set forth herein (e.g., a variant or fusion of FGF19 and/or FGF21 as set forth in Tables 1-8 or Figure 1, for example) in an amount effective to treat obesity or an undesirable body mass. In particular aspects, a subject has a body mass index greater than 25, for example, 25-30, 30-35, 35-40, or greater than 40.

[0142] Moreover, the invention includes methods of preventing (e.g., in subjects predisposed to having a particular disorder(s)), slowing or inhibiting the progression of, delaying the onset of, or treating undesirable levels or abnormally elevated serum/plasma LDL, VLDL, triglycerides or cholesterol, all of which, alone or in combination, can lead to, for example, plaque formation, narrowing or blockage of blood vessels, and increased risk of hypertension, stroke and coronary artery disease. Such disorders can be due to, for example, genetic predisposition or diet, for example.

[0143] The term "subject" refers to an animal. Typically, the animal is a mammal that would benefit from treatment with a peptide sequence of the invention. Particular examples include primates (*e.g.*, humans), dogs, cats, horses, cows, pigs, and sheep.

[0144] Subjects include those having a disorder, *e.g.*, a hyperglycemic disorder, such as diabetes, or subjects that do not have a disorder but may be at risk of developing the disorder, *e.g.*, pre-diabetic subjects having FPG levels greater than 100 mg/dl, for example, between about 100 and 126 mg/dl. Subjects at risk of developing a disorder include, for example, those whose diet may contribute to development of acute or chronic hyperglycemia (e.g., diabetes), undesirable body mass or obesity, as well as those which may have a family history or genetic predisposition towards development of acute or chronic hyperglycemia, or undesirable body mass or obesity.

[0145] As disclosed herein, treatment methods include contacting or administering a peptide of the invention as set forth herein (e.g., a variant or fusion of FGF19 and or FGF21 as set forth in Tables 1-8 or Figure 1, for example) in an amount effective to achieve a desired outcome or result in a subject. A treatment that results in a desired outcome or result includes decreasing, reducing or preventing severity or frequency of one or more symptoms of the condition in the subject, *e.g.*, an improvement in the subject's condition or a "beneficial effect" or "therapeutic effect." Therefore, treatment can decrease or reduce or prevent the severity or frequency of one or more symptoms of the disorder, stabilize or inhibit progression or worsening of the disorder, and in some instances, reverse the disorder, transiently (e.g., for 1-6, 6-12, or 12-24 hours), for medium term (e.g., 1-6, 6-12, 12-24 or 24-48 days) or long term (e.g., for 1-6, 6-12, 12-24, 24-48 weeks, or greater than 24-48 weeks). Thus, in the case of a hyperglycemic disorder, for example, treatment can lower or reduce blood glucose, improve glucose tolerance, improve glucose metabolism, provide normal glucose homeostasis, lower or reduce insulin resistance, lower or reduce insulin levels, or decrease, prevent, improve, or reverse metabolic syndrome, or a histopathological change associated with or that results from the hyperglycemic disorder, such as diabetes.

[0146] For example, a peptide sequence, method or use can lower or reduce glucose in one or more subjects having FPG levels greater than 100 mg/dl, for example, between about 100 and 125 mg/dl, or greater than 125 mg/dl, by 5-10%, 10-20%, 20-30%, or 30-50%, or more, or for example from greater than 200 mg/dl to less than 200 mg/dl, for greater than 150 mg/dl to less than 150 mg/dl, from greater than 125 mg/dl to less than 125 mg/dl, etc. In addition, a peptide sequence, method or use can lower or reduce glucose, for example, for pre-diabetes or for diabetes (e.g., Type 2) subjects with baseline HbAIc levels greater than about 5%, 6%, 7%, 8%, 9% or 10%, in particular 5%, 6%, or 7%.

[0147] Non-limiting examples of an improvement of a histopathological change associated with a hyperglycemic condition include, for example, decreasing, inhibiting, reducing or arresting: the destruction or degeneration of pancreas cells (e.g., β-cells), kidney damage such as tubule calcification or nephropathy, degeneration of liver, eye damage (e.g., diabetic retinopathy, cataracts), diabetic foot, ulcerations in mucosa such as mouth and gums, periodontitis, excess bleeding, slow or delayed healing of injuries or wounds (*e.g.*, that lead to diabetic carbuncles), skin infections and other cutaneous disorders, cardiovascular and coronary heart disease, peripheral vascular disease, stroke, dyslipidemia, hypertension, obesity, or the risk of developing any of the foregoing. Improvement in undesirable body mass or obesity can include, for example, a reduction of body mass (as reflected by BMI or the like) or an improvement in an associated disorder, such as a decrease in triglyceride, cholesterol, LDL or VLDL levels, a decrease in blood pressure, a decrease in intimal thickening of the blood vessel, a decreased or reduced risk of cardiovascular disease, or stroke, decrease in resting heart rate, etc.

[0148] An "effective amount" or a "sufficient amount" for use and/or for treating a subject refer to an amount that provides, in single or multiple doses, alone, or in combination with one or more other compositions (therapeutic agents such as a drug or treatment for hyperglycemia), treatments, protocols, or therapeutic regimens agents, a detectable response of any duration of time (transient, medium or long term), a desired outcome in or an objective or subjective benefit to a subject of any measurable or detectable degree or for any duration of time (e.g., for hours, days, months, years, or cured). Such amounts typically are effective to ameliorate a disorder, or one, multiple or all adverse symptoms, consequences or complications of the disorder, to a measurable extent, although reducing or inhibiting a progression or worsening of the disorder, is considered a satisfactory outcome.

[0149] As used herein, the term "ameliorate" means an improvement in the subject's disorder, a reduction in the severity of the disorder, or an inhibition of progression or worsening of the disorder (*e.g.*, stabilizing the disorder). In the case of a hyperglycemic disorder (*e.g.*, diabetes, insulin resistance, glucose intolerance, metabolic syndrome, etc.), for example, an improvement can be a lowering or a reduction in blood glucose, a reduction in insulin resistance, a reduction in glucagon, an improvement in glucose tolerance, or glucose metabolism or homeostasis. An improvement in a hyperglycemic disorder also can include improved pancreatic function (*e.g.*, inhibit or prevent β-cell/islet destruction or enhance β -cell number and/or function), a decrease in a pathology associated with or resulting from the disorder, such as an improvement in histopathology of an affected tissue or organ, as set forth herein. In the case of undesirable body mass or obesity, for example, an improvement can be a decrease in weight gain, a reduction of body mass (as reflected in reduced BMI, for example) or an improvement in a condition associated with undesirable body mass obesity, for example, as set forth herein (*e.g.*, a lowering or a reduction of blood glucose, triglyceride, cholesterol, LDL or VLDL levels, a decrease in blood pressure, a decrease in intimal thickening of the blood vessel, etc.).

[0150] A therapeutic benefit or improvement therefore need not be complete ablation of any one, most or all symptoms, complications, consequences or underlying causes associated with the disorder or disease. Thus, a satisfactory endpoint is achieved when there is a transient, medium or long term, incremental improvement in a subject's condition, or a partial reduction in the occurrence, frequency, severity, progression, or duration, or inhibition or reversal, of one or more associated adverse symptoms or complications or consequences or underlying causes, worsening or progression (e.g., stabilizing one or more symptoms or complications of the condition, disorder or disease), of the disorder or disease, over a duration of time (hours, days, weeks, months, etc.).

[0151] Thus, in the case of a disorder treatable by a peptide sequence of the invention, the amount of peptide sufficient to ameliorate a disorder will depend on the type, severity and extent, or duration of the disorder, the therapeutic effect or outcome desired, and can be readily ascertained by the skilled artisan. Appropriate amounts will also depend upon the individual subject (*e.g.*, the bioavailability within the subject, gender, age, etc.). For example, a transient, or partial, restoration of normal glucose homeostasis in a subject can reduce the dosage amount or frequency of insulin injection, even though complete freedom from insulin has not resulted.

[0152] An effective amount can be ascertained, for example, by measuring one or more relevant physiological effects. In a particular non-limiting example in the case of a hyperglycemic condition, a lowering or reduction of blood glucose or an improvement in glucose tolerance test can be used to determine whether the amount of invention peptide sequence, including subsequences, sequence variants and modified forms of the exemplified peptide sequences (e.g., sequences listed in Tables 1-8 and Figure 1) is effective to treat a hyperglycemic condition. In another particular non-limiting example, an effective amount is an amount sufficient to reduce or decrease any level (e.g., a baseline level) of FPG, wherein, for example, an amount sufficient to reduce a FPG level greater than 200 mg/dl to less than 200 mg/dl, an amount sufficient to reduce a FPG level between 175 mg/dl and 200 mg/dl to less than the pre-administration level, an amount sufficient to reduce a FPG level between 150 mg/dl and 175 mg/dl to less than the pre-administration level, an amount sufficient to reduce a FPG level between 125 mg/dl and 150 mg/dl to less than the pre-administration level, and so on (e.g., reducing FPG levels to less than 125 mg/dl, to less than 120 mg/dl, to less than 115 mg/dl, to less than 110 mg/dl, etc.). In the case of HbAIc levels, an effective amount includes an amount sufficient to reduce or decrease levels by more than about 10% to 9%, by more than about 9% to 8%, by more than about 8% to 7%, by more than about 7% to 6%, by more than about 6% to 5%, and so on. More particularly, a reduction or decrease of HbAIc levels by about 0.1%, 0.25%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 33%, 35%, 40%, 45%, 50%, or more is an effective amount in accordance with the invention. In yet another particular non-limiting example in the case of undesirable body mass or obesity, an effective amount is an amount sufficient to decrease or reduce the body mass index (BMI) of a subject, a decrease or reduction of glucose, a decrease or reduction in serum/plasma levels of triglyceride, lipid, cholesterol, fatty acids, LDL and/or VLDL. In yet further particular non-limiting examples, an amount is an amount sufficient to decrease or reduce any of the aforementioned parameters by, for example, about 0.1%, 0.25%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 33%, 35%, 40%, 45%, 50%, or more.

[0153] Methods and uses of the invention for treating a subject are applicable for prophylaxis to prevent a disorder in a subject, such as a hyperglycemic disorder, or development of undesirable body mass or obesity. Alternatively, methods and uses can be practiced during or following treatment of a subject. For example, prior to, during or following treatment of a subject to lower glucose using insulin or another glucose lowering drug or therapeutic agent, for example, a method or use of the invention can, for example, a peptide sequence of the invention can be administered to the subject. In addition, a composition such as a peptide sequence of the invention can be combined with another drug or agent, such as a glucose lowering drug or therapeutic agent, for example.

[0154] Accordingly, methods and uses of the invention for treating a subject can be practiced prior to, substantially contemporaneously with or following another treatment, and can be supplemented with other forms of therapy. Supplementary therapies include other glucose lowering treatments, such as insulin, an insulin sensitivity enhancer and other drug treatments, a change in diet (low sugar, fats, etc.), weight loss surgery- (reducing stomach volume by gastric bypass, gastrectomy), gastric banding, gastric balloon, gastric sleeve, etc. For example, a method or use of the invention for treating a hyperglycemic or insulin resistance disorder can be used in combination with drugs or other pharmaceutical compositions that lower glucose or increase insulin sensitivity in a subject. Drugs for treating diabetes include, for example, biguanides and sulphonylureas (e.g., tolbutamide, chlorpropamide, acetohexamide, tolazamide, glibenclamide and glipizide), thiazolidinediones (rosiglitazone, pioglitazone), GLP-1 analogues, Dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine formulations (e.g. and bile acid sequestrants (e.g., colesevelam), and insulin (bolus and basal analogs), metformin (e.g., metformin hydrochloride) with or without a thiazolidinedione (TZD), and SGLT-2 inhibitors. Appetite suppression drugs are also well known and can be used in combination with the methods of the invention. Supplementary therapies can be administered prior to, contemporaneously with or following invention methods and uses.

[0155] Peptide sequences of the invention including subsequences, sequence variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1), may be formulated in a unit dose or unit dosage form. In a particular embodiment, a peptide sequence is in an amount effective to treat a subject in need of treatment, e.g., due to hyperglycemia. Exemplary unit doses range from about 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 25,000-50,000 ng; from about 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 25,000-50,000 μg; and from about 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 25,000-50,000 mg.

[0156] Peptide sequences of the invention including subsequences, sequence variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1) can be administered to provide the intended effect as a single dose or multiple dosages, for example, in an effective or sufficient amount. Exemplary doses range from about 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 25,000-50,000 pg/kg; from about 50-500, 500-5000, 5000-25,000 or 25,000-50,000 ng/kg; and from about 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 25,000-50,000 μg/kg. Single or multiple doses can be administered, for example, multiple times per day, on consecutive days, alternating days, weekly or intermittently (e.g., twice per week, once every 1, 2, 3, 4, 5, 6, 7 or 8 weeks, or once every 2, 3, 4, 5 or 6 months).

[0157] Peptide sequences of the invention including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1) can be administered and methods may be practiced via systemic, regional or local administration, by any route. For example, a peptide sequence can be administered parenterally (*e.g.*, subcutaneously, intravenously, intramuscularly, or intraperitoneally), orally (*e.g.*, ingestion, buccal, or sublingual), inhalation, intradermally, intracavity, intracranially, transdermally (topical), transmucosally or rectally. Peptide sequences of the invention including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1) and methods of the invention including pharmaceutical compositions can be administered via a (micro)encapsulated delivery system or packaged into an implant for administration.

[0158] The invention further provides "pharmaceutical compositions," which include a peptide sequence (or sequences) of the invention, including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1), and one or more pharmaceutically acceptable or physiologically acceptable diluent, carrier or excipient. In particular embodiments, a peptide sequence or sequences are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in accordance with the invention methods and uses. Thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice treatment methods and uses of the invention.

[0159] Pharmaceutical compositions of the invention can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. In addition, the pharmaceutical compositions may further comprise other therapeutically active agents or compounds disclosed herein (e.g., glucose lowering agents) or known to the skilled artisan which can be used in the treatment or prevention of various diseases and disorders as set forth herein.

[0160] Pharmaceutical compositions typically comprise a therapeutically effective amount of at least one of the peptide sequences of the invention, including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-8 and Figure 1) and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that could be used in the pharmaceutical compositions and dosage forms used in the invention. Typical buffers include, but are not limited to pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. Buffer components also include water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof.

[0161] A primary solvent in a vehicle may be either aqueous or non-aqueous in nature. In addition, the vehicle may contain other pharmaceutically acceptable excipients for modifying or maintaining the pH, osmolarity, viscosity, sterility or stability of the pharmaceutical composition. In certain embodiments, the pharmaceutically acceptable vehicle is an aqueous buffer. In other embodiments, a vehicle comprises, for example, sodium chloride and/or sodium citrate.

[0162] Pharmaceutical compositions of the invention may contain still other pharmaceutically-acceptable formulation agents for modifying or maintaining the rate of release of an invention peptide. Such formulation agents include those substances known to artisans skilled in preparing sustained release formulations. For further reference pertaining to pharmaceutically and physiologically acceptable formulation agents, see, for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712, The Merck Index, 12th Ed. (1996, Merck Publishing Group, Whitehouse, NJ); and Pharmaceutical Principles of Solid Dosage Forms (1993, Technonic Publishing Co., Inc., Lancaster, Pa.). Additional pharmaceutical compositions appropriate for administration are known in the art and are applicable in the methods and compositions of the invention.

[0163] A pharmaceutical composition may be stored in a sterile vial as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such compositions may be stored either in a ready to use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, a pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampoule, syringe, or autoinjector (similar to, *e.g.*, an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments. Any drug delivery apparatus may be used to deliver invention peptides, including implants (e.g., implantable pumps) and catheter systems, both of which are known to the skilled artisan. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release invention peptides over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. The skilled artisan is familiar with possible formulations and uses of depot injections.

[0164] A pharmaceutical composition can be formulated to be compatible with its intended route of administration. Thus, pharmaceutical compositions include carriers, diluents, or excipients suitable for administration by routes including parenteral (*e.g.*, subcutaneous (s.c.), intravenous, intramuscular, or intraperitoneal), intradermal, oral (*e.g.*, ingestion), inhalation, intracavity, intracranial, and transdermal (topical).

[0165] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated using suitable dispersing or wetting agents and suspending agents disclosed herein or known to the skilled artisan. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. Moreover, fatty acids such as oleic acid find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0166] Pharmaceutical compositions may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents such as sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing an invention peptide may be in admixture with non-toxic pharmaceutically acceptable excipients suitable for the manufacture of tablets. These excipients include, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0167] Tablets, capsules and the like suitable for oral administration may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by techniques known in the art to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for preparation of such formulations are known to those skilled in the art and are commercially available.

[0168] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0169] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives.

[0170] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0171] Dispersible powders and granules suitable for preparation of an aqueous suspension by addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0172] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth; naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0173] Pharmaceutical compositions can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including implants, liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Prolonged absorption of injectable pharmaceutical compositions can be achieved by including an agent that delays absorption, for example, aluminum monostearate or gelatin. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

[0174] The invention also includes invention peptides in the form of suppositories for rectal administration. The suppositories can be prepared by mixing an invention peptide with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0175] In accordance with the invention, there are provided methods of identifying a peptide (or a subsequence, variant or modified form as set forth herein) having glucose lowering activity without substantial hepatocellular carcinoma (HCC) activity. In one embodiment, a method includes: screening (e.g., assaying or measuring) a peptide sequence (or a subsequence, variant or modified form as set forth herein) for glucose lowering activity; and screening (e.g., assaying or measuring) a peptide sequence (or a subsequence, variant or modified form as set forth herein) for HCC activity, or expression of a marker correlating with HCC activity. A peptide having glucose lowering activity and reduced or absent HCC activity thereby identifies the peptide. In particular aspects, the marker correlating with HCC activity comprises lipid profile- a peptide that has less lipid increasing activity compared to FGF19 indicates the peptide has reduced or absent HCC activity; or the marker correlating with HCC activity comprises aldo-keto reductase gene expression- a peptide that down-regulates or decreases aldo-keto reductase gene expression compared to FGF19 indicates that the peptide has reduced or absent HCC activity; or the marker indicative of HCC activity comprises Slc1a2 gene expression- a peptide that up-regulates or increases Slc1a2 gene expression compared to FGF19 indicates that the peptide has reduced or absent HCC activity.

[0176] The terms "assaying" and "measuring" and grammatical variations thereof are used interchangeably herein and refer to either qualitative or quantitative determinations, or both qualitative and quantitative determinations. When the terms are used in reference to detection, any means of assessing the relative amount is contemplated, including the various methods set forth herein and known in the art. For example, gene expression can be assayed or measured by a Northern blot, Western blot, immunoprecipitation assay, or by measuring activity, function or amount of the expressed protein (e.g., aldo-keto reductase or Slc1a2).

[0177] Risk factors for HCC, the most common type of liver cancer, include type 2 diabetes (probably exacerbated by obesity). The risk of HCC in type 2 diabetics is greater (from ~2.5 to ~7 times the non-diabetic risk) depending on the duration of diabetes and treatment protocol.

[0178] Various methodologies can be used in the screening and diagnosis of HCC and are well known to the skilled artisan. Indicators for HCC include detection of a tumor maker such as elevated alpha-fetoprotein (AFP) or des-gamma carboxyprothrombin (DCP) levels. A number of different scanning and imaging techniques are also helpful, including ultrasound, CT scans and MRI. In relation to the invention, evaluation of whether a peptide (e.g., a candidate peptide) exhibits evidence of inducing HCC may be determined *in vivo* by, for example, quantifying HCC nodule formation in an animal model, such as db/db mice, administered a peptide, compared to HCC nodule formation by wild type FGF19. Macroscopically, liver cancer may be nodular, where the tumor nodules (which are round-to-oval, grey or green, well circumscribed but not encapsulated) appear as either one large mass or multiple smaller masses. Alternatively, HCC may be present as an infiltrative tumor which is diffuse and poorly circumscribed and frequently infiltrates the portal veins.

[0179] Pathological assessment of hepatic tissue samples is generally performed after the results of one or more of the aforementioned techniques indicate the likely presence of HCC. Thus, methods of the invention may further include assessing a hepatic tissue sample from an *in vivo* animal model (e.g., a db/db mouse) useful in HCC studies in order to determine whether a peptide sequence exhibits evidence of inducing HCC. By microscopic assessment, a pathologist can determine whether one of the four general architectural and cytological types (patterns) of HCC are present (i.e., fibrolamellar, pseudoglandular (adenoid), pleomorphic (giant cell) and clear cell).

[0180] The invention also includes the generation and use of antibodies, and fragments thereof, that bind the peptide sequences of the invention, including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-8 and Figure 1).

[0181] As used herein, the terms "antibodies" (Abs) and "immunoglobulins" (Igs) refer to glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to an antigen, immunoglobulins include both antibodies and other antibody-like molecules which may lack antigen specificity.

[0182] The term "antibody" includes intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies) formed from at least two intact antibodies, and antibody binding fragments including Fab and $F(ab)'_2$, provided that they exhibit the desired biological activity. The basic antibody structural unit comprises a tetramer, and each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" chain (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. In contrast, the carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains, whereas human heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgA, and IgE, respectively. Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Binding fragments include Fab, Fab', $F(ab')_2$, Fv, and single-chain antibodies.

[0183] Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. The antibody chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper-variable regions, also called complementarity-determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

[0184] An intact antibody has two binding sites and, except in bifunctional or bispecific antibodies, the two binding sites are the same. A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments.

[0185] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, that is, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[0186] A "neutralizing antibody" is an antibody molecule that is able to eliminate or significantly reduce an effector function of a target antigen to which it binds.

[0187] Antibody binding fragments may be produced by enzymatic or chemical cleavage of intact antibodies. Digestion of antibodies with the enzyme papain results in two identical antigen-binding fragments, also known as "Fab" fragments, and an "Fc" fragment which has no antigen-binding activity. Digestion of antibodies with the enzyme pepsin results in a $F(ab')_2$ fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The $F(ab')_2$ fragment has the ability to crosslink antigen.

[0188] The term "Fab" refers to a fragment of an antibody that comprises the constant domain of the light chain and the CH1 domain of the heavy chain. The term "Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites. In a two-chain Fv species, this region consists of a dimer of one heavy-chain and one light-chain variable domain in non-covalent association. In a single-chain Fv species, one heavy-chain and one light-chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a "dimeric" structure analogous to that in a two-chain Fv species. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. While the six CDRs, collectively, confer antigen-binding specificity to the antibody, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen.

[0189] The term "complementarity determining regions" or "CDRs" refers to parts of immunological receptors that make contact with a specific ligand and determine its specificity. The term "hypervariable region" refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" and/or those residues from a "hypervariable loop".

[0190] As used herein, the term "epitope" refers to binding sites for antibodies on protein antigens. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains, as well as specific three dimensional structural and charge characteristics. An antibody is said to bind an antigen when the dissociation constant is ≤ 1 μM, preferably ≤ 100 nM, and most preferably ≤ 10 nM. An increased equilibrium constant ("K_D") means that there is less affinity between the epitope and the antibody, whereas a decreased equilibrium constant means that there is a higher affinity between the epitope and the antibody. An antibody with a K_D of "no more than" a certain amount means that the antibody will bind to the epitope with the given K_D or more strongly. Whereas K_D describes the binding characteristics of an epitope and an antibody, "potency" describes the effectiveness of the antibody itself for a function of the antibody. There is not necessarily a correlation between an equilibrium constant and potency; thus, for example, a relatively low K_D does not automatically mean a high potency.

[0191] The term "selectively binds" in reference to an antibody does not mean that the antibody only binds to a single substance, but rather that the K_D of the antibody to a first substance is less than the K_D of the antibody to a second substance. An antibody that exclusively binds to an epitope only binds to that single epitope.

[0192] When administered to humans, antibodies that contain rodent (murine or rat) variable and/or constant regions are sometimes associated with, for example, rapid clearance from the body or the generation of an immune response by the body against the antibody. In order to avoid the utilization of rodent-derived antibodies, fully human antibodies can be generated through the introduction of human antibody function into a rodent so that the rodent produces fully human antibodies. Unless specifically identified herein, "human" and "fully human" antibodies can be used interchangeably herein. The term "fully human" can be useful when distinguishing antibodies that are only partially human from those that are completely, or fully human. The skilled artisan is aware of various methods of generating fully human antibodies.

[0193] In order to address possible human anti-mouse antibody responses, chimeric or otherwise humanized antibodies can be utilized. Chimeric antibodies have a human constant region and a murine variable region, and, as such, human anti-chimeric antibody responses may be observed in some patients. Therefore, it is advantageous to provide fully human antibodies against multimeric enzymes in order to avoid possible human anti-mouse antibody or human anti-chimeric antibody responses.

[0194] Fully human monoclonal antibodies can be prepared, for example, by the generation of hybridoma cell lines by techniques known to the skilled artisan. Other preparation methods involve the use of sequences encoding particular antibodies for transformation of a suitable mammalian host cell, such as a CHO cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example, packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to CHO cells, HeLa cells, and human hepatocellular carcinoma cells.

[0195] Antibodies can be used diagnostically and/or therapeutically. For example, the antibodies can be used as a diagnostic by detecting the level of one or more peptides of the invention in a subject, and either comparing the detected level to standard control level or to a baseline level in a subject determined previously (e.g., prior to any illness). The antibodies can be used as a therapeutic to modulate the activity of one or more peptides of the invention, thereby having an effect on a condition or disorder.

[0196] The invention provides kits including, but not limited to, peptide sequences of the invention, optionally in combination with one or more therapeutic agents, compositions and pharmaceutical compositions thereof, packaged into suitable packaging material. A kit optionally includes a label or packaging insert including a description of the components or instructions for use *in vitro*, *in vivo*, or *ex vivo*, of the components therein. Exemplary instructions include instructions for reducing or lowering blood glucose, treatment of hyperglycemia, treatment of diabetes, etc.

[0197] A kit can contain a collection of such components, e.g., two or more peptide sequences alone, or a combination of a peptide sequence with another therapeutically useful composition (e.g., an anti-diabetic drug, such as a gastrin compound).

[0198] The term "packaging material" refers to a physical structure housing the components of the kit. The packaging material can maintain the components sterilely, and can be made of material commonly used for such purposes (*e.g.*, paper, corrugated fiber, glass, plastic, foil, ampules, vials, tubes, etc.).

[0199] Kits of the invention can include labels or inserts. Labels or inserts include "printed matter," e.g., paper or cardboard, separate or affixed to a component, a kit or packing material (e.g., a box), or attached to, for example, an ampule, tube or vial containing a kit component. Labels or inserts can additionally include a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory type cards.

[0200] Labels or inserts can include identifying information of one or more components therein, dose amounts, clinical pharmacology of the active ingredient(s) including mechanism of action, pharmacokinetics and pharmacodynamics. Labels or inserts can include information identifying manufacturer information, lot numbers, manufacturer location and date.

[0201] Labels or inserts can include information on a condition, disorder, disease or symptom for which a kit component may be used. Labels or inserts can include instructions for the clinician or for a subject for using one or more of the kit components in a method, treatment protocol or therapeutic regimen. Instructions can include dosage amounts, frequency or duration, and instructions for practicing any of the methods, treatment protocols or therapeutic regimes set forth herein. Exemplary instructions include instructions for treatment or use of a peptide sequence as set forth herein. Kits of the invention therefore can additionally include labels or instructions for practicing any of the methods and uses of the invention described herein including treatment methods and uses.

[0202] Labels or inserts can include information on any benefit that a component may provide, such as a prophylactic or therapeutic benefit. Labels or inserts can include information on potential adverse side effects, such as warnings to the subject or clinician regarding situations where it would not be appropriate to use a particular composition. Adverse side effects could also occur when the subject has, will be or is currently taking one or more other medications that may be incompatible with the composition, or the subject has, will be or is currently undergoing another treatment protocol or therapeutic regimen which would be incompatible with the composition and, therefore, instructions could include information regarding such incompatibilities.

[0203] Invention kits can additionally include other components. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package. Invention kits can be designed for cold storage. Invention kits can further be designed to contain peptide sequences of the invention, or that contain nucleic acids encoding peptide sequences. The cells in the kit can be maintained under appropriate storage conditions until ready to use.

[0204] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described herein.

[0205] All applications, publications, patents and other references, GenBank citations and ATCC citations cited herein are incorporated by reference in their entirety. In case of conflict, the specification, including definitions, will control. As used herein, the singular forms "a", "and," and "the" include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to "a peptide sequence" or a "treatment," includes a plurality of such sequences, treatments, and so forth.

[0206] As used herein, numerical values are often presented in a range format throughout this document. The use of a range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention unless the context clearly indicates otherwise. Accordingly, the use of a range expressly includes all possible subranges, all individual numerical values within that range, and all numerical values or numerical ranges including integers within such ranges and fractions of the values or the integers within ranges unless the context clearly indicates otherwise. This construction applies regardless of the breadth of the range and in all contexts throughout this patent document. Thus, for example, reference to a range of 90-100% includes 91-99%, 92-98%, 93-95%, 91-98%, 91-97%, 91-96%, 91-95%, 91-94%, 91-93%, and so forth. Reference to a range of 90-100% also includes 91%, 92%, 93%, 94%, 95%, 95%, 97%, etc., as well as 91.1%, 91.2%, 91.3%, 91.4%, 91.5%, etc., 92.1%, 92.2%, 92.3%, 92.4%, 92.5%, etc., and so forth.

[0207] In addition, reference to a range of 1-3, 3-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250 includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, etc. In a further example, reference to a range of 25-250, 250-500, 500-1000, 1000-2500 or 2500-5000, 5000-25,000, 5000-50,000 includes any numerical value or range within or encompassing such values, e.g., 25, 26, 27, 28, 29...250, 251, 252, 253, 254....500, 501, 502, 503, 504..., etc.

[0208] As also used herein a series of ranges are disclosed throughout this document. The use of a series of ranges include combinations of the upper and lower ranges to provide another range. This construction applies regardless of the breadth of the range and in all contexts throughout this patent document. Thus, for example, reference to a series of ranges such as 5-10, 10-20, 20-30, 30-40, 40-50, 50-75, 75-100, 100-150, includes ranges such as 5-20, 5-30, 5-40, 5-50, 5-75, 5-100, 5-150, and 10-30, 10-40, 10-50, 10-75, 10-100, 10-150, and 20-40, 20-50, 20-75, 20-100, 20-150, and so forth.

[0209] For the sake of conciseness, certain abbreviations are used herein. One example is the single letter abbreviation to represent amino acid residues. The amino acids and their corresponding three letter and single letter abbreviations are as follows:

alanine	Ala	(A)
arginine	Arg	(R)
asparagine	Asn	(N)
aspartic acid	Asp	(D)
cysteine	Cys	(C)
glutamic acid	Glu	(E)
glutamine	Gln	(Q)
glycine	Gly	(G)

histidine	His	(H)
isoleucine	Ile	(I)
leucine	Leu	(L)
lysine	Lys	(K)
methionine	Met	(M)
phenylalanine	Phe	(F)
proline	Pro	(P)
serine	Ser	(S)
threonine	Thr	(T)
tryptophan	Trp	(W)
tyrosine	Tyr	(Y)
valine	Val	(V)

[0210] The invention is generally disclosed herein using affirmative language to describe the numerous embodiments. The invention also specifically includes embodiments in which particular subject matter is excluded, in full or in part, such as substances or materials, method steps and conditions, protocols, procedures, assays or analysis. Thus, even though the invention is generally not expressed herein in terms of what the invention does not include, aspects that are not expressly included in the invention are nevertheless disclosed herein.

[0211] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the following examples are intended to illustrate but not limit the scope of invention described in the claims.

Examples

Example 1

[0212] The following is a description of various methods and materials used in the studies herein.

[0213] **Animals.** *db/db* mice were purchased from The Jackson Laboratory (Bar Habor, ME), Mice were kept in accordance with welfare guidelines under controlled light (12 hr light and 12 hr dark cycle, dark 6:30 pm-6:30 am), temperature (22±4°C) and humidity (50%±20%) conditions. They had free access to water (autoclaved distilled water) and were fed *ad libitum* on a commercial diet (Harlan Laboratories, Indianapolis, IN, Irradiated 2018 Teklad Global 18% Protein Rodent Diet) containing 17 kcal% fat, 23 kcal% protein and 60 kcal% carbohydrate. For diet-induced obesity, C57BL6/J mice (Jackson Laboratory) were maintained on a high-fat diet

(D12492, Research Diet, New Brunswick, NJ. USA) containing 60 kcal% fat, 20 kcal% protein and 20 kcal% carbohydrate for 16-20 weeks. All animal studies were approved by the NGM Institutional Animal Care and Use Committee.

[0214] **DNA and amino acid sequences.** cDNA of ORF encoding human FGF19 (*Homo sapiens* FGF19, GenBank Accession No. NM_005117.2) variants

[0215] Protein sequence encoded by the cDNA (GenBank Accession No. NP_005108.1) **PCR.** FGF19 ORF was amplified with polymerase chain reaction (PCR) using recombinant DNA (cDNA) prepared from human small intestinal tissue. PCR reagents kits with Phusion high-fidelity DNA polymerase were purchased from New England BioLabs (F-530L, Ipswich, MA). The following primers were used: forward PCR primer: 5' CCGACTAGTCACCatgcggagcgggtgtgtgg and reverse PCR primer: 5' ATAAGAATGCGGCCGCTTACTTCTCAAAGCTGGGACTCCTC.

[0216] Amplified DNA fragment was digested with restriction enzymes Spe I and Not I (the restriction sites were included in the 5' or 3' PCR primers, respectively) and was then ligated with AAV transgene vectors that had been digested with the same restriction enzymes. The vector used for expression contained a selectable marker and an expression cassette composed of a strong eukaryotic promoter 5' of a site for insertion of the cloned coding sequence, followed by a 3' untranslated region and bovine growth hormone polyadenylation tail. The expression construct is also flanked by internal terminal repeats at the 5' and 3' ends.

[0217] **Production and purification of AAV.** AAV293 cells (obtained from Agilent Technologies, Santa Clara, CA) were cultured in Dulbeco's Modification of Eagle's Medium (DMEM, Mediatech, Inc. Manassas, VA) supplemented with 10% fetal bovine serum and 1x antibiotic-antimycotic solution (Mediatech, Inc. Manassas, VA). The cells were plated at 50% density on day 1 in 150 mm cell culture plates and transfected on day 2, using calcium phosphate precipitation method with the following 3 plasmids (20 μg/plate of each): AAV transgene plasmid, pHelper plasmids (Agilent Technologies) and AAV2/9plasmid (Gao et al., *J. Virol.* 78:6381 (2004)). 48 hours after transfection, the cells were scraped off the plates, pelleted by centrifugation at 3000xg and resuspended in buffer containing 20 mM Tris pH 8.5, 100 mM NaCl and 1 mM $MgCl_2$. The suspension was frozen in an alcohol dry ice bath and was then thawed in 37 °C water bath. The freeze and thaw cycles were repeated three times; Benzenase (Sigma-aldrich, St. Louis, MO) was added to 50 units/ml; deoxycholate was added to a final concentration of 0.25%. After an incubation at 37°C for 30 min, cell debris was pelleted by centrifugation at 5000 x g for 20 min. Viral particles in the supernatant were purified using a discontinued iodixanal (Sigma-aldrich, St. Louis, MO) gradient as previously described (Zolotukhin S. et al (1999) *Gene Ther.* 6:973). The viral stock was concentrated using Vivaspin

20 (MW cutoff 100,000 Dalton, Sartorius Stedim Biotech, Aubagne, France) and re-suspended in phosphate-buffered saline (PBS) with 10% glycerol and stored at -80°C. To determine the viral genome copy number, 2 μl of viral stock were incubated in 6 μl of solution containing 50 units/ml Benzonase, 50 mM Tris-HCl pH 7.5, 10 mM $MgCl_2$ and 10 mM $CaCl_2$ at 37°C for 30 minutes.

[0218] Afterwards, 15 μl of the solution containing 2 mg/ml of Proteinase K, 0.5% SDS and 25 mM EDTA were added and the mixture was incubated for additional 20 min at 55°C to release viral DNA. Viral DNA was cleaned with mini DNeasy Kit (Qiagen, Valencia, CA) and eluted with 40 μl of water. Viral genome copy (GC) was determined by using quantitative PCR.

[0219] Viral stock was diluted with PBS to desirable GC/ml. Viral working solution (200 μl) was delivered into mice via tail vein injection.

[0220] **Blood glucose assay.** Blood glucose in mouse tail snip was measured using ACCU-CHEK Active test strips read by ACCU-CHEK Active meter (Roche Diagnostics, Indianapolis, IN) following manufacturer's instruction.

[0221] **Lipid profile assay.** Whole blood from mouse tail snips was collected into plain capillary tubes (BD Clay Adams SurePrep, Becton Dickenson and Co. Sparks, MD). Serum and blood cells were separated by spinning the tubes in an Autocrit Ultra 3 (Becton Dickinson and Co. Sparks, MD). Serum samples were assayed for lipid profile (triglyceride, total cholesterol, HDL, and non-HDL) using Integra 400 Clinical Analyzer (Roche Diagnostics, Indianapolis, IN) following the manufacturer's instructions.

[0222] **Serum FGF19/FGF21/variants exposure level assay.** Whole blood (about 50 μl/mouse) from mouse tail snips was collected into plain capillary tubes (BD Clay Adams SurePrep, Becton Dickenson and Co. Sparks, MD). Serum and blood cells were separated by spinning the tubes in an Autocrit Ultra 3 (Becton Dickinson and Co. Sparks, MD). FGF19, FGF21, and variant exposure levels in serum were determined using EIA kits (Biovendor) by following the manufacturer's instructions.

[0223] **Hepatocellular carcinoma (HCC) assay.** Liver specimen was harvested from *db/db* mice 6 months after AAV injection. HCC score is recorded as the number of HCC nodules on the surface of the entire liver from variants-injected mice divided by the number of HCC nodules from wildtype FGF19-injected mice.

[0224] **Liver gene expression assay.** Liver specimen was harvested and homogenized in Trizol reagent (Invitrogen). Total RNA was extracted following manufacturer's instruction. RNA was treated with DNase (Ambion) followed by quantitative RT-PCR analysis using Taqman primers and reagents from Applied Biosystems. Relative mRNA levels of aldo-keto reductase and slc1a2 in the liver was calculated using ΔΔCt method.

[0225] **FGFR4 binding and activity assays.** Solid phase ELISA (binding) and ERK phosphorylation assay were performed using purified recombinant proteins. FGFR binding assay was conducted using solid phase ELISA. Briefly, 96well plate was coated with 2 ug/ml anti-hFc antibody and incubated with1 ug/ml FGFR1-hFc or FGFR4-hFc. Binding to FGF19 variants in the presence of 1 ug/ ml soluble b- klotho and 20 ug/ml heparin were detected by biotinylated anti- FGF19 antibodies (0.2ug/mL), followed by streptavidin- HRP incubation (100ng/mL). For FGFR4 activation assay, Hep3B cells were stimulated with FGF19 variants for 10 minutes at 37C, then immediately lysed and assayed for ERK phosphorylation using a commercially available kit from Cis-Bio.

Example 2

[0226] The following is a description of studies showing the glucose lowering activity of various sequence variants of FGF19 and FGF21, and FGF19/FGF21 fusion constructs.

[0227] Figure 2 illustrates exemplary FGF19/FGF21 fusion constructs, and the segments from each of FGF19 and FGF21 present in the fusion peptides. These peptides were analyzed for glucose lowering activity and statistically significant lipid elevating or increasing activity (Tables 1-8 and Figure 1).

[0228] Mice (*db/db*) were injected with viral vector expressing FGF19, FGF21 or variants, and analyzed after injection. Glucose-lowering activity of each sequence is represented by a "+" symbol (a "-" symbol means no glucose lowering activity, a "+/-" symbol means variants retain minimal glucose-lowering activity); lipid elevating activity is represented by a "+" symbol (a "-" symbol means no lipid elevating activity, a "+/-" symbol means variants retain minimal lipid-elevating activity, Figure 2).

[0229] Two fusions of FGF21 and FGF19, denoted variant M5 and variant 45 (M45), exhibited glucose lowering activity and an absence of statistically significant lipid elevating or increasing activity. Variants denoted M1, M2 and M69, respectively (Figure 1, also exhibited glucose lowering activity (Figures 3B and 3C, Table 5). Data comparing M5, M1, M2 and M69 glucose lowering activity and lipid elevating or increasing activity to FGF19 and FGF21 are illustrated in Figures 3A-3C and 4A-4C.

Example 3

[0230] The following is a description of studies showing that variants M5, M1, M2 and M69 are not tumorigenic, as determined by hepatocellular carcinoma (HCC) formation, and that variants M5, M2 and M69 also do not reduce lean muscle and fat mass.

[0231] Animals (*db/db*) were injected with AAV vectors expressing FGF19, FGF21, M5, M1, M2, or M69, or injected with saline, and analyzed 6 months after injection. The data indicate that variants M5, M1, M2, and M69 did not induce (HCC) formation significantly (Figures 5A-5C).

[0232] Animals (*db/db* mice) were also injected with viral vector expressing FGF19, FGF21, M5, M1, M2 or M69, or injected with saline, and analyzed 6 months after injection for the effect of on lean mass and fat mass. The data indicate that M5, M2 and M69 peptides did not cause a statistically significant reduction in lean mass or fat mass, in contrast to FGF21, and that M1 peptide reduces lean mass (Figures 6A-6C).

Example 4

[0233] The following is a data summary of 25 additional variant peptides analyzed for lipid elevating activity and tumorigenesis. The data clearly show a positive correlation between lipid elevation and tumorigenesis, as determined by hepatocellular carcinoma (HCC) formation in *db/db* mice.

[0234] Tables 1 to 3 summarize data for 26 different variant peptides. Such exemplified variant peptides have FGF19 C-terminal sequence: PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK at the C-terminal portion, e.g., following the "TSG" amino acid residues. Notably, variant peptides (7 total, including M5) that did not cause a statistically significant elevation of lipids did not induce hepatocellular carcinoma (HCC) formation. In contrast, all variant peptides (17 total) that caused a statistically significant elevation of lipids also caused hepatocellular carcinoma (HCC) formation in mice. This data indicates that there is a strong positive correlation between lipid elevating activity and hepatocellular carcinoma (HCC) formation. Accordingly, lipid elevating activity can be used as an indicator and/or predictor of hepatocellular carcinoma (HCC) formation in animals.

Table 1: Elevated Triglyceride and Cholesterol in *db/db* Mice Appears to Positively Correlate With HCC Formation.

	N-terminal Domain	Core	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	-	-
M5	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	-	-
M74	R-----------------DAGPHVHYGWGDPI	RLRHLYTSG	+	+
M75	R--------------------------VHYGWGDPI	RLRHLYTSG	-	-
M76	R-------------------------------------GDPI	RLRHLYTSG	-	-
M77	R--	RLRHLYTSG	-	-
M78	R------------------AGPHVHYGWGDPI	RLRHLYTSG	+	+
M79	R--------------------GPHVHYGWGDPI	RLRHLYTSG	+	+
M80	R----------------------PHVHYGWGDPI	RLRHLYTSG	-	-

M81	R-------------------------HVHYGWGDPI	RLRHLYTSG	-	-

Table 2: Elevated Triglyceride and Cholesterol in db/db Mice Appears to Positively Correlate with HCC Formation

	N-terminal Domain	Core	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	-	-
M82	RPLAFSAAGPHVHYGWGDPI	RLRHLYTSG	+	+
M83	RPLAFSDAAPHVHYGWGDPI	RLRHLYTSG	+/-	+/
M84	RPLAFSDAGAHVHYGWGDPI	RLRHLYTSG	+/-	+/
M85	RPLAFSDAGPHVHYGAGDPI	RLRHLYTSG	-	-
M86	RPLAFSDAGPHVHYGWGAPI	RLRHLYTSG	+	+
M87	RPLAFSDAGPHVHYGWGDAI	RLRHLYTSG	+	+

Table 3: Elevated Triglyceride and Cholesterol in db/db Mice Appears to Positively Correlate with HCC Formation

	N-terminal Domain	Core	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	-	-
H31A/S141A(M88)		FGF19	+	+
H31A/H142A(M89)		FGF19	+	+
K127A/R129A(M90)		FGF19	+	+
K127A/S141A(M91)		FGF19	+	+
K127A/H142A(M92)		FGF19	+	+
R129A/S141A(M93)		FGF19	+	+
S141A/H142A(M94)		FGF19	+	+
K127A/H142A(M95)		FGF19	+	+
K127A/R129A/S141A(M97)		FGF19	+	+
K127A/R129A/H142A(M98)		FGF19	+	+
K127A/R129A/S141A/H142A(M99)		FGF19	+	+

Example 5

[0235] The following is a data summary of additional FGF19 variant peptides analyzed for glucose lowering activity and lipid elevating activity.

[0236] Table 4 illustrates the peptide "core sequences" of 35 additional FGF19 variants, denoted M5 to M40. Such exemplified variant peptides have FGF19 C-terminal sequence, PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKM

QGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPML PMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK at the C-terminal portion, e.g., following the "TSG" amino acid residues of the core sequence. The data clearly show that variants M6, M7, M8, mM38 and M39 have the desired characteristics of glucose lowering activity and not statistically significant lipid elevating activity in *db/db* mice.

Table 4: Additional Variants and Fine Mapping of the N-terminal Domain

	N-terminal Domain	Core	Glucose Lowering	Lipid Elevation
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	+	-
M5	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	+	-
M6	R-------DSSPLLQ--FGGQV	RLRHLYTSG	+	-
M7	RPLAFSDSSPLLQ--FGGQV	RLRHLYTSG	+	-
M8	R-HPIPDSSPLLQ--WGDPI	RLRHLYTSG	+	-
M9	R-HPIPDSSPLLQFGWGDPI	RLRHLYTSG	+	+
M10	R-HPIPDSSPHVHYGWGDPI	RLRHLYTSG	-	+
M11	RPLAFSDAGPLLQ--WGDPI	RLRHLYTSG	N/D	N/D
M12	RPLAFSDAGPLLQFGWGDPI	RLRHLYTSG	-	+
M13	RPLAFSDAGPLLQ--FGGQV	RLRHLYTSG	-	-
M14	R-HPIPDSSPHVHYG--GQV	RLRHLYTSG	-	-
M15	RPLAFSDAGPHVHYG--GQV	RLRHLYTSG	+	+
M16	RPLAFSDAGPHVH--WGDPI	RLRHLYTSG	N/D	N/D
M17	RPLAFSDAGPHV--GWGDPI	RLRHLYTSG	N/D	N/D
M18	RPLAFSDAGPH--YGWGDPI	RLRHLYTSG	N/D	N/D
M19	RPLAFSDAGP-V-YGWGDPI	RLRHLYTSG	N/D	N/D
M20	RPLAFSDAGP-VH-GWGDPI	RLRHLYTSG	N/D	N/D
M21	RPLAFSDAGP-VHY-WGDPI	RLRHLYTSG	N/D	N/D
M22	RPLAFSDAGPHVH-GWGDPI	RLRHLYTSG	N/D	N/D
M23	RPLAFSDAGPH-H-GWGDPI	RLRHLYTSG	N/D	N/D
M24	RPLAFSDAGPH-HY-WGDPI	RLRHLYTSG	N/D	N/D
M25	RPLAFSDAGPHV-Y-WGDPI	RLRHLYTSG	N/D	N/D
M26	RPLAFSDSSPLVH--WGDPI	RLRHLYTSG	N/D	N/D
M27	RPLAFSDSSPHVH--WGDPI	RLRHLYTSG	N/D	N/D
M28	RPLAFSDAPHV---WGDPI	RLRHLYTSG	N/D	N/D
M29	RPLAFSDAGPHVHY-WGDPI	RLRHLYTSG	N/D	N/D
M30	RPLAFSDAGPHVHYAWGDPI	RLRHLYTSG	N/D	N/D
M31	R-HPIPDSSPLLQ--FGAQV	RLRHLYTSG	+/-	-
M32	R-HPIPDSSPLLQ--FGIYQV	RLRHLYTSG	-	-
M33	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	-	-
M34	R-HPIPDSSPLLQ--FG7AV	RLRHLYTSG	+/-	-
M35	R-HPIPDSSPLLQ--FGGEV	RLRHLYTSG	+/-	+/
M36	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	+/-	-
M37	R-HPIPDSSPLLQ--FGGUA	RLRHLYTSG	-	-
M38	R-HPIPDSSPLLQ--FGGQT	RLRHLYTSG	+	-
M39	R-HPIPDSSPLLQ--FGGQT	RLRHLYTSG	+	-
M40	R-HPIPDSSPLLQFGWGQPO	RLRHLYTSG	-	+

Table 4a:

	N-terminal Domain — Core	Glucose Lowering	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	+	-	-
M9	R-HPIPDSSPLLQFGWGDPI RLRHLYTSG	+	+	+
M8	R-HPIPDSSPLLQ--WGDPI RLRHLYTSG	+	+	+
M12	RPLAFSDAGPLLQFGWGDPI RLRHLYTSG	-	+	+
M10	R-HPIPDSSPHVHYGWGDPI RLRHLYTSG	-	+	+
M13	RPLAFSDAGPLLQ--FGGQV RLRHLYTSG	-	+	+
M15	RPLAFSDAGPHVHYG--GQV RLRHLYTSG	-	-	+/-
M14	R-HPIPDSSPHVHYG--GQV RLRHLYTSG	-	-	+/-
M43	RPLAFSDAGPHVHYG-GD-I RLRHLYTSG	-	-	+/-
M6	R-----DSSPLLQ--FGGQV RLRHLYTSG	+	-	-
M7	RPLAFSDSSPLLQ--FGGQV RLRHLYTSG	+	-	-

Table 4b:

	N-terminal Domain — Core	Glucose Lowering	Lipid Elevation	HCC Formatioı
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	+	-	-
M31	R-HPIPDSSPLLQ--FGAQV RLRHLYTSG	+	-	+
M32	R-HPIPDSSPLLQ--FGDQV RLRHLYTSG	+	-	-
M33	R-HPIPDSSPLLQ--FGPQV RLRHLYTSG	-	-	+
M34	R-HPIPDSSPLLQ--FGGAV RLRHLYTSG	-	-	+
M35	R-HPIPDSSPLLQ--FGGEV RLRHLYTSG	-	-	+
M36	R-HPIPDSSPLLQ--FGGNV RLRHLYTSG	+	-	+/-
M37	R-HPIPDSSPLLQ--FGGQA RLRHLYTSG	-	-	+
M38	R-HPIPDSSPLLQ--FGGQI RLRHLYTSG	-	-	+
M39	R-HPIPDSSPLLQ--FGGQT RLRHLYTSG	-	-	+
M40	R-HPIPDSSPLLQFGWGQPV RLRHLYTSG	-	+	+

Table 4c:

	N-terminal Domain / Core	Glucose Lowering	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	+	-	-
M52	R-----DSSPLLQ--WGDPI RLRHLYTSG	+	+	-
M54	RPLAFSDAGPLLQ--WGDPI RLRHLYTSG	-	+	+
M55	RPLAFSDAGPH--YGWGDPI RLRHLYTSG	-	+	+
M56	RPLAFSDAGP-V-YGWGDPI RLRHLYTSG	-	+	+
M57	RPLAFSDAGP-VH-GWGDPI RLRHLYTSG	-	+	+
M58	RPLAFSDAGP-VHY-WGDPI RLRHLYTSG	-	+	+
M59	RPLAFSDAGPH-H-GWGDPI RLRHLYTSG	-	+	+
M60	RPLAFSDAGPH-HY-WGDPI RLRHLYTSG	-	+	+
M61	RPLAFSDAGPHV--GWGDPI RLRHLYTSG	-	+	+
M62	RPLAFSDAGPHV-Y-WGDPI RLRHLYTSG	-	+	+
M63	RPLAFSDAGPHVH--WGDPI RLRHLYTSG	+	+	+
M64	RPLAFSDSSPLVH--WGDPI RLRHLYTSG	+	+	+
M65	RPLAFSDSSPHVH--WGDPI RLRHLYTSG	-	+	+
M66	RPLAFSDAGPHLQ--WGDPI RLRHLYTSG	+	+	+
M67	RPLAFSDAGPHV---WGDPI RLRHLYTSG	-	-	+/-
M68	RPLAFSDAGPHVHY-WGDPI RLRHLYTSG	-	+	-
M4	RPLAFSDAGPHVHYAWGDPI RLRHLYTSG	+	+	+
M69	R-----DSSPLVHYGWGDPI RLRHLYTSG	+	+	-
M70	MR----DSSPLVHYGWGDPI RLRHLYTSG	+	+	-
M53	M-----DSSPLVHYGWGDPI RLRHLYTSG	+	+	-

[0237] Table 5 illustrates the peptide sequences of 3 additional FGF19 variants, denoted M1, M2 and M69. The data clearly show that these three variants have the desired characteristics of glucose lowering activity in *db/db* mice (Figures 3B and 3C). These three variants appear to elevate lipids in *db/db* mice Figures 4B and 4C).

Table 5: Additional Variants

M1:RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL
LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK
HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMD
PFGLVTGLEAVRSPSFEK

M2:RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL
LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK
HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMD
PFGLVTGLEAVRSPSFEK

M69:RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLP
VSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGL
VTGLEAVRSPSFEK

Example 6

[0238] The following is a data summary showing that FGF19 reduces body weight in diet-induced obese mice and in ob/ob mice, and liver tumor formation activity and body weight in *db/db* mice.

[0239] Mice were injected with FGF19 or FGF21 in AAV vector. Body weight was recorded 4 weeks after injection.

Table 6: FGF19 reduces body weight in diet-induced obese mice and in ob/ob mice

	N-terminal Domain	Core	Body Weight-Lowering in DIO	Body Weight-Lowering in *Ob/ob*
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	+	+

Table 7: Correlation of body weight and liver tumor formation of FGF19, FGF21 and selected variants in *db/db* mice

	N-terminal Domain	Core	Liver Tumor Nodule	Body Weight
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	+	Increased
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	-	Decreased
M5	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	-	Increased
M6	R-----DSSPLLQ--FGGQV	RLRHLYTSG	-	Decreased
M32	R-HPIPDSSPLLQ--FGDQV	RLRHLYTSG	-	Decreased
M52	R-----DSSPLLQ--WGDPI	RLRHLYTSG	-	Decreased
M69	R-----DSSPLVHYGWGDPI	RLRHLYTSG	-	Increased

Example 7

[0240] The following is a study showing that variant M5 and variant M69 peptides reduce blood glucose.

[0241] Mice (ob/ob) were injected (subcutaneously) with M5 (0.1 and 1 mg/kg, s.c.) or FGF19 (1 mg/kg, s.c.), or variant M69 (0.1 and 1 mg/kg, s.c.) or FGF19 (1 mg/kg, s.c.). Plasma glucose levels were measured at 2, 4, 7, and 24 hours after injection, and the results are shown in Figure 7. M5 (Figure 7A) and variant M69 (Figure 7B) showed similar glucose lowering effects as wild type FGF19.

Example 8

[0242] This example describes a study showing that liver expression of aldo-keto reductase family 1, member C18 (Akr1C18) and solute carrier family 1, member 2 (slc1a2) appears to correlate with HCC activity.

[0243] Mice (*db/db*) were injected with viral vector expressing FGF19 (HCC+), FGF21 (HCC-), dN2 (HCC-) or M5 (HCC-), or injected with GFP. Liver samples were harvested and analyzed by quantitative RT-PCR 2 weeks after injection. The data, shown in Figure 8, shows that liver expression of Akr1C18 and slc1a2 appears to correlate with HCC activity.

Table 8: Summary of FGF19 Variants in 3T3L1 Adipocyte Signaling Assay

P-Erk assay in 3T3L1 adipocytes	FGF19	FGF21	M5	M2	M63	M64	M1	M8
Experiment#1:								
Emax	3.67	4.33	3.52	4.19	3.21	3.67	4.24	4.16
EC50 (nM)	0.05	0.65	0.03	0.05	0.92	0.02	0.03	0.03
Experiment#2:								
Emax	4.52	4.83	4.01	5.56	4.17	4.85	5.30	5.34
EC50 (nM)	0.33	1.48	0.14	0.15	0.66	0.12	0.09	0.09
Experiment#3:								
Emax	4.09	4.14	3.74	4.24	3.15	4.15	4.77	4.16
EC50 (nM)	0.16	1.50	0.24	0.14	0.28	0.14	0.07	0.14

What is Claimed is:

1. A chimeric peptide sequence, comprising:
a) an N-terminal region comprising at least seven amino acid residues, the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises DSSPL or DASPH; and
b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position,
wherein the C-terminal region comprises amino acid residues 16-29 of SEQ ID NO:99 [FGF19], WGDPIRLRHLYTSG, wherein the W residue corresponds to the first amino acid position of the C-terminal region.

2. A chimeric peptide sequence, comprising:
a) an N-terminal region comprising a portion of SEQ ID NO:100 [FGF21], the N-terminal region having a first amino acid position and a last amino acid position,
wherein the N-terminal region comprises amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region; and
b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 [FGF19], RLRHLYTSG, and wherein the R residue corresponds to the first position of the C-terminal region.

3. A chimeric peptide sequence, comprising:
a) an N-terminal region comprising a portion of SEQ ID NO:100 [FGF21], the N-terminal region having a first amino acid position and a last amino acid position,
wherein the N-terminal region comprises at least 5 contiguous amino acids of SEQ ID NO:100 [FGF21] including the amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region; and
b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 [FGF19], RLRHLYTSG, and wherein the R residue corresponds to the first position of the C-terminal region.

4. The peptide sequence of claim 3, wherein the N-terminal region comprises at least 6 contiguous amino acids of SEQ ID NO:100 [FGF21] including the amino acid residues GQV.

5. The peptide sequence of claim 3, wherein the N-terminal region comprises at least 7 contiguous amino acids of SEQ ID NO:100 [FGF21] including the amino acid residues GQV.

6. A peptide sequence, comprising or consisting of any of:
a) a fibroblast growth factor 19 (FGF19) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19;
b) a fibroblast growth factor 21 (FGF21) sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21;
c) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence; or
d) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence, wherein the FGF19 and/or FGF21 sequence portion(s) have one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19 and/or FGF21.

7. The peptide sequence of claim 6, wherein the peptide sequence has amino-terminal amino acids 1-16 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 21-194 of SEQ ID NO:99 [FGF19], or wherein the peptide sequence has amino-terminal amino acids 1-147 of SEQ ID NO:99 [FGF19] fused to carboxy-terminal amino acids 147-181 of SEQ ID NO:100 [FGF21] (M41), or wherein the peptide sequence has amino-terminal amino acids 1-20 of SEQ ID NO:99 [FGF19] fused to carboxy-terminal amino acids 17-181 of SEQ ID NO:100 [FGF21] (M44), or wherein the peptide sequence has amino-terminal amino acids 1-146 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 [FGF19] (M45), or wherein the peptide sequence has amino-terminal amino acids 1-20 of SEQ ID NO:99 [FGF19] fused to internal amino acids17-146 of SEQ ID NO:100 [FGF21] fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 [FGF19] (M46).

8. The chimeric peptide sequence or peptide sequence of claims 1, 2 or 6, wherein the peptide sequence has a WGDPI sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of SEQ ID NO:99 [FGF19].

9. The chimeric peptide sequence or peptide sequence of claim 8, wherein the peptide sequence maintains or increases an FGFR4 mediated activity.

10. The chimeric peptide sequence or peptide sequence of claims 1, 2 or 6, wherein the peptide sequence has a substituted, mutated or absent WGDPI sequence motif corresponding to FGF19 WGDPI sequence of amino acids 16-20 of FGF19.

11. The chimeric peptide sequence or peptide sequence of claim 10, wherein the WGDPI sequence has one or more amino acids substituted, mutated or absent.

12. The chimeric peptide sequence or peptide sequence of claims 1, 2 or 6, wherein the peptide sequence is distinct from an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the FGF19 WGDPI sequence at amino acids 16-20.

13. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the N-terminal or C-terminal region is from about 20 to about 200 amino acid residues in length.

14. The chimeric peptide sequence of claim 1, wherein the N-terminal region comprises amino acid residues VHYG, wherein the N-terminal region comprises amino acid residues DASPHVHYG, or wherein the N-terminal region comprises amino acid residues DSSPLVHYG.

15. The chimeric peptide sequence of claim 14, wherein the G corresponds to the last position of the N-terminal region.

16. The chimeric peptide sequence of claims 1 or 6, wherein the N-terminal region comprises amino acid residues DSSPLLQ, and wherein the Q residue is the last amino acid position of the N-terminal region.

17. The chimeric peptide sequence of claim 15 or 16, wherein the N-terminal region further comprises: RHPIP, wherein R is the first amino acid position of the N-terminal region; or HPIP, wherein H is the first amino acid position of the N-terminal region; or RPLAF, wherein R is the first amino acid position of the N-terminal region; or PLAF, wherein P is the first amino acid position of the N-terminal region; or R, wherein R is the first amino acid position of the N-terminal region.

18. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of any of M1-M98 variant peptide sequences, or a subsequence or fragment of any of the M1-M98 variant peptide sequences.

19. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of any of:
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR
SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS
PLETDSMDPFGLVTGLEAVRSPSFEK (M69);
RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK
HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE
TDSMDPFGLVTGLEAVRSPSFEK (M52);
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR
SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS
PLETDSMDPFGLVTGLEAVRSPSFEK (M5);
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL
KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE
AHSLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLS
MVGPSQGRSPSYAS (M71);
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL
KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE
AHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLS
MVGPSQGRSPSYAS (M72);
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL
KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE
AHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLS
MVVQDELQGVGGEGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE (M73);
RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH
SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGY
NVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD
MFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M1);
RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH

SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGY NVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD MFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M2);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M3);

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK (M48);

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK (M49);

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK (M50);

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK (M51);

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK (M53); and

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDS16MDPFGLVTGLEAVRSPSFEK (M70), or a subsequence or fragment of any of the foregoing peptide sequences, or any of the foregoing peptide sequences wherein the R terminal residue is deleted.

20. The chimeric peptide sequence of claims 1 or 2, wherein the N-terminal region comprises amino acid residues DSSPLLQFGGQV, and wherein the V residue corresponds to the last position of the N-terminal region.

21. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein amino acid residues HPIP are the first 4 amino acid residues of the N-terminal region.

22. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3, 6 or 19, wherein the first position of the N-terminal region is an R residue, or wherein the first position of the N-terminal region is an M residue, or wherein the first and second positions of the N-terminal region is an MR sequence, or wherein the first and second positions of the N-terminal region is an RM sequence, or wherein the first and second positions of the N-terminal region is an RD sequence, or wherein the first and second positions of the N-terminal region is an DS sequence, or wherein the first and second positions of the N-terminal region is an MD sequence, or wherein the first and second positions of the N-terminal region is an MS sequence, or wherein the first through third positions of the N-terminal region is an MDS sequence, or wherein the first through third positions of the N-terminal region is an RDS sequence, or wherein the first through third positions of the N-terminal region is an MSD sequence, or wherein the first through third positions of the N-terminal region is an MSS sequence, or wherein the first through third positions of the N-terminal region is an DSS sequence, or wherein the first through fourth positions of the N-terminal region is an RDSS sequence, or wherein the first through fourth positions of the N-terminal region is an MDSS sequence, or wherein the first through fifth positions of the N-terminal region is an MRDSS sequence, or wherein the first through fifth positions of the N-terminal region is an MSSPL sequence, or wherein the first through sixth positions of the N-terminal region is an MDSSPL sequence, or wherein the first through seventh positions of the N-terminal region is an MSDSSPL sequence.

23. The chimeric peptide sequence or peptide sequence of any one of claims 1 to 3 or 6, wherein the last position of the C-terminal region corresponds to about residue 194 of SEQ ID NO:99 [FGF19].

24. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of:
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR

SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; or DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof; DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK, or a subsequence or fragment thereof.

25. The chimeric peptide sequence or peptide sequence of claim 18, 19 or 24, wherein the subsequence or fragment thereof has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally.

26. The chimeric peptide sequence of claims 1, 2 or 6, wherein said N-terminal region, or said C-terminal region, comprises or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids.

27. The peptide sequence of claims 3 or 6, wherein said FGF19 sequence portion, or said FGF21 sequence portion, comprises or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids of FGF19 or FGF21.

28. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein said N-terminal region, or said C-terminal region, or said FGF19 sequence portion, or said FGF21 sequence portion, are joined by a linker or spacer.

29. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the N-terminus of the peptide sequence at comprises or consists of any of: HPIPDSSPLLQFGGQVRLRHLYTSG (M5); DSSPLLQFGGQVRLRHLYTSG (M6); RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7); HPIPDSSPLLQWGDPIRLRHLYTSG (M8); HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9); HPIPDSSPHVHYGWGDPIRLRHLYTSG (M10); RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11); RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12); RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13); HPIPDSSPHVHYGGQVRLRHLYTSG (M14); RPLAFSDAGPHVHWGDPIRLRHLYTSG (M15); RPLAFSDAGPHVHWGDPIRLRHLYTSG (M16); RPLAFSDAGPHVGWGDPIRLRHLYTSG (M17); RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18); RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19); RPLAFSDAGPVHGWGDPIRLRHLYTSG (M20); RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21); RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22); RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23); RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24); RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25); RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26); RPLAFSDSSPHVHWGDPIRLRHLYTSG (M22); RPLAFSDAGPHVWGDPIRLRHLYTSG (M28); RPLAFSDAGPHVHYWGDPIRLRHLYTSG (M29); RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30); RHPIPDSSPLLQFGAQVRLRHLYTSG (M31); RHPIPDSSPLLQFGDQVRLRHLYTSG (M32); RHPIPDSSPLLQFGPQV RLRHLYTSG (M33); RHPIPDSSPLLQFGGAVRLRHLYTSG (M34); RHPIPDSSPLLQFGGEVRLRHLYTSG (M35); RHPIPDSSPLLQFGGNVRLRHLYTSG (M36); RHPIPDSSPLLQFGGQARLRHLYTSG (M37); RHPIPDSSPLLQFGGQIRLRHLYTSG (M38); RHPIPDSSPLLQFGGQT RLRHLYTSG (M39);RHPIPDSSPLLQFGWGQPVRLRHLYTSG (M40); DAGPHVHYGWGDPIRLRHLYTSG (M74); VHYGWGDPIRLRHLYTSG (M75);

RLRHLYTSG (M77); or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted.

30. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the N-terminus of the peptide sequence at comprises or consists of any of: RHPIPDSSPLLQFGWGDPIRLRHLYTSG; RHPIPDSSPLLQWGDPIRLRHLYTSG; RPLAFSDAGPLLQFGWGDPIRLRHLYTSG; RHPIPDSSPHVHYGWGDPIRLRHLYTSG; RPLAFSDAGPLLQFGGQVRLRHLYTSG; RHPIPDSSPHVHYGGQVRLRHLYTSG; RPLAFSDAGPHVHYGGDIRLRHLYTSG; RDSSPLLQFGGQVRLRHLYTSG; RPLAFSDSSPLLQFGGQVRLRHLYTSG; RHPIPDSSPLLQFGAQVRLRHLYTSG; RHPIPDSSPLLQFGDQVRLRHLYTSG; RHPIPDSSPLLQFGPQVRLRHLYTSG; RHPIPDSSPLLQFGGAVRLRHLYTSG; RHPIPDSSPLLQFGGEVRLRHLYTSG; RHPIPDSSPLLQFGGNVRLRHLYTSG; RHPIPDSSPLLQFGGQARLRHLYTSG; RHPIPDSSPLLQFGGQIRLRHLYTSG; RHPIPDSSPLLQFGGQTRLRHLYTSG; RHPIPDSSPLLQFGWGQPVRLRHLYTSG; or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted.

31. The chimeric peptide sequence or peptide sequence of claims 29 or 30, wherein the peptide sequence further comprises the addition of amino acid residues 30-194 of SEQ ID NO:99 [FGF19] at the C-terminus, resulting in a chimeric polypeptide.

32. The chimeric peptide sequence or peptide sequence of any of claims 29 or 30, wherein the peptide sequence further comprises all or a portion of an FGF19 sequence set forth as: PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGA DGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGF LPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE K positioned at the C-terminus of the peptide, or wherein the amino terminal "R" residue is deleted from the peptide.

33. A subsequence of a chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the subsequence has at least one amino acid deletion.

34. The subsequence of claim 33, wherein the subsequence has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally.

35. The peptide sequence of claim 6, wherein the reference or wild type FGF19 sequence is set forth as:
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDG
YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES
DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:99).

36. The peptide sequence of claim 6, wherein the reference or wild type FGF21 sequence is set forth as:
RHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQ
LKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQS
EAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPL
SMVGPSQGRSPSYAS (SEQ ID NO:100).

37. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the N-terminal region first amino acid position is a "M" residue, an "R" residue, a "S" residue, a "H" residue, a "P" residue, a "L" residue or an "D" residue, or wherein the peptide sequence does not have a "M" residue or an "R" residue at the first amino acid position of the N-terminal region.

38. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the N-terminal region comprises any one of the following sequences: MDSSPL, MSDSSPL, SDSSPL, MSSPL or SSPL.

39. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has reduced hepatocellular carcinoma (HCC) formation compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

40. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has greater glucose lowering activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

41. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has less lipid increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

42. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has less triglyceride, cholesterol, non-HDL or HDL increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, WGDPV, WGDI, GDPI, GPI, WGQPI, WGAPI, AGDPI, WADPI, WGDAI, WGDPA, WDPI, WGDI, WGDP or FGDPI substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

43. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has less lean mass reducing activity compared to FGF21.

44. The chimeric peptide sequence or peptide sequence of any of claims 39 to 43, wherein the hepatocellular carcinoma (HCC) formation, glucose lowering activity, lipid increasing activity, or lean mass reducing activity is ascertained in a *db/db* mouse.

45. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence binds to fibroblast growth factor receptor 4 (FGFR4) or activates FGFR4, or does not detectably bind to fibroblast growth factor receptor 4 (FGFR4) or activate FGFR4.

46. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence binds to FGFR4 with an affinity less than, comparable to or greater than FGF19 binding affinity for FGFR4.

47. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence activates FGFR4 to an extent or amount less than, comparable to or greater than FGF19 activates FGFR4.

48. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions, deletions or insertions.

49. The chimeric peptide sequence or peptide sequence of claim 48, wherein the amino acid deletions are at the N- or C-terminus, or internal.

50. The chimeric peptide sequence or peptide sequence of claim 48, wherein the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI).

51. The chimeric peptide sequence or peptide sequence of any of claims 1 to 3 or 6, wherein the peptide sequence comprises one or more L-amino acids, D-amino acids, non-naturally occurring amino acids, or amino acid mimetic, derivative or analogue.

52. A composition, comprising the chimeric peptide sequence or peptide sequence of any of claims 1 to 51.

53. A pharmaceutical composition, comprising the chimeric peptide sequence or peptide sequence of any of claims 1 to 51.

54. A pharmaceutical composition, comprising the chimeric peptide sequence or peptide sequence of any of claims 1 to 51, and a glucose lowering agent.

55. The chimeric peptide sequence or peptide sequence of any of claims 1 to 51, wherein the peptide sequence is isolated or purified.

56. A nucleic acid molecule encoding the chimeric peptide sequence or peptide sequence of any of claims 1 to 51.

57. The nucleic acid molecule of claim 56, further comprising an expression control element in operable linkage that confers expression of the nucleic acid molecule encoding the peptide in vitro, in a cell or in vivo.

58. A vector comprising the nucleic acid molecule of claims 56 or 57.

59. The vector of claim 58, wherein the vector comprises a viral vector.

60. A transformed or host cell that expresses the chimeric peptide sequence or peptide sequence of any of claims 1 to 51.

61. A method of treating a subject having, or at risk of having, a disease or disorder treatable by the chimeric peptide sequence or peptide sequence of any of claims 1 to 51,

comprising administering the chimeric peptide sequence or peptide sequence to a subject in an amount effective for treating the disorder.

62. The method of claim 61, wherein the disease or disorder comprises a hyperglycemic condition, insulin resistance, hyperinsulinemia, glucose intolerance or metabolic syndrome.

63. The method of claim 62, wherein the hyperglycemic condition comprises diabetes.

64. The method of claim 62, wherein the hyperglycemic condition comprises insulin-dependent (type I) diabetes, type II diabetes, or gestational diabetes.

65. The method of claim 61, wherein the disorder comprises obesity or an undesirable body mass.

66. A method of improving glucose metabolism in a subject in need thereof, comprising administering the chimeric peptide sequence or peptide sequence of any of claims 1 to 51 to a subject in an amount effective to improve glucose metabolism in the subject.

67. The method of claim 63, wherein the subject has a fasting plasma glucose level greater than 100 mg/dl or has a hemoglobin A1c (HbA1c) level above 6%.

68. The method of claims 63 or 67, wherein the method results in reduced glucose levels, increased insulin sensitivity, reduced insulin resistance, reduced glucagon, an improvement in glucose tolerance, or glucose metabolism or homeostasis, improved pancreatic function, a reduced triglyceride, cholesterol, IDL, LDL or VLDL levels, a decrease in blood pressure, a decrease in intimal thickening of the blood vessel, or a decrease in body mass or weight gain.

69. A method for identifying a peptide sequence having glucose lowering activity without substantial hepatocellular carcinoma (HCC) activity, comprising:
a) providing a candidate peptide sequence;
b) administering the candidate peptide sequence to a test animal;
c) measuring glucose levels of the animal after administration of the candidate peptide sequence, to determine if the candidate peptide sequence reduces glucose levels; and
d) analyzing the candidate peptide sequence for induction of HCC in the animal, or expression of a marker correlating with HCC activity, wherein a candidate peptide having glucose lowering activity and not substantial HCC activity thereby identifies the

candidate peptide sequence as a peptide sequence having glucose lowering activity without substantial hepatocellular carcinoma (HCC) activity.

70. The method of claim 69, wherein the test animal is a db/db mouse.

71. The method of claim 69, further comprising assessing a hepatic tissue sample from the test animal to determine whether the candidate peptide sequence exhibits evidence of inducing HCC.

72. The method of claim 69, wherein the marker correlating with HCC activity comprises lipid profile, and wherein less lipid increasing activity compared to FGF19 indicates the peptide does not have substantial HCC activity.

73. The method of claim 69, wherein the marker correlating with HCC activity comprises aldo-keto reductase gene expression, and wherein up-regulating or increasing aldo-keto reductase gene expression compared to FGF19 indicates that the peptide does not have substantial HCC activity.

74. The method of claim 69, wherein the marker indicative of HCC activity comprises Slc1a2 gene expression, and wherein down-regulating or decreasing Slc1a2 gene expression compared to FGF21 indicates that the peptide does not have substantial HCC activity.

Figure 1

FGF19
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

FGF21
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M5
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA
LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS
LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT
GLEAVRSPSFEK

M71
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M72
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M73
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGG
EGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE

M1
RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

M2

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

M69

RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA
LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS
LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT
GLEAVRSPSFEK

M3

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHR
LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPF
GLVTGLEAVRSPSFEK

M48

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

M49

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLP
VSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGL
VTGLEAVRSPSFEK

M50

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

M51

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

M52

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

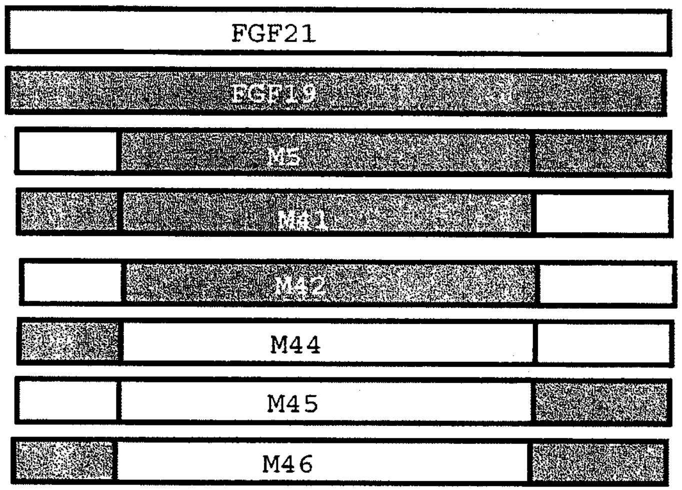
M53

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

M70

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

Figure 2



FGF21 (amino acid position)	FGF19	Glucose Lowering	Lipid Elevation
1-181	-	+	-
-	1-194	+	+
1-16	21-194	+	-
147-181	1-147	+/-	+
1-16 & 147-181	21-147	-	-
17-181	1-20	+	+
1-146	148-194	+	-
17-146	1-20 & 148-194	+/-	-

Figure 3A

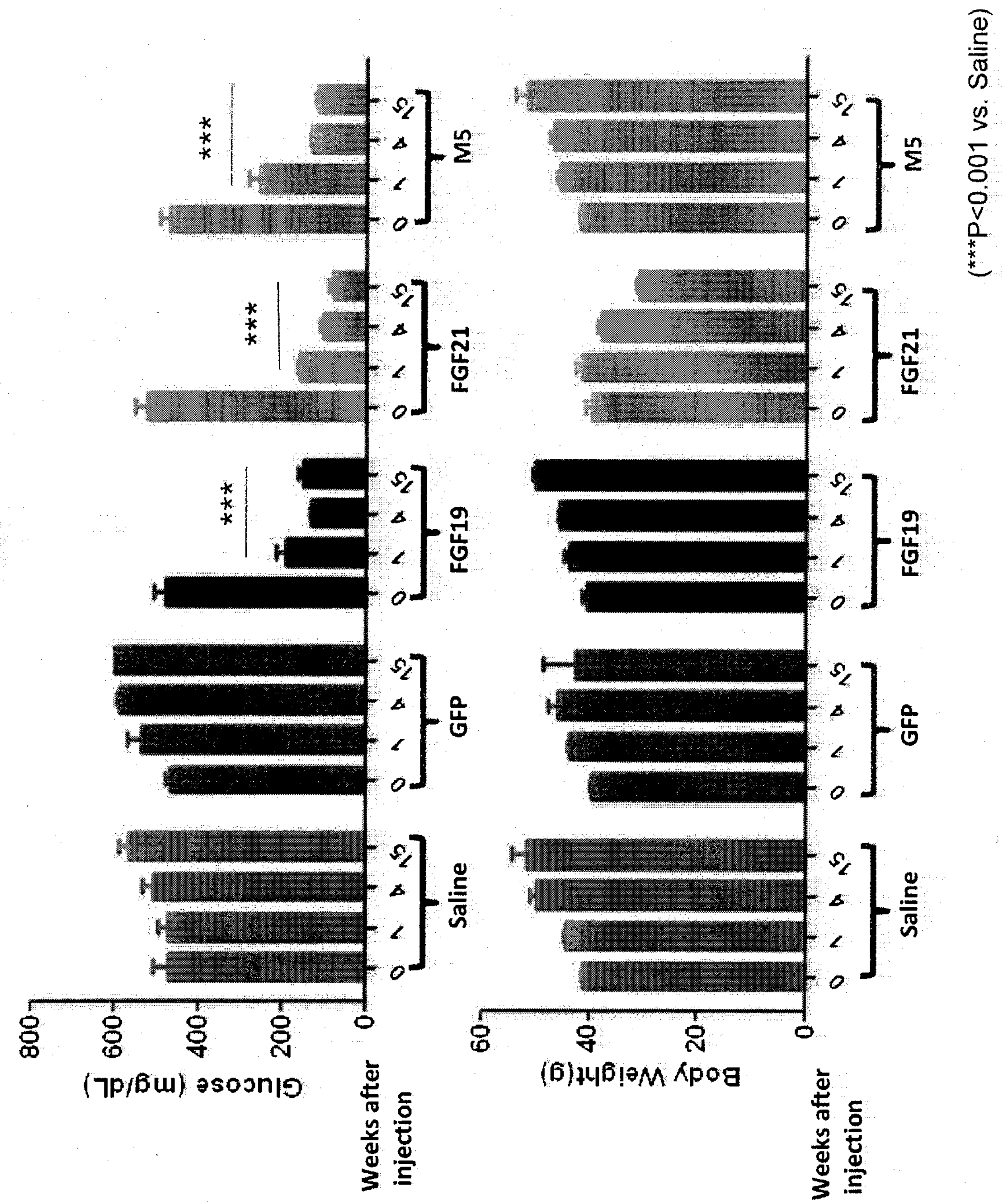

Glucose (mg/dL)
800
600
400
200
0
***
***
***
Weeks after injection
0
1
4
15
Saline
GFP
FGF19
FGF21
M5
Body Weight(g)
60
40
20
0
Weeks after injection
(***P<0.001 vs. Saline)

Figure 3B

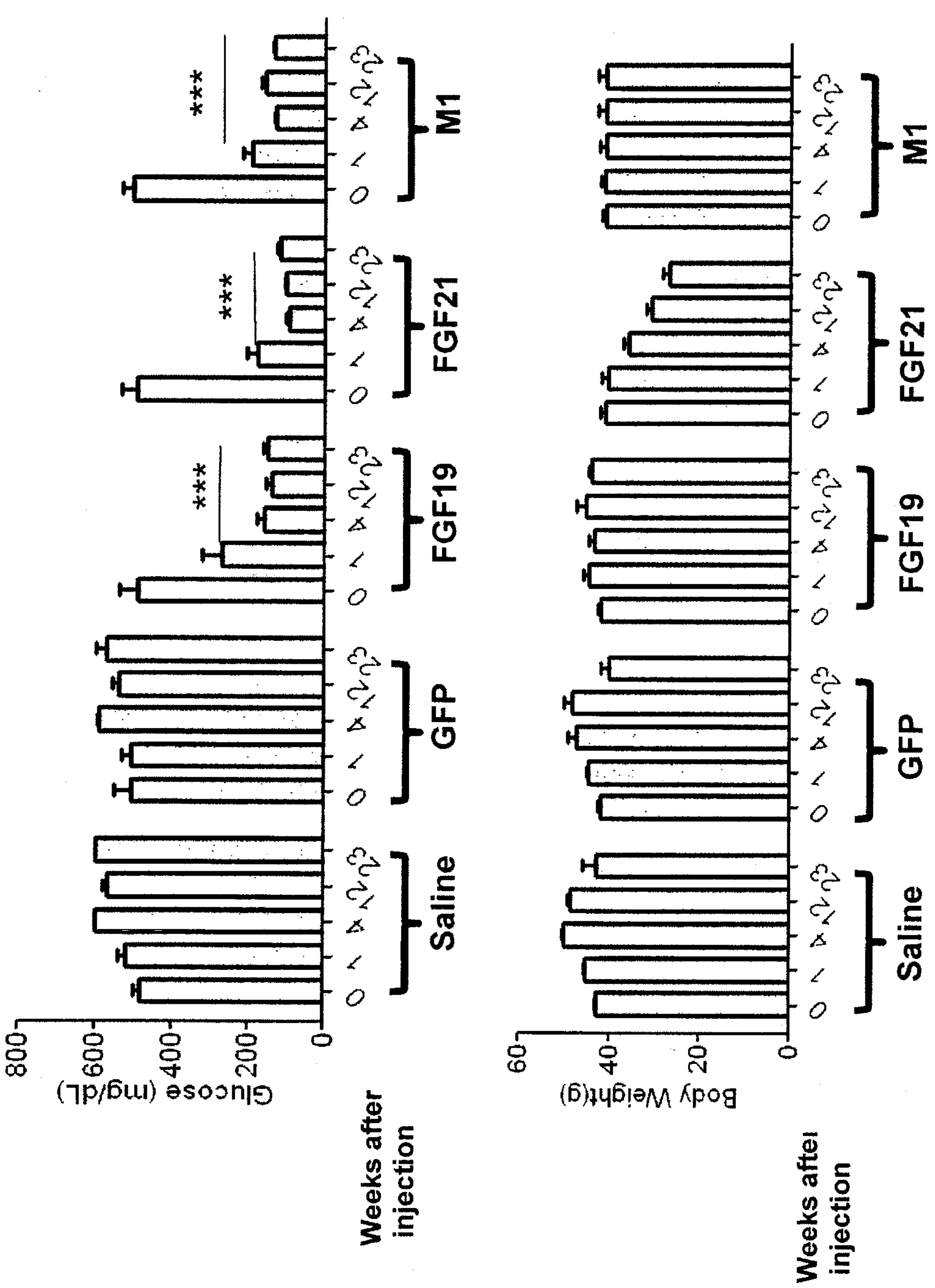

Glucose (mg/dL)
0
200
400
600
800
Body Weight(g)
0
20
40
60
***
Saline
GFP
FGF19
FGF21
M1
Weeks after injection
Weeks afte injection

Figure 3C

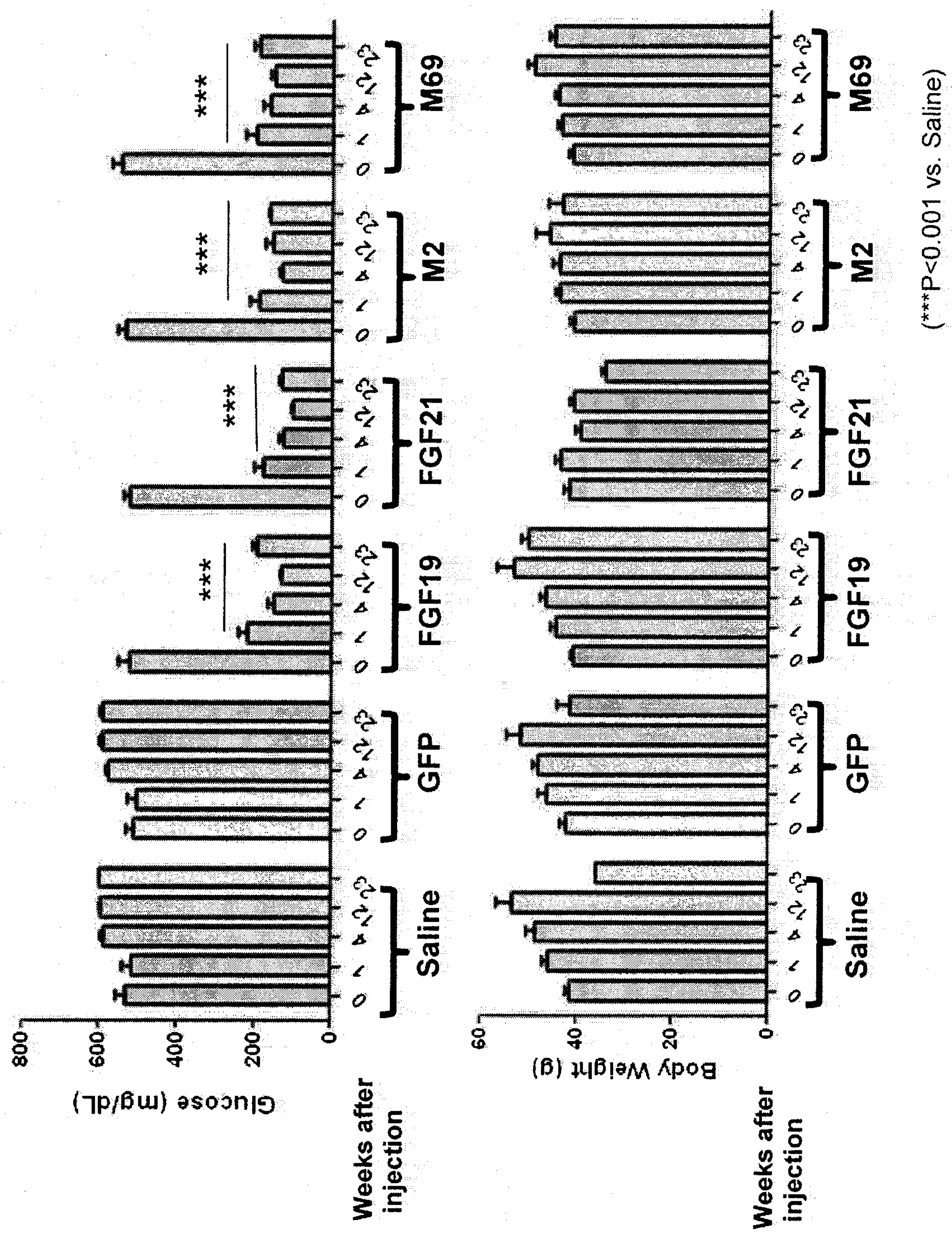

Glucose (mg/dL)
800
600
400
200
0
Body Weight (g)
60
40
20
0
Weeks after injection
0
1
4
12
13
Saline
GFP
FGF19
FGF21
M2
M69
***
(***P<0.001 vs. Saline)

Figure 3D

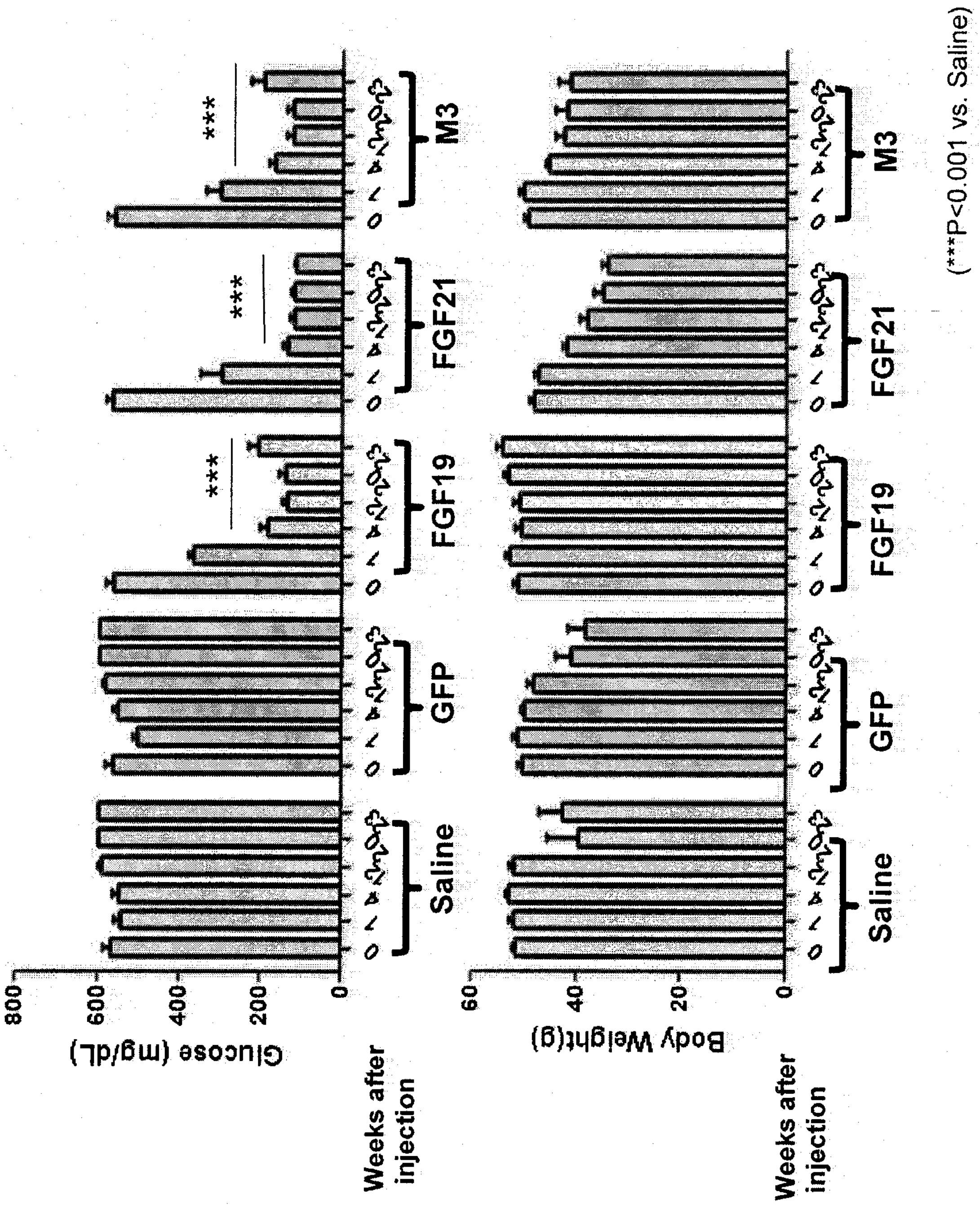
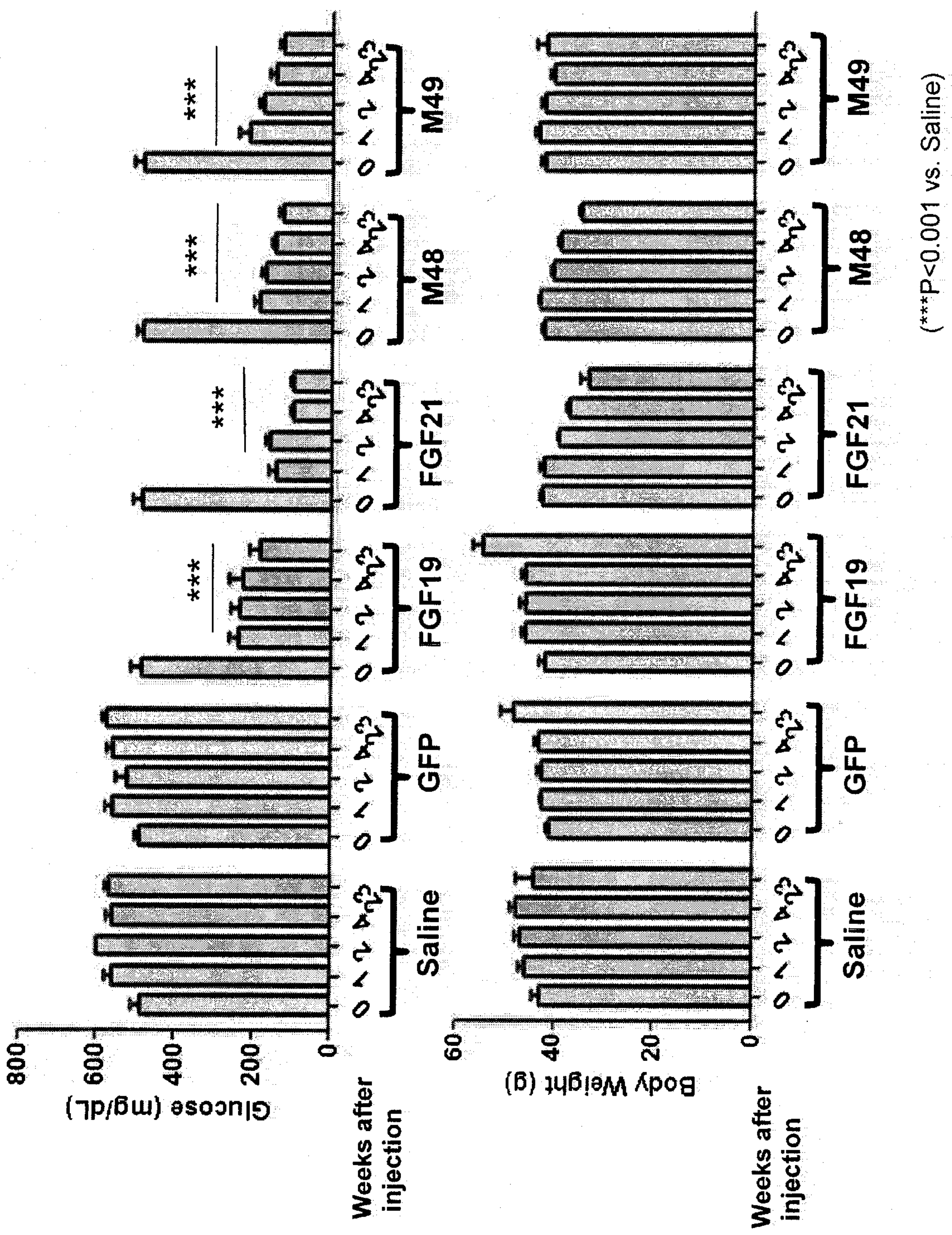

Glucose (mg/dL)
800
600
400
200
0
***
Weeks after injection
Saline
GFP
FGF19
FGF21
M3
Body Weight(g)
60
40
20
0
Weeks after injection
Saline
GFP
FGF19
FGF21
M3
(***P<0.001 vs. Saline)

Figure 3E



Glucose (mg/dL)
800
600
400
200
0
Weeks after injection
0 1 2 4 12
Saline
GFP
FGF19
FGF21
M48
M49
***
Body Weight (g)
60
40
20
0
Weeks after injection
(***P<0.001 vs. Saline)

Figure 3F

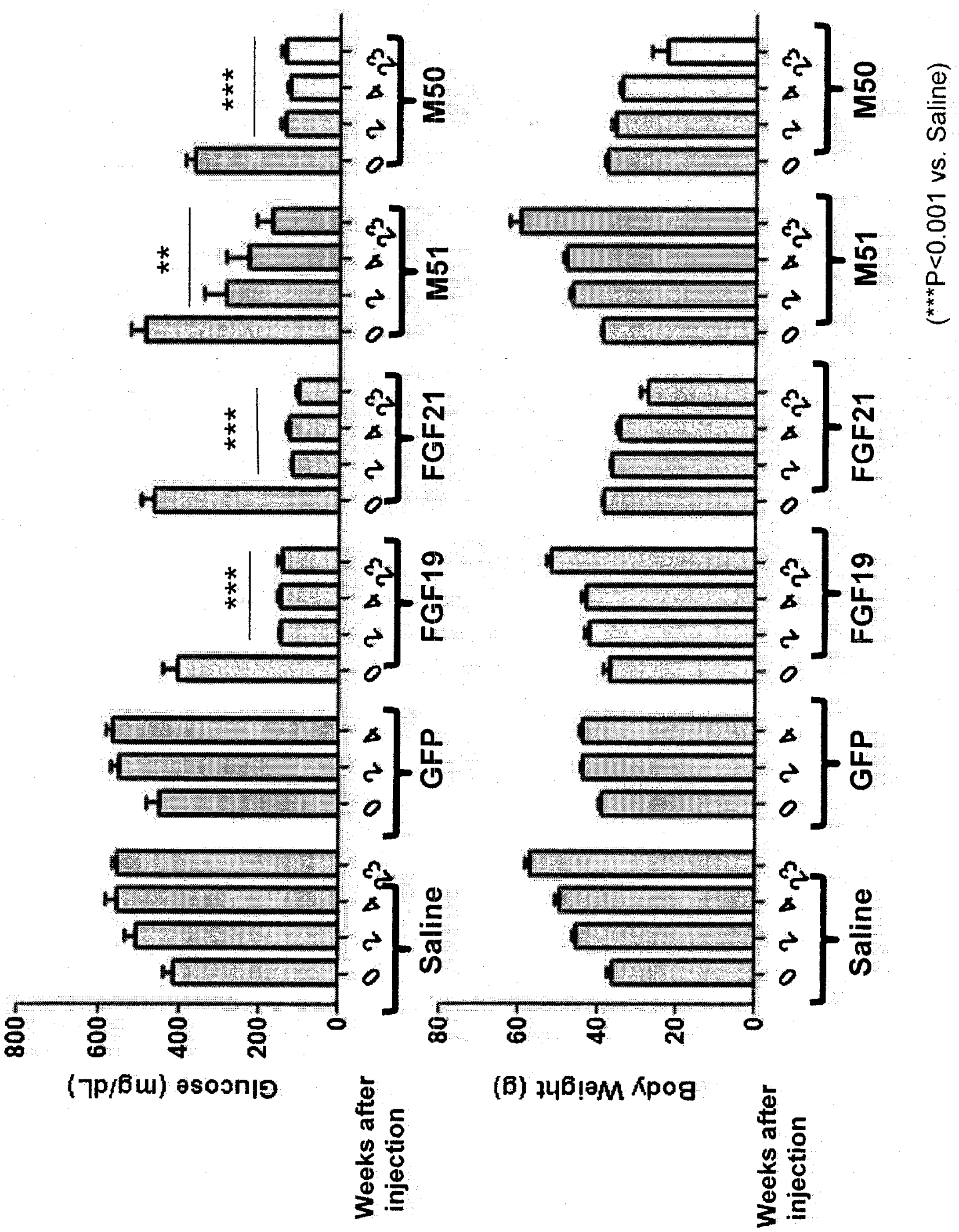

Glucose (mg/dL)
800
600
400
200
0
***
**
***
***
Weeks after injection
Saline
GFP
FGF19
FGF21
M51
M50
Body Weight (g)
80
60
40
20
0
Weeks after injection
Saline
GFP
FGF19
FGF21
M51
M50
(***P<0.001 vs. Saline)

Figure 3G

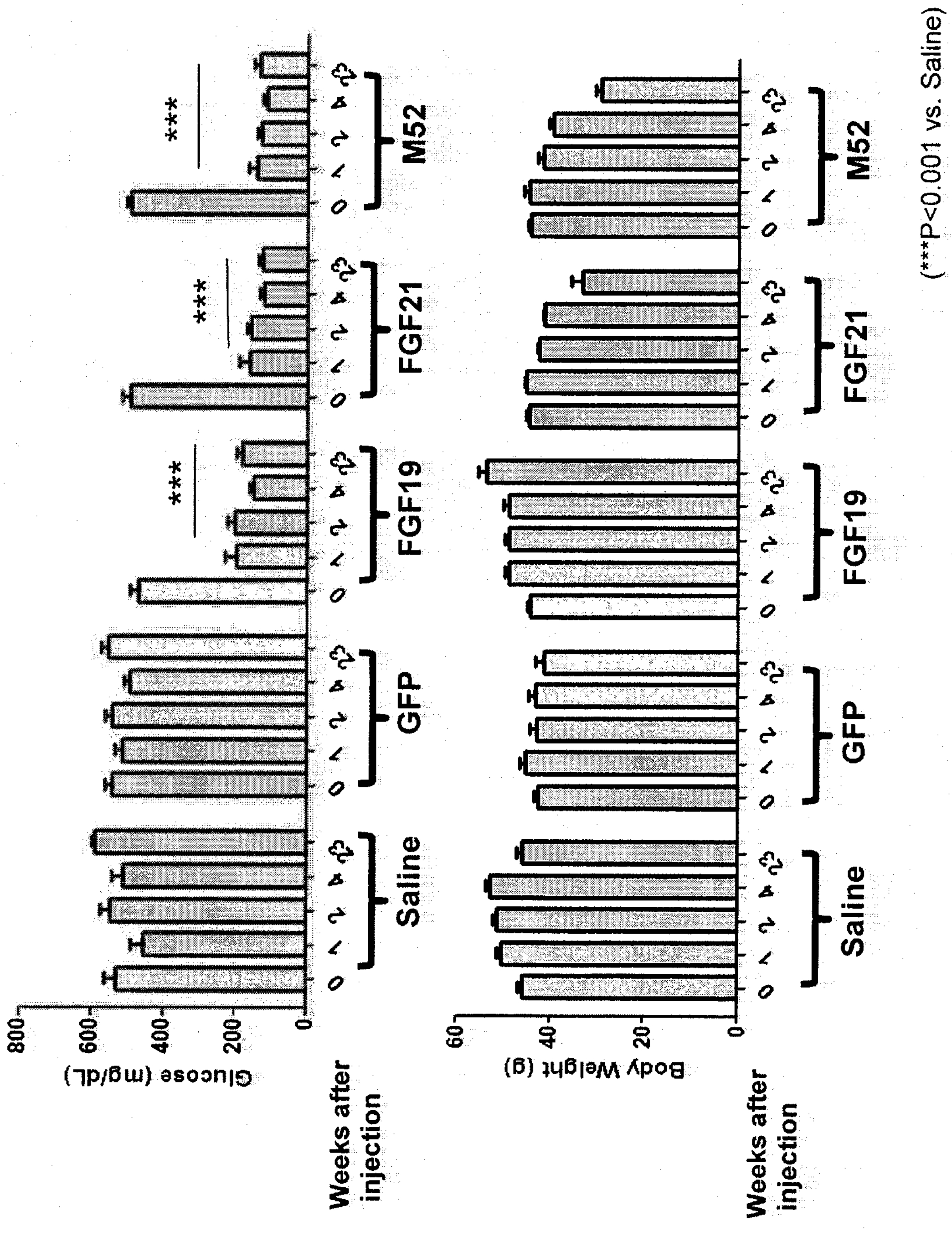

Glucose (mg/dL)
800
600
400
200
0
Weeks after injection
0 1 2 4 8
Saline
GFP
FGF19
FGF21
M52
***
Body Weight (g)
60
40
20
0
Weeks after injection
(***P<0.001 vs. Saline)

Figure 3H

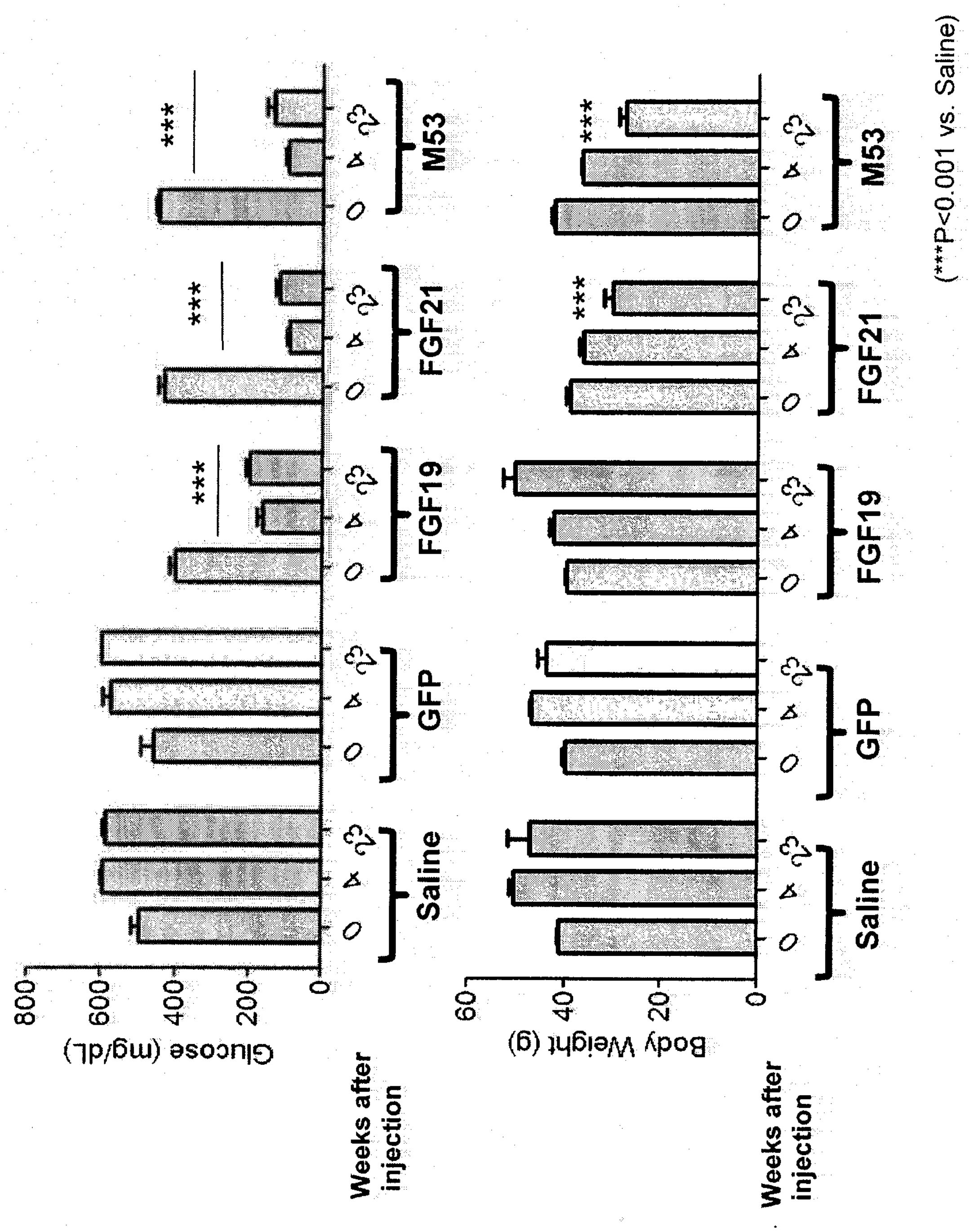

Glucose (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M53
Weeks after injection
Body Weight (g)
60
40
20
0
(***P<0.001 vs. Saline)

Figure 3I

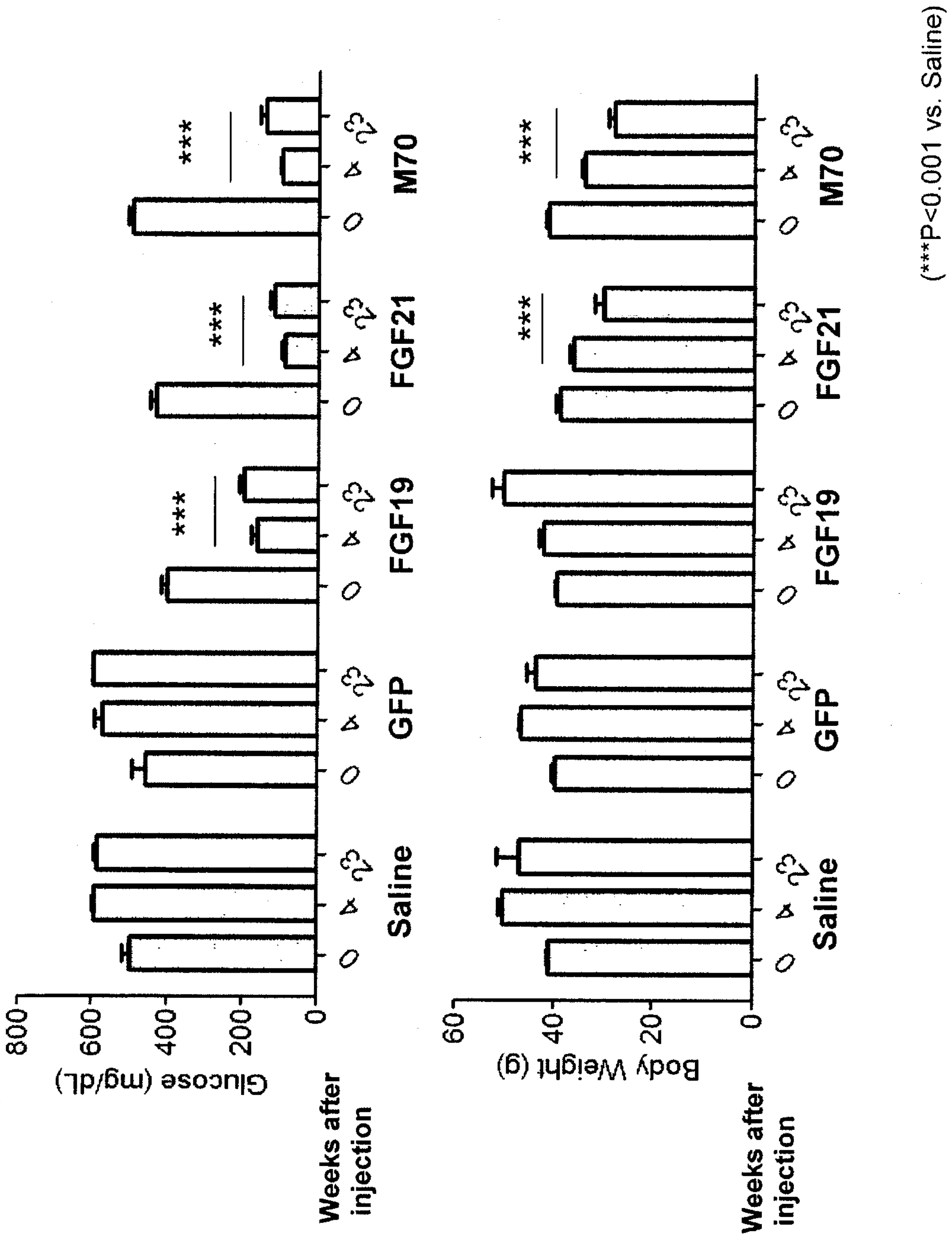

Glucose (mg/dL)
800
600
400
200
0
Body Weight (g)
60
40
20
0
Weeks after injection
0
4
12
Saline
GFP
FGF19
FGF21
M70
***
(***P<0.001 vs. Saline)

Figure 4A

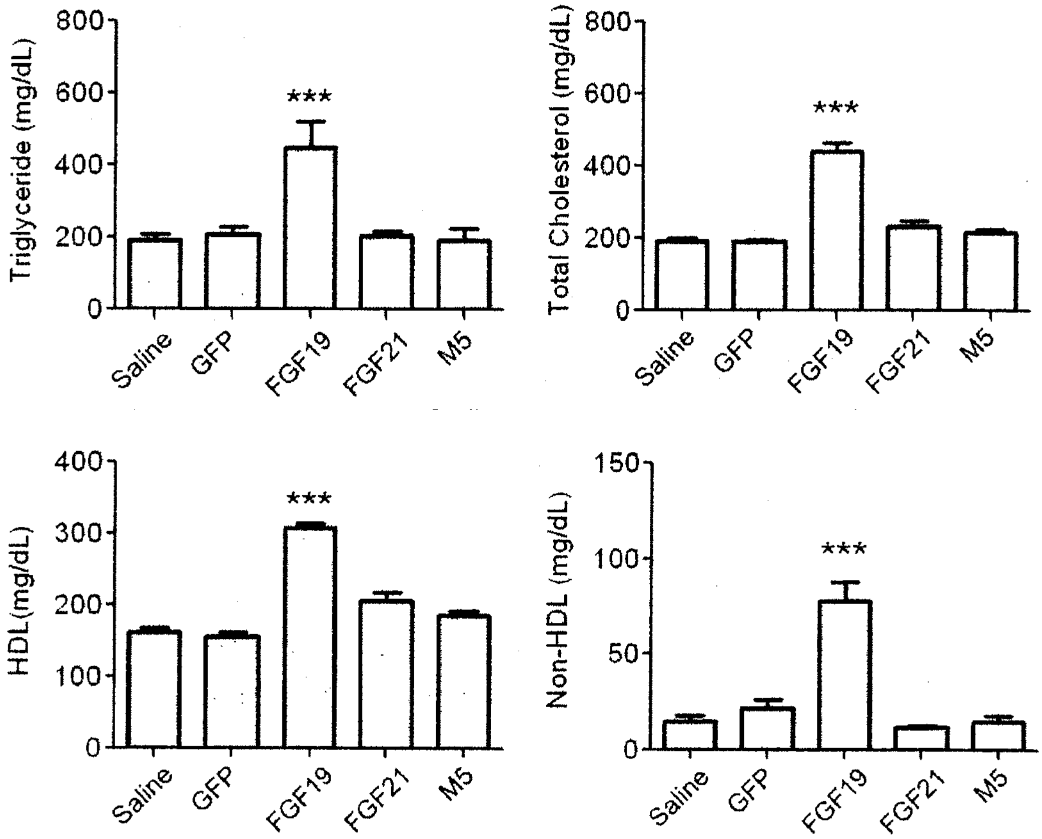

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M5
Total Cholesterol (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M5
HDL(mg/dL)
400
300
200
100
0
***
Saline
GFP
FGF19
FGF21
M5
Non-HDL (mg/dL)
150
100
50
0
***
Saline
GFP
FGF19
FGF21
M5

Figure 4B

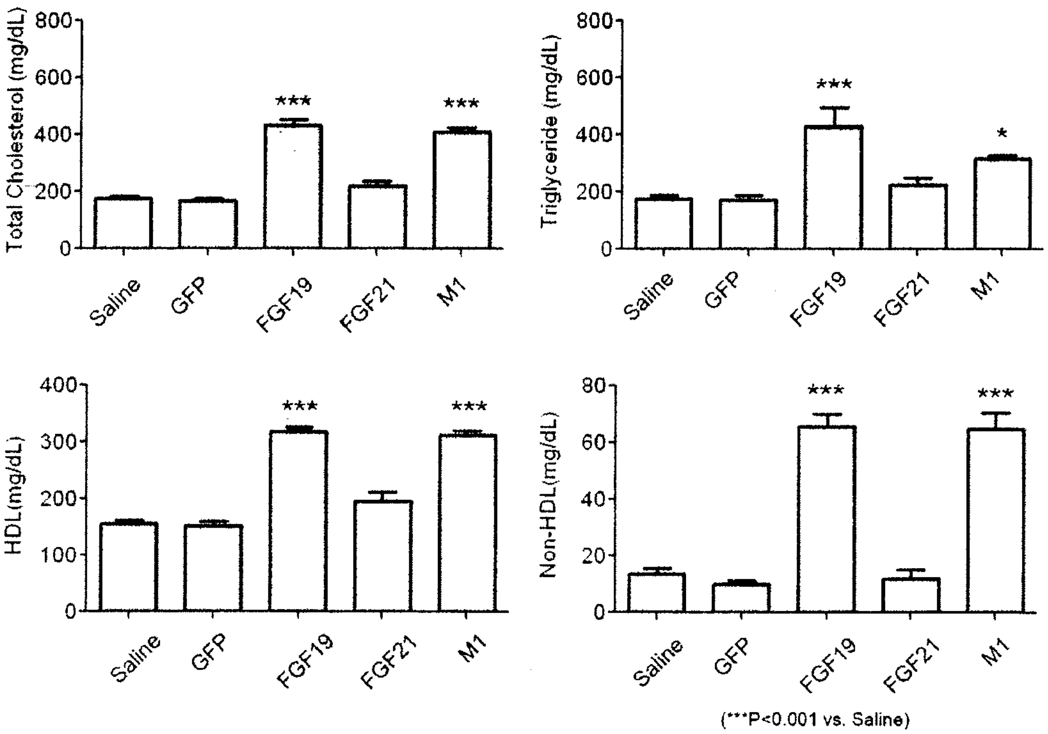
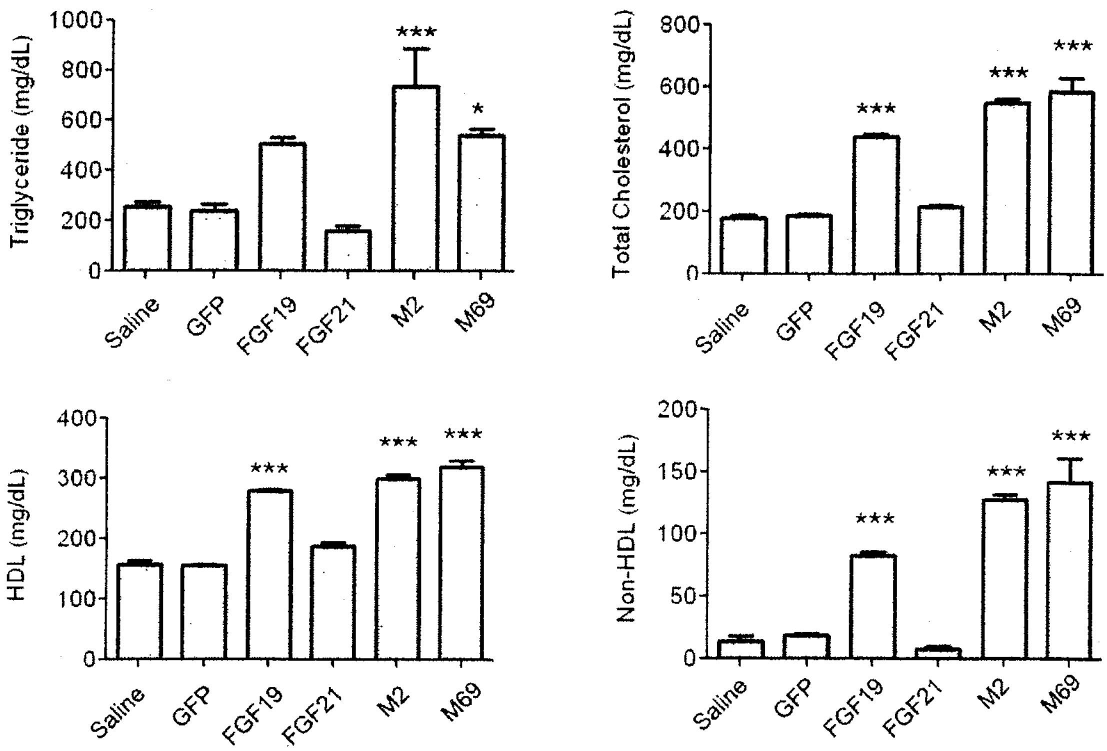

Total Cholesterol (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M1
Triglyceride (mg/dL)
800
600
400
200
0
***
*
Saline
GFP
FGF19
FGF21
M1
HDL(mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M1
Non-HDL(mg/dL)
80
60
40
20
0
***
***
Saline
GFP
FGF19
FGF21
M1
(***P<0.001 vs. Saline)

Figure 4C



(***P<0.001 vs. Saline)

Figure 4D

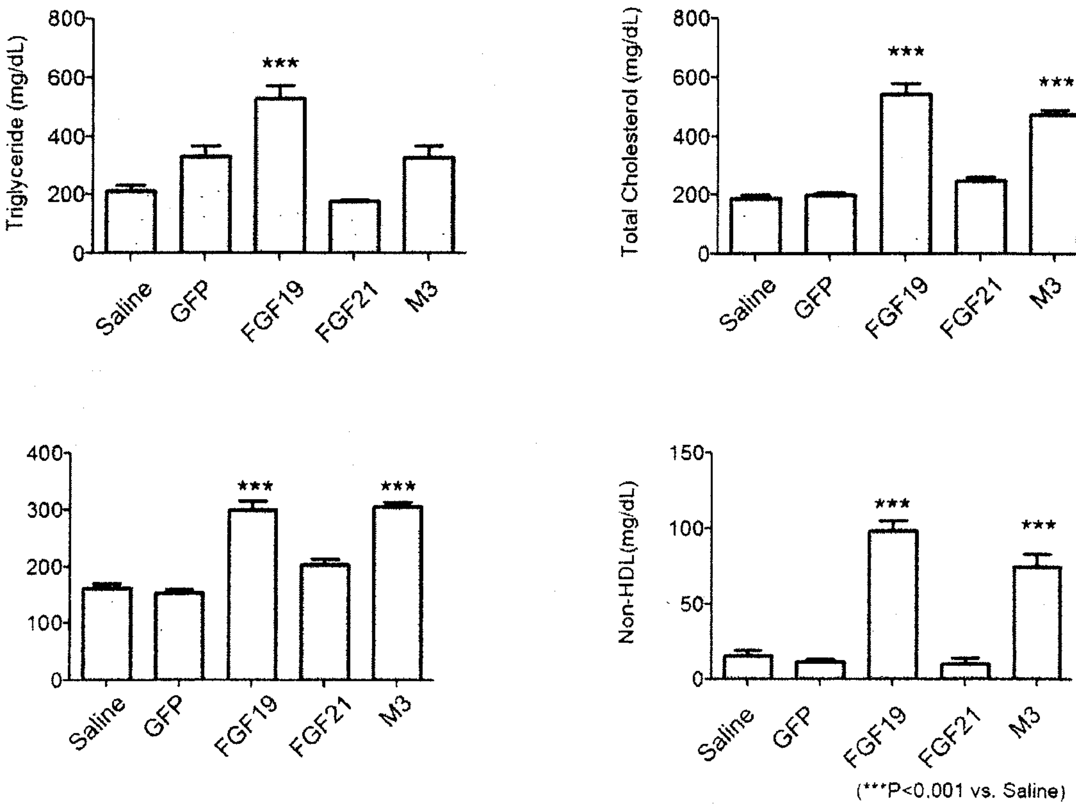

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M3
Total Cholesterol (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M3
HDL(mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M3
Non-HDL(mg/dL)
150
100
50
0
***
***
Saline
GFP
FGF19
FGF21
M3
(***P<0.001 vs. Saline)

Figure 4E

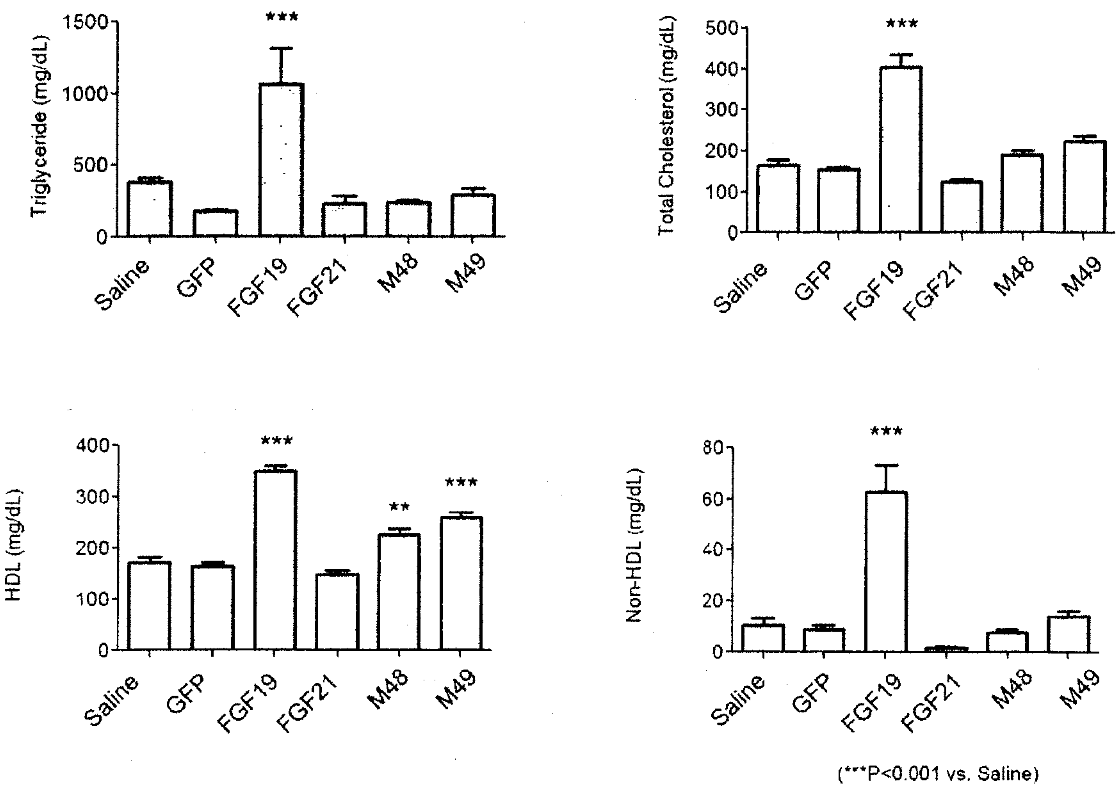
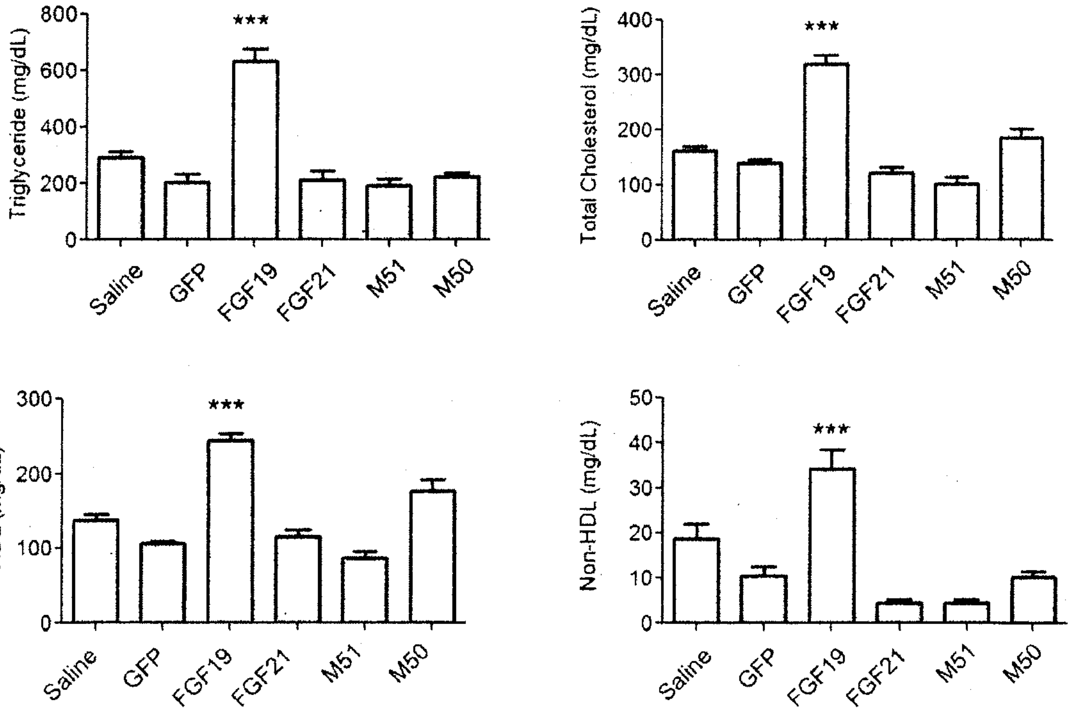
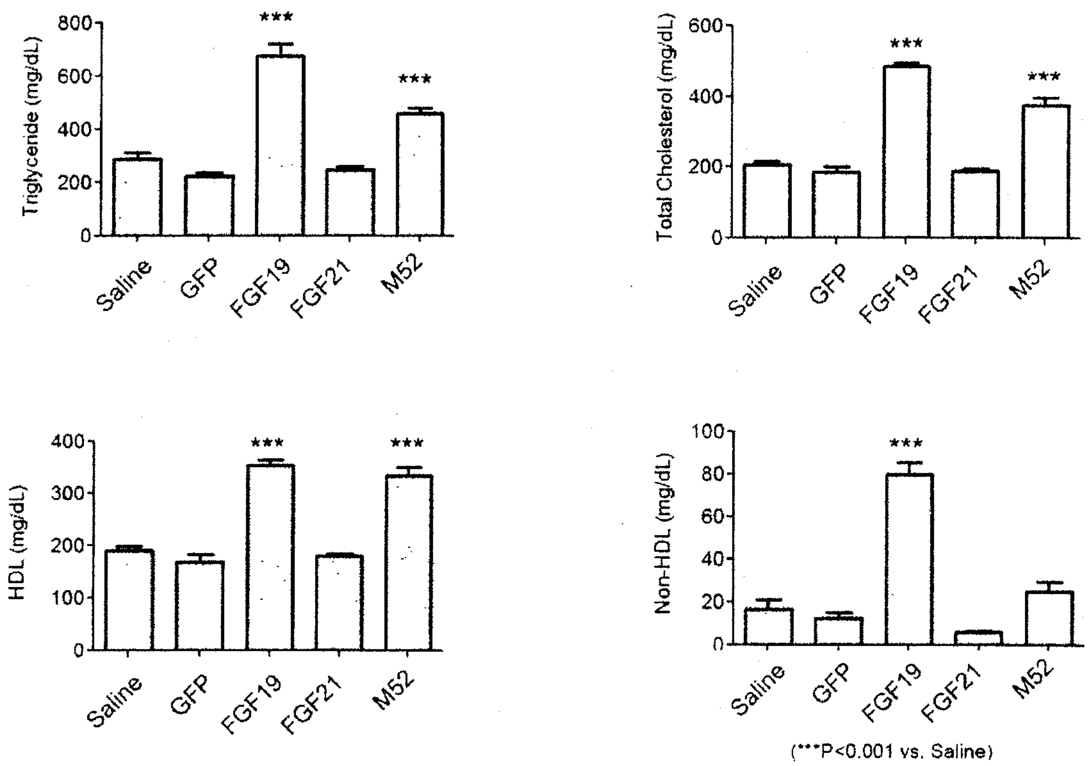

Triglyceride (mg/dL)
1500
1000
500
0
***
Saline
GFP
FGF19
FGF21
M48
M49
Total Cholesterol (mg/dL)
500
400
300
200
100
0
***
HDL (mg/dL)
400
300
200
100
0
***
**
***
Non-HDL (mg/dL)
80
60
40
20
0
***
(***P<0.001 vs. Saline)

Figure 4F



(***P<0.001 vs. Saline)

Figure 4G



Triglyceride (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M52
Total Cholesterol (mg/dL)
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M52
HDL (mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M52
Non-HDL (mg/dL)
100
80
60
40
20
0
***
Saline
GFP
FGF19
FGF21
M52
(***P<0.001 vs. Saline)

Figure 4H

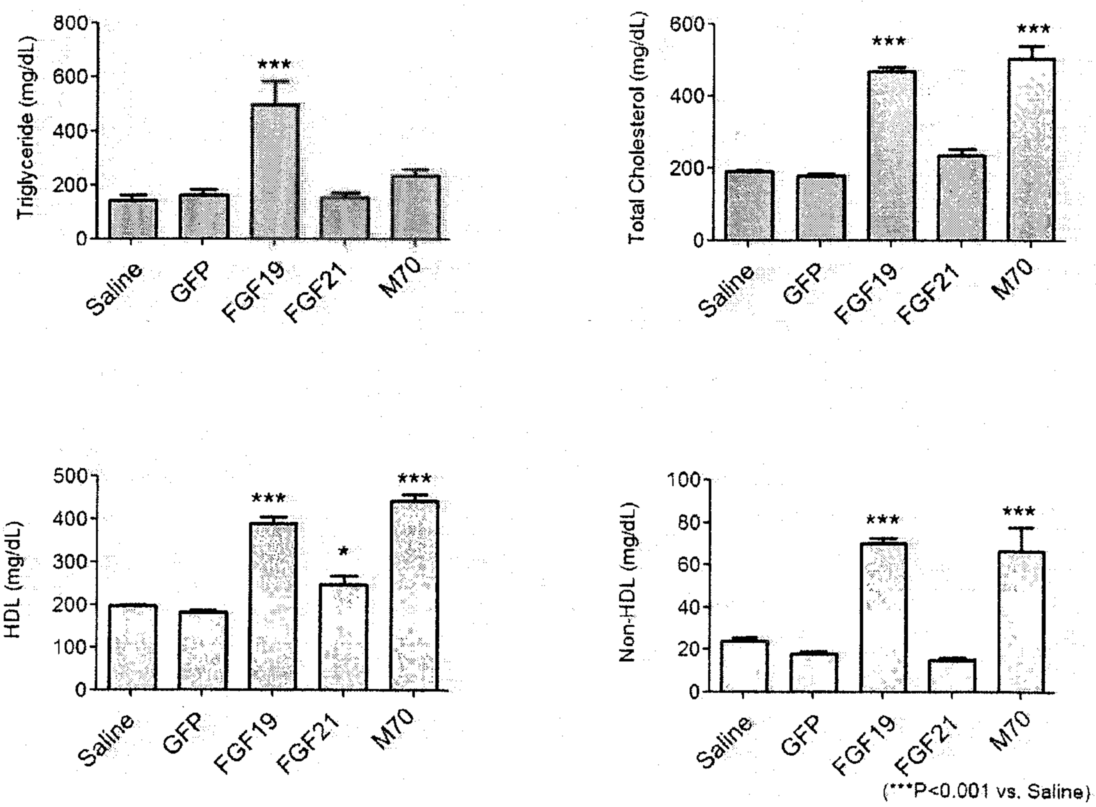

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M70
Total Cholesterol (mg/dL)
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M70
HDL (mg/dL)
500
400
300
200
100
0
***
*
***
Saline
GFP
FGF19
FGF21
M70
Non-HDL (mg/dL)
100
80
60
40
20
0
***
***
Saline
GFP
FGF19
FGF21
M70
(***P<0.001 vs. Saline)

Figure 4I

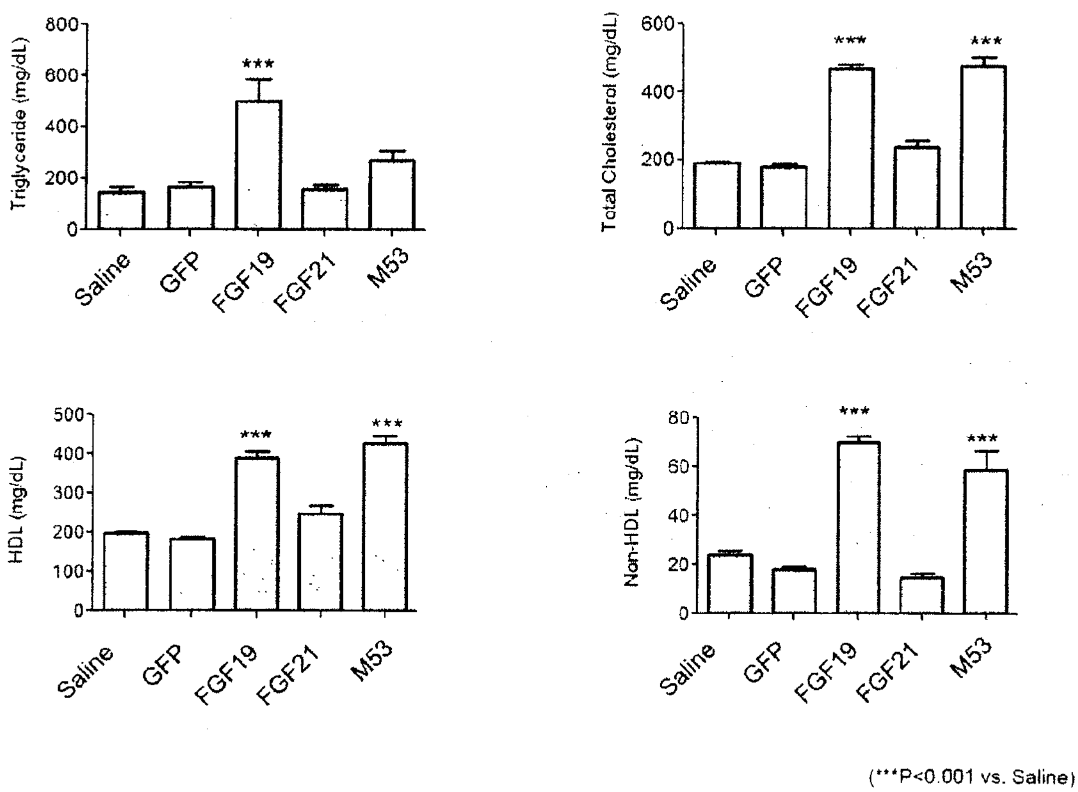
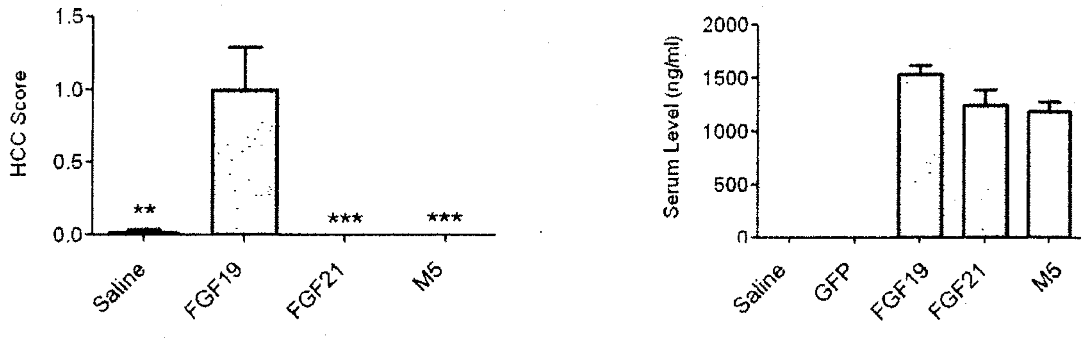
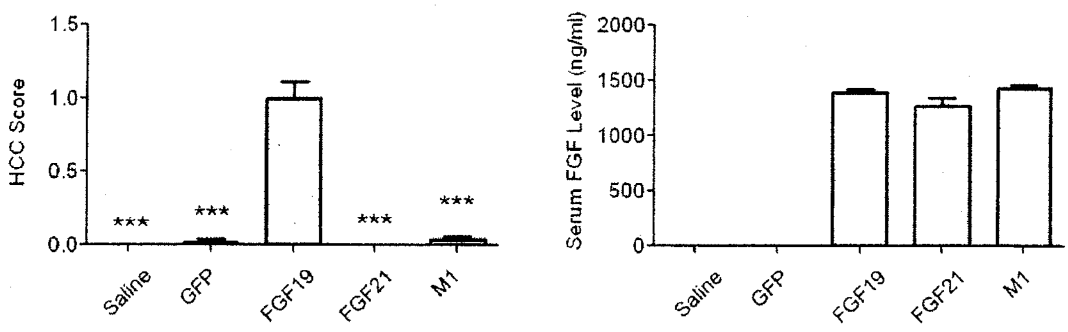

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M53
Total Cholesterol (mg/dL)
600
400
200
0
***
***
HDL (mg/dL)
500
400
300
200
100
0
Non-HDL (mg/dL)
80
60
40
20
0
(***P<0.001 vs. Saline)

Figure 5A



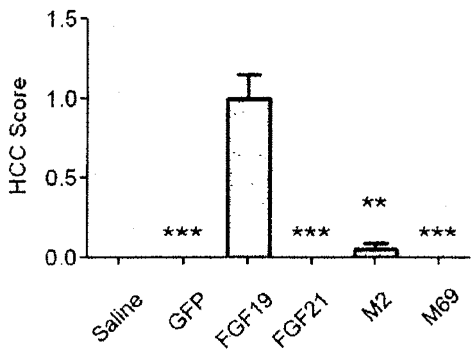
(***P<0.001 vs. FGF19)

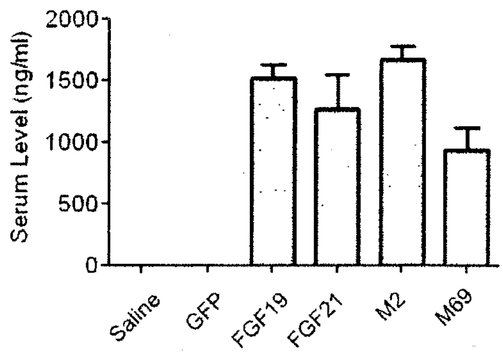
Figure 5B



(***P<0.001 vs. FGF19)

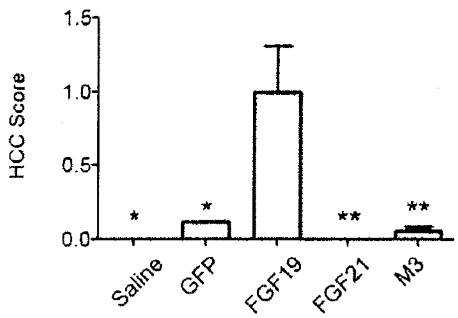
Figure 5C

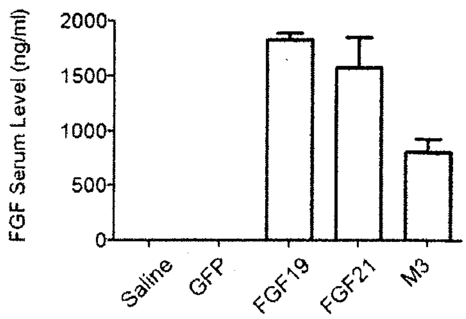




(***P<0.001 vs. FGF19)

Figure 5D





(***P<0.001 vs. FGF19)

Figure 5E

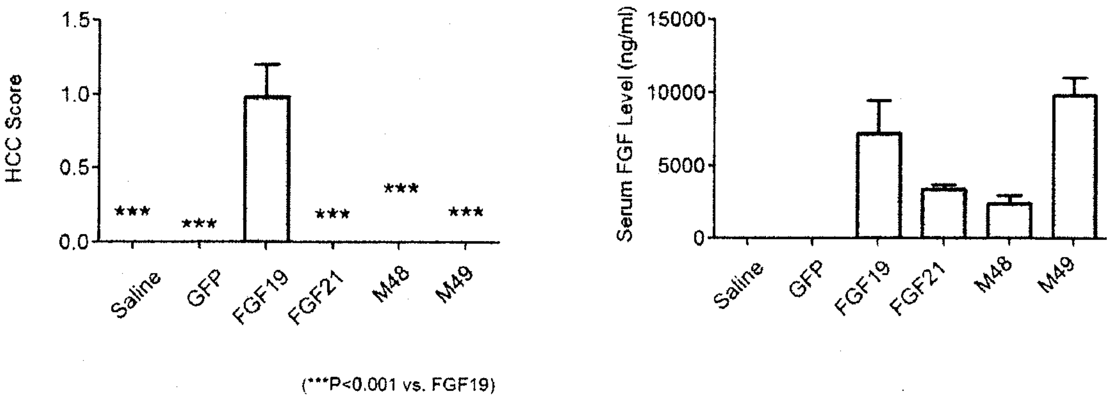


Figure 5F

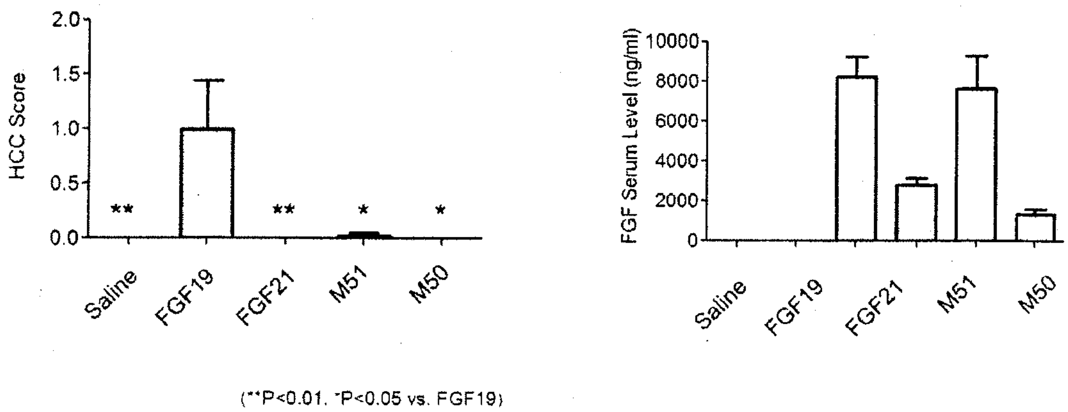
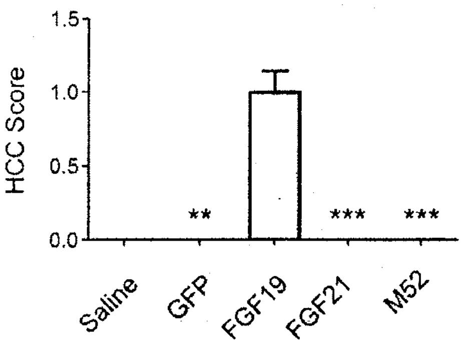
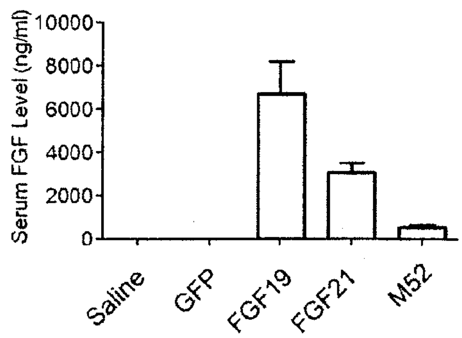


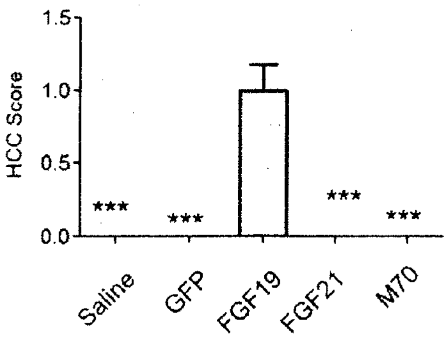
Figure 5G

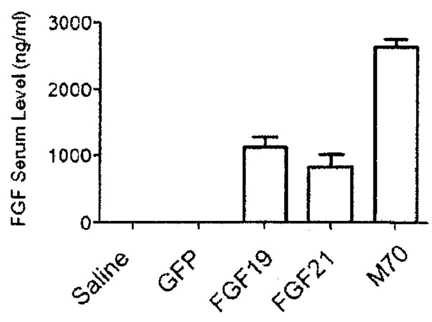




(***P<0.001 vs. FGF19)

Figure 5H





(***P<0.001 vs. FGF19)

Figure 5I

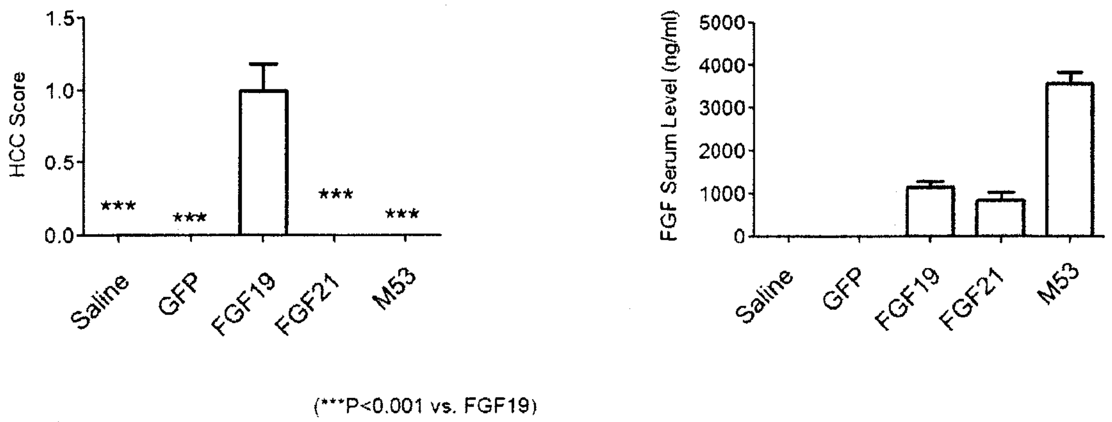
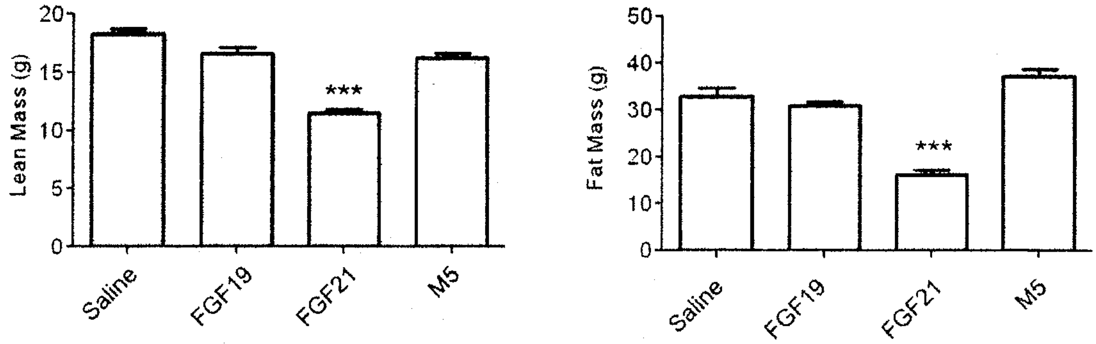
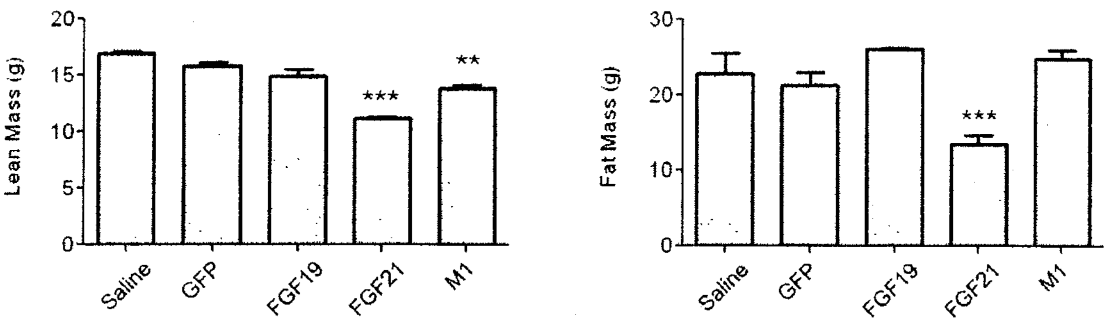

1.5
1.0
0.5
0.0
HCC Score
***
***
***
***
Saline
GFP
FGF19
FGF21
M53
5000
4000
3000
2000
1000
0
FGF Serum Level (ng/ml)
Saline
GFP
FGF19
FGF21
M53
(***P<0.001 vs. FGF19)

Figure 6A



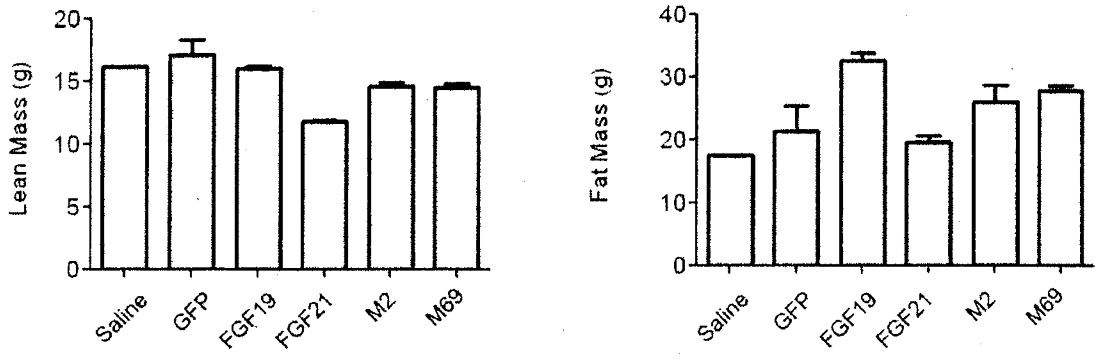
(***P<0.001 vs. Saline)

Figure 6B



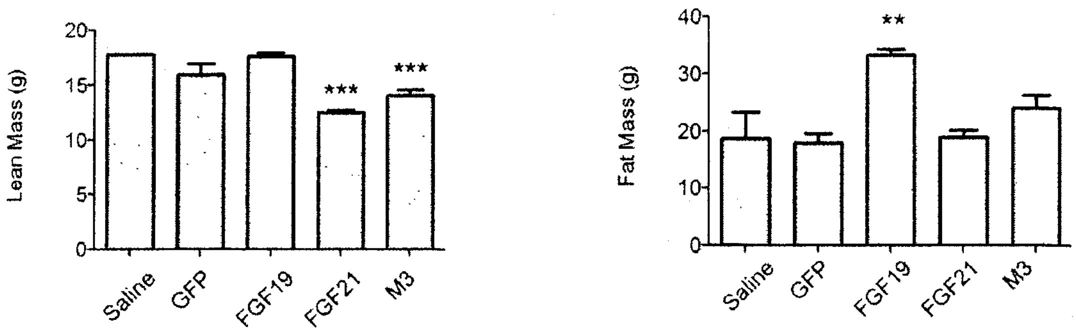
(***P<0.001 vs. Saline)

Figure 6C



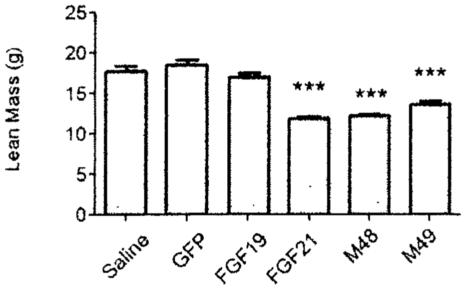
(***P<0.001 vs. Saline)

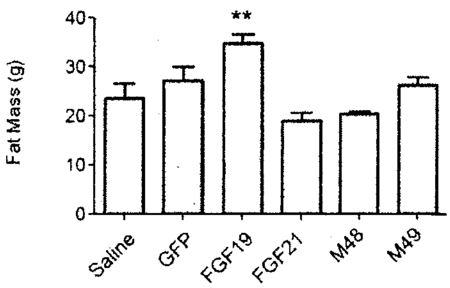
Figure 6D



(***P<0.001 vs. Saline)

Figure 6E

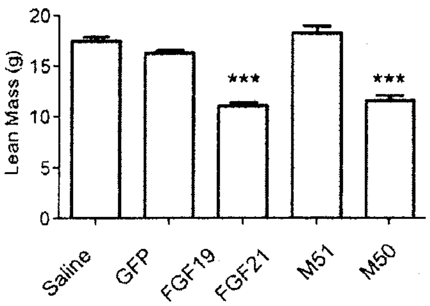


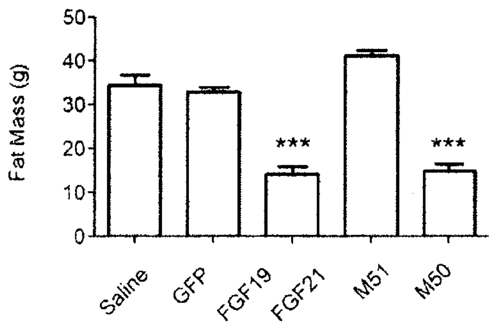


(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 6F

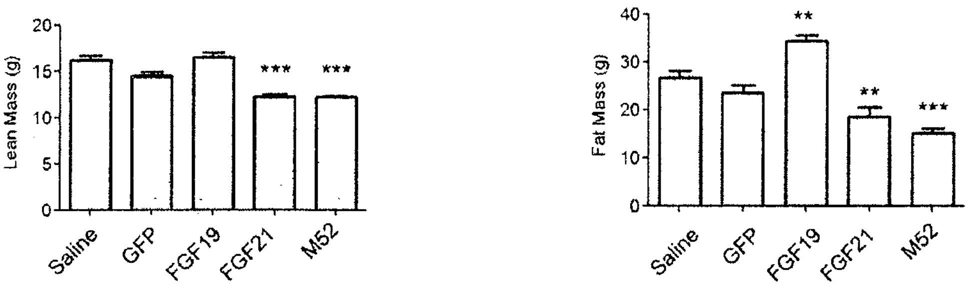




(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

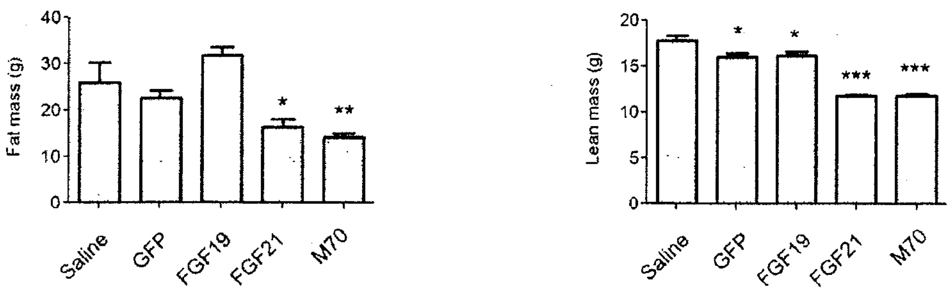
Figure 6G



(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

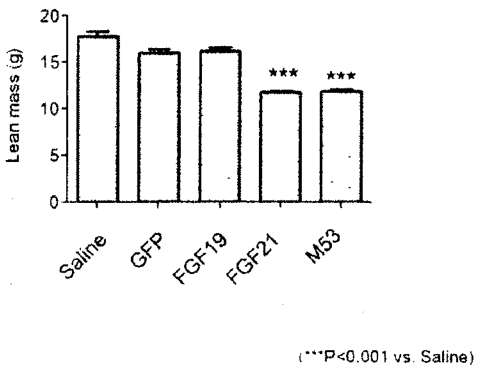
Figure 6H

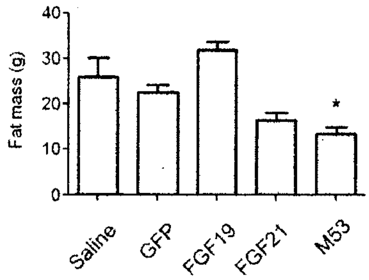


(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 6I





(*db/db* mice, 6 months after AAV injection)

Figure 7A

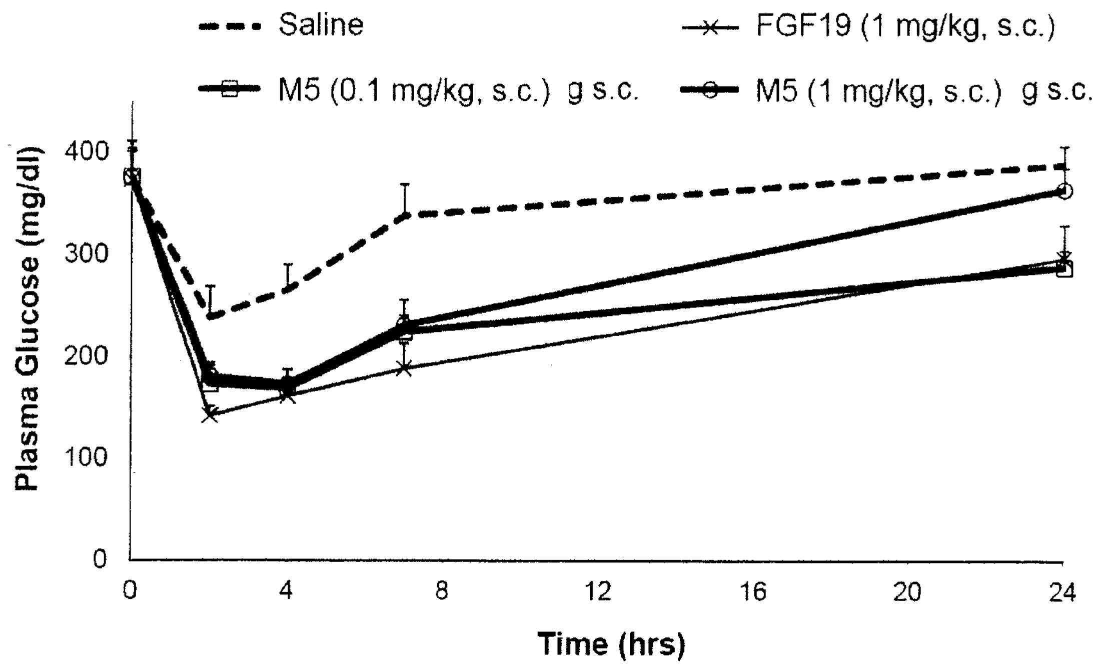


Figure 7B

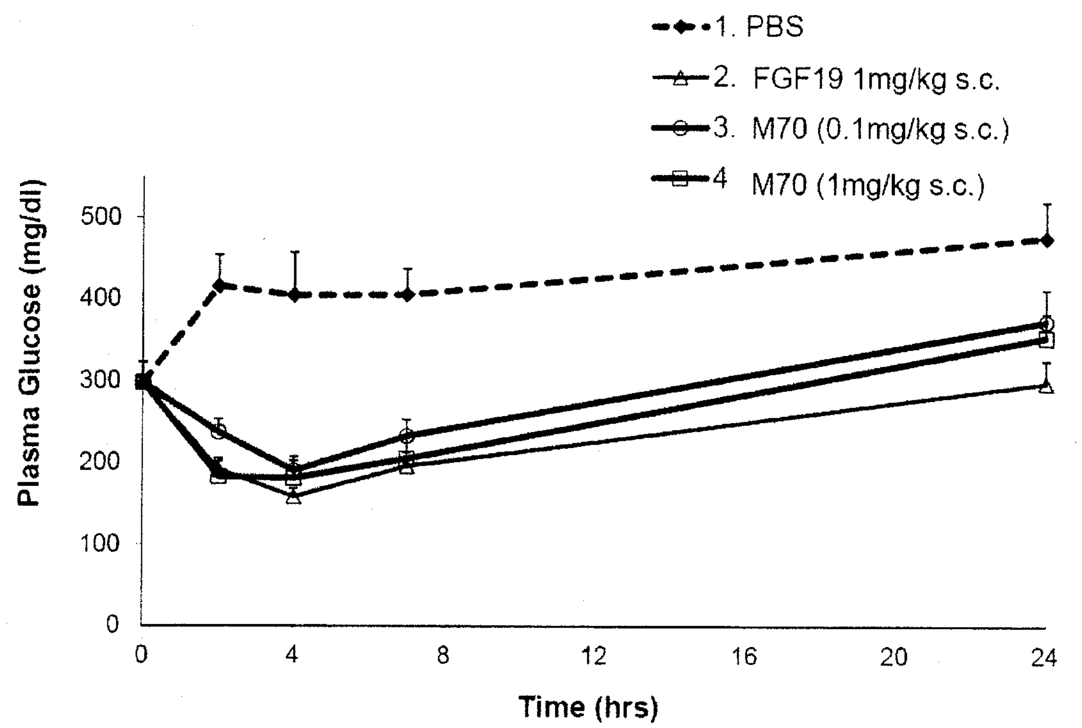
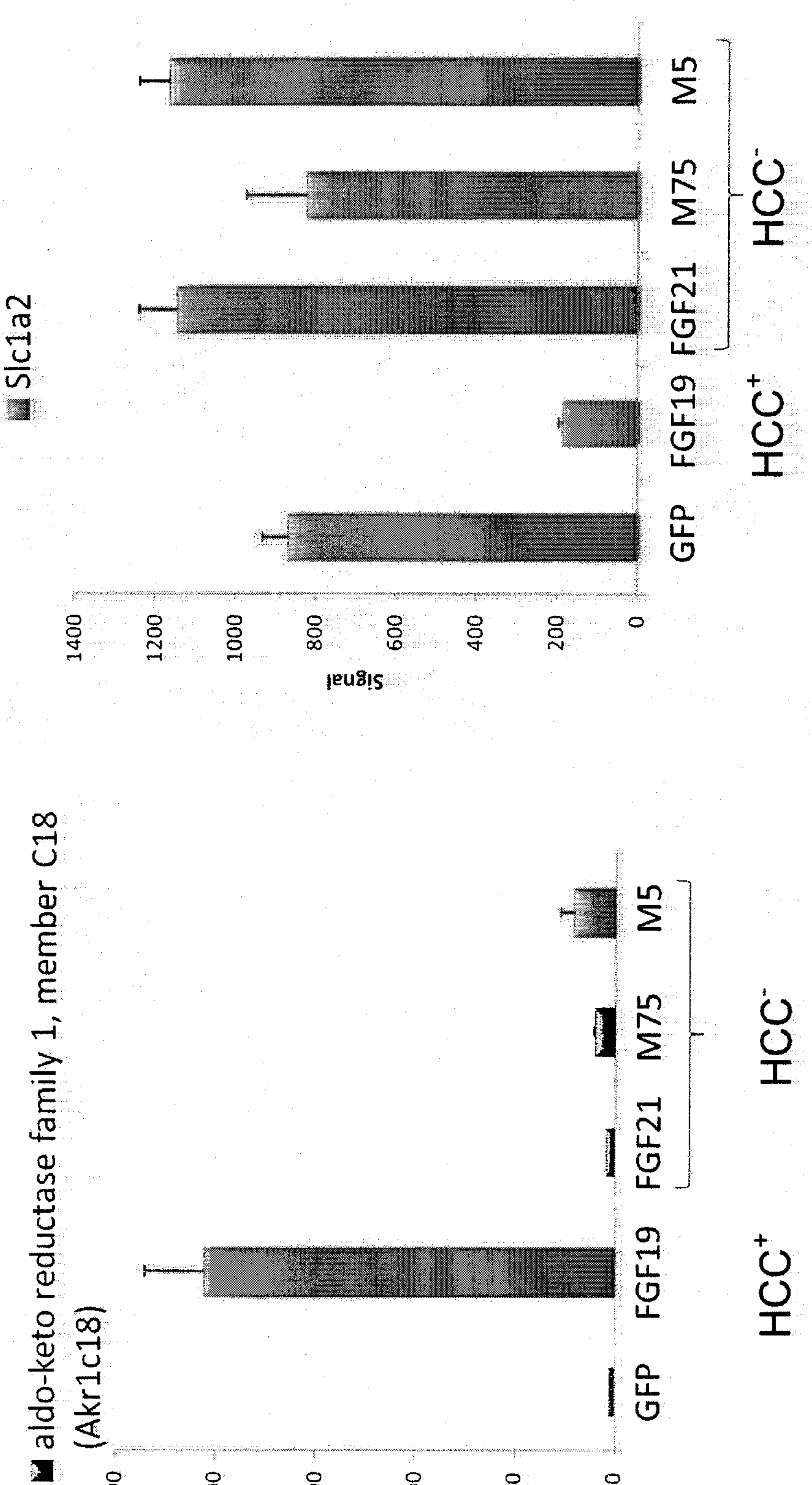


Figure 8



Slc1a2
Signal
1400
1200
1000
800
600
400
200
0
GFP
FGF19
FGF21
M75
M5
HCC+
HCC-
aldo-keto reductase family 1, member C18 (Akr1c18)
Signal
2500
2000
1500
1000
500
0
GFP
FGF19
FGF21
M75
M5
HCC+
HCC-