(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 December 2015 (23.12.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/195509 A3

(51) International Patent Classification:
C07K 14/50 (2006.01) *G01N 33/68* (2006.01)

(21) International Application Number:
PCT/US2015/035752

(22) International Filing Date:
15 June 2015 (15.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/012,899 16 June 2014 (16.06.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
11 February 2016

(54) **Title**: METHODS AND USES FOR MODULATING BILE ACID HOMEOSTASIS AND TREATMENT OF BILE ACID DISORDERS AND DISEASES

(57) **Abstract**: Provided herein are methods of modulating bile acid homeostasis or treating a bile-acid related or associated disorder, comprising using variants and fusions of fibroblast growth factor 19 (FGF19), variants and fusions of fibroblast growth factor 21 (FGF21), fusions of FGF19 and/or FGF21, and variants or fusions of FGF19 and/or FGF21 proteins and peptide sequences (and peptidomimetics), in combination with agents effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder.

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Methods and Uses for Modulating Bile Acid Homeostasis and Treatment of Bile Acid Disorders and Diseases

Cross-Reference to Related Applications

This application claims the benefit of priority to U.S. Serial No. 62/012,809 filed June 16, 2014, which is incorporated herein by reference in its entirety.

Field

[0001] The invention relates, in part, to the treatment or prevention of bile acid-related and associated disorders with variants of fibroblast growth factor 19 (FGF19) proteins and peptide sequences (and peptidomimetics) and fusions of FGF19 and/or fibroblast growth factor 21 (FGF21) proteins and peptide sequences (and peptidomimetics), and variants of fusions of FGF19 and/or FGF21 proteins and peptide sequences (and peptidomimetics) in combination with one or more additional therapeutic agents.

Introduction

[0002] Bile acids, steroid acids that are found predominantly in the bile of mammals, regulate cholesterol, triglyceride, glucose and energy homeostasis, and facilitate digestion and absorption of lipids in the small intestine. In humans, bile acid production occurs primarily in the perivenous hepatocytes through a series of enzymatic reactions that convert cholesterol into the two primary bile acids, cholic acid and chenodeoxycholic acid.

[0003] The primary bile acids are synthesized by two distinct pathways. In the "classic" or "neutral" pathway, the primary bile acids are produced by hydroxylation of cholesterol through catalysis by the cytochrome P450 enzyme cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the first and rate-limiting step. The conversion of cholesterol to bile acids is primarily effected by this pathway. See, *e.g.*, Inagaki *et al.*, Cell Metabolism 2:217-25 (Oct 2005). CYP7A1 activity is down-regulated by cholic acid and up-regulated by cholesterol; thus, CYP7A1 is regulated by bile acids themselves. Thus, repression of CYP7A1 results in the decreased synthesis of bile acids from intrahepatic cholesterol in response to the daily feeding-fasting cycle. In addition, in most individuals approximately 6% of bile acids are synthesized by an "alternative" or "acidic" pathway. This pathway is regulated by the enzyme CYP27A1, which converts oxysterols to bile acids. In contrast to CYP7A1, CYP27A1 is not regulated by bile acids.

[0004] When cholic acid and chenodeoxycholic acid are secreted into the lumen of the intestine, intestinal bacteria dehydroxylate a portion of each to form the secondary bile acids, deoxycholic acid (derived from cholic acid) and lithocholic acid (derived from chenodeoxycholic acid). Enterohepatic circulation enables ~90-95% of all four bile acids to be reabsorbed from the distal ileum and transported back to the liver. The approximately 5% of bile acids that are not reabsorbed are eliminated in the feces, and that amount of loss is subsequently replaced by de novo bile acid synthesis in the liver See, *e.g.*, Rose *et al.*, Cell Metabolism, 14:1, pp 123-130 (6 July 2011).

[0005] As surfactants or detergents, bile acids are potentially toxic to cells, and the size of the bile acid pool is tightly regulated within the liver and intestine to prevent cytotoxic accumulation. When the bile acid pool size increases, a feedback mechanism involving the interplay of several nuclear receptors, including FXR, is activated to inhibit de novo bile acid synthesis. See, *e.g.*, Fiorucci *et al.*, Prog Lipid Res. 2010 Apr; 49(2):171-85. Epub 2009 Dec 2. In one signaling pathway, intestinal FXR activation due to transintestinal bile acid flux after a meal induces the expression of the hormone FGF19, which is released by small intestinal epithelial cells and circulates to bind to hepatocyte FGF receptor 4 (FGFR4) receptors. The FGFR4 receptors signal a reduction in bile acid synthesis via c-Jun NH_2-terminal kinase (JNK) pathway activation.

[0006] Cholestasis, one of the most common bile acid-related disorders, is a condition characterized by a reduction or cessation of bile flow from the liver to the small intestine (principally the duodenum). Primary biliary cirrhosis (PBC) is the most common cholestatic liver disease and is the fifth most common cause of liver transplant in the United States. PBC is a progressive hepatic disease that primarily results from autoimmune destruction of the bile ducts that transport bile acids out of the liver. As the disease progresses, persistent toxic build-up of bile acids causes progressive liver damage marked by chronic inflammation and fibrosis. A majority of PBC patients are asymptomatic at the time of initial diagnosis, but most develop symptoms, such as fatigue and pruritus, over time. Jaundice may result from advanced disease.

[0007] Though several therapeutic modalities exist for the treatment and prevention of bile acid-related disorders in general, and primary biliary cirrhosis in particular, many patients are inadequately treated with current agents as monotherapy, and such patients would benefit from new treatment regimens.

Summary

[0008] The invention is based, in part, on the use of variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of bile acid-related disorders, in combination with other therapeutic agents and/or treatment modalities. Such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences include sequences that do not substantially increase or induce hepatocellular carcinoma (HCC) formation or HCC tumorigenesis and/or do not induce a substantial elevation or increase in lipid profile. Examples of such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences further include those sequences disclosed in PCT Pub. No. WO 2013/006486 and US Pub. No. 2013/0023474, published January 20, 2013 and January 24, 2013, respectively; as well as PCT Publ. No. WO 2014/085365, published June 5, 2014.

[0009] Provided herein are compositions and mixtures comprising certain peptide sequences, including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in the Sequence Listing or Table 1, and the FGF19/FGF21 fusions and chimeras listed in the Sequence Listing or Table 1), and one or more pharmaceutically acceptable carriers or excipients. Combinations, such as one or more peptide sequences in a pharmaceutically acceptable carrier or excipient, with one or more therapeutic agents or treatment modalities useful in the treatment and/or prevention of a bile acid-related disease, disorder, or condition are also provided. Such combinations of peptide sequence(s) provided herein with one or more additional agents or modalities are useful in accordance with the methods and uses provided herein.

[0010] Uses and methods of treatment that include administration or delivery of a chimeric peptide or peptide sequence in combination with an agent that improves bile acid homeostasis are also provided herein. In particular embodiments, a use or method of treatment of a subject includes administering a chimeric peptide or peptide sequence provided herein to a subject having, or at risk of having, a disorder of bile acid homeostasis treatable by a peptide sequence provided herein, in an amount effective for treating the disorder, in combination with at least one additional agent or treatment modality having an additive, synergistic or complementary effect.

The additional agent or treatment modality may also confer one or more further benefits, such as, but not limited to, the ability to lower the dose of one or more of the peptide sequence(s) provided herein or the additional agent(s) in order to favorably impact one or more of the adverse effects experienced by the subject (*e.g.*, decreasing the frequency or severity of an adverse effect).

[0011] In one embodiment, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: a) administering a chimeric peptide sequence, comprising: i) 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 (SEQ ID NO:121) or DASPH (SEQ ID NO:122), and ii) 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 (SEQ ID NO:169), wherein the W residue corresponds to the first amino acid position of the C-terminal region; and b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder; to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0012] In another embodiment, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: a) administering a chimeric peptide sequence, comprising: i) 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 ii) 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 (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region; and b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder; to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0013] In a further embodiment, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: a) administering a chimeric peptide sequence, comprising: ii) 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 ii) 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 (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region; and b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder; to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0014] In an additional embodiment, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: administering a) peptide sequence, comprising or consisting of any of: i) a FGF19 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19, ii) a FGF21 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21, iii) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence, or iv) 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; and b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder; to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0015] In various particular embodiments, a chimeric peptide sequence has an N-terminal region with at least 6 contiguous amino acids of SEQ ID NO:100 (FGF21) including the amino acid residues GQ; or has an N-terminal region with at least 7 contiguous amino acids of SEQ ID NO:100 (FGF21) including the amino acid residues GQV.

[0016] In various additional embodiments, a 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 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 acids 17-146 of SEQ ID NO:100 (FGF21) or fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 (FGF19) (M46).

[0017] In various further embodiments, a peptide sequence has at least one amino acid substitution to amino acid residues 125-129 of SEQ ID NO:99 (FGF19), EIRPD; at least one amino acid substitution to amino acid residues 126-128 of SEQ ID NO:99 (FGF19), IRP; or at least one amino acid substitution to amino acid residues 127-128 of SEQ ID NO:99 (FGF19), RP, or at least one amino acid substitution to amino acid residues 1-124 of SEQ ID NO:99 (FGF19) and/or to amino acid residues 130-194 of SEQ ID NO:99 (FGF19). More specifically, for example, a peptide sequence with a substitution to one of amino acid residues 127-128 of SEQ ID NO:99 (FGF19), IRP, wherein at least one amino acid substitution is R127L or P128E. In certain embodiments, the amino acid sequence of the peptide comprises at least one amino acid substitution in the Loop-8 region of FGF19, or the corresponding FGF19 sequence thereof in a variant peptide provided herein. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In other embodiments, the amino acid sequence of the peptide comprises three amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises four amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises five amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In other embodiments, the amino acid sequence of the peptide comprises three amino acid substitutions to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is an Arg (R) to Leu (L) substitution. In other embodiments, the substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is a Pro (P) to Glu (E) substitution. In some embodiments, the substitutions to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is an Arg (R) to Leu (L) substitution and a Pro (P) to Glu (E) substitution. In specific embodiments, the foregoing substitution(s) in the Loop-8 region of FGF19 is in the corresponding FGF19 sequence thereof in a variant peptide provided herein. That is, said substitutions within a corresponding FGF19 sequence (e.g., EIRPD, IRP or RP) of a peptide variant provided herein is also contemplated.

[0018] Methods and uses provided herein can be practiced using a peptide or chimeric sequence, as set forth herein. For example, a sequence that includes or consists of any peptide sequence set forth herein as M1-M98, M101 to M160, or M200 to M207, or SEQ ID NOs:1 to 98, or 101 to 135, or 138 to 212. In other embodiments, the peptide sequence includes or consists of any sequence set forth in Table 1. In yet other embodiments, the peptide sequence that includes or consists of any sequence set forth in the Sequence Listing herein.

[0019] Methods and uses provided herein can be practiced using a peptide or chimeric sequence of any suitable length. In particular embodiments, the N-terminal or C-terminal region of the peptide or chimeric sequence is from about 20 to about 200 amino acid residues in length. In other particular aspects, a peptide or chimeric sequence 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 further particular embodiments, a peptide or chimeric sequence has an N-terminal region, or a C-terminal region that 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 additional more particular embodiments, a peptide or chimeric sequence has an FGF19 sequence portion, or an FGF21 sequence portion that 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.

[0020] In yet additional embodiments, a peptide sequence or a chimeric peptide sequence has a WGDPI (SEQ ID NO:170) sequence motif corresponding to the WGDPI (SEQ ID NO:170) sequence of amino acids 16-20 of SEQ ID NO:99 (FGF19); has a substituted, mutated or absent WGDPI (SEQ ID NO:170) sequence motif corresponding to FGF19 WGDPI (SEQ ID NO:170) sequence of amino acids 16-20 of FGF19; has a WGDPI (SEQ ID NO:170) sequence with one or more amino acids substituted, mutated or absent. In various other further aspects, the peptide sequence is distinct from an FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the FGF19 WGDPI (SEQ ID NO:170) sequence at amino acids 16-20.

[0021] In yet further embodiments, a peptide sequence or a chimeric peptide sequence has N-terminal region comprises amino acid residues VHYG (SEQ ID NO:101), wherein the N-terminal region comprises amino acid residues DASPHVHYG (SEQ ID NO:102), or the N-terminal region comprises amino acid residues DSSPLVHYG (SEQ ID NO:103). More particularly, in one aspect the G corresponds to the last position of the N-terminal region.

[0022] In various additional aspects, the N-terminal region comprises amino acid residues DSSPLLQ (SEQ ID NO:104), where the Q residue is the last amino acid position of the N-terminal region, or comprises amino acid residues DSSPLLQFGGQV (SEQ ID NO:105), where the V residue corresponds to the last position of the N-terminal region.

[0023] In certain embodiments, an N-terminal region comprises or consists of (or further comprises or consists of): RHPIP (SEQ ID NO:106), where R is the first amino acid position of the N-terminal region; or HPIP (SEQ ID NO:107), where H is the first amino acid position of the N-terminal region; or RPLAF (SEQ ID NO:108), where R is the first amino acid position of the N-terminal region; or PLAF (SEQ ID NO:109), 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.

[0024] In various other aspects, a peptide or chimeric sequence has: amino acid residues HPIP (SEQ ID NO:107), which are the first 4 amino acid residues of the N-terminal region. In various still further aspects, a peptide or chimeric sequence has: an R residue at the first position of the N-terminal region, or the first position of the N-terminal region is an M residue, or the first and second positions of the N-terminal region is an MR sequence, or the first and second positions of the N-terminal region is an RM sequence, or the first and second positions of the N-terminal region is an RD sequence, or the first and second positions of the N-terminal region is an DS sequence, or the first and second positions of the N-terminal region is an MD sequence, or the first and second positions of the N-terminal region is an MS sequence, or the first through third positions of the N-terminal region is an MDS sequence, or the first through third positions of the N-terminal region is an RDS sequence, or the first through third positions of the N-terminal region is an MSD sequence, or the first through third positions of the N-terminal region is an MSS sequence, or the first through third positions of the N-terminal region is an DSS sequence, or the first through fourth positions of the N-terminal region is an RDSS (SEQ ID NO:115), sequence, or the first through fourth positions of the N-terminal region is an MDSS (SEQ ID NO:116), sequence, or the first through fifth positions of the N-terminal region is an MRDSS (SEQ ID NO:117), sequence, or the first through fifth positions of the N-terminal region is an MSSPL (SEQ ID NO:113) sequence, or the first through sixth positions of the N-terminal region is an MDSSPL (SEQ ID NO:110) sequence, or the first through seventh positions of the N-terminal region is an MSDSSPL (SEQ ID NO:111) sequence.

[0025] In various other particular aspects, a peptide or chimeric sequence has at the N-terminal region first amino acid position an “M” residue, an “R” residue, a “S” residue, a “H” residue, a “P” residue, a “L” residue or an “D” residue. In various alternative particular aspects, a peptide or chimeric sequence peptide sequence does not have a “M” residue or an “R” residue at the first amino acid position of the N-terminal region.

[0026] In further various other aspects, a peptide or chimeric sequence has an N-terminal region with any one of the following sequences: MDSSPL (SEQ ID NO:110), MSDSSPL (SEQ ID NO:111), SDSSPL (SEQ ID NO:112), MSSPL (SEQ ID NO:113) or SSPL (SEQ ID NO:114).

[0027] In various still additional aspects, a peptide or chimeric sequence has a residue at the last position of the C-terminal region that corresponds to about residue 194 of SEQ ID NO:99 (FGF19). 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.

[0028] In more particular embodiments, a chimeric peptide sequence or 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. Methods and uses provided herein can also be practiced using a peptide or chimeric sequence, as set forth herein. For example, a sequence that comprises or consists of any peptide sequence set forth herein as M1 to M98, M101 to M160, or M200 to M207 or SEQ ID NOs:1 to 98, 101 to 135, 138 to 212, or a peptide sequence that comprises of consists of any sequence set forth in Table 1, or a peptide sequence that comprises or consists of any sequence set forth in the Sequence Listing herein.

[0029] In various more particular aspects, a peptide sequence comprises or consists of any one of the following sequences:

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M3) (SEQ ID NO:3);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M140) (SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK (M160) (SEQ ID NO:196);

RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT GLEAVRSPSFEK (M69) (SEQ ID NO:69);

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL EAVRSPSFEK (M52) (SEQ ID NO:52);

RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M5) (SEQ ID NO:5);

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT GLEAVRSPSFEK (M5-R) (SEQ ID NO:160);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLP GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA S (M71) (SEQ ID NO:71);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP GNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA S (M72) (SEQ ID NO:72);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGG EGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE (M73) (SEQ ID NO:73);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK (M1) (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK (M2) (SEQ ID NO:2 or 140);

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL EAVRSPSFEK (M48) (SEQ ID NO:48 or 6 or 148);

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLP VSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGL VTGLEAVRSPSFEK (M49) (SEQ ID NO:49 or 7 or 149);

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M50) (SEQ ID NO:50);

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M51) (SEQ ID NO:51 or 36 or 155);

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M53) (SEQ ID NO:192);

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M70) (SEQ ID NO:70);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M139) (SEQ ID NO:193); or

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M141) (SEQ ID NO:195);
RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M160);

or a subsequence or fragment thereof of any of the foregoing peptide sequences. In certain embodiments of any of the foregoing peptide sequences, the R terminal residue (R residue at the N-terminus) is deleted.

[0030] In other embodiments, the peptide comprises or consists of: RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M200) (SEQ ID NO:197); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0031] In some embodiments, the peptide comprises or consists of: RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M201) (SEQ ID NO:198); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0032] In certain embodiments, the peptide comprises or consists of: RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M202) (SEQ ID NO:199); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0033] In other embodiments, the peptide comprises or consists of: RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M203) (SEQ ID NO:200); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0034] In some embodiments, the peptide comprises or consists of: RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M204) (SEQ ID NO:201); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0035] In certain embodiments, the peptide comprises or consists of: RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M205) (SEQ ID NO:202); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0036] In some embodiments, the peptide comprises or consists of:

RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M206) (SEQ ID NO:203); or a subsequence or fragment thereof. In one embodiment, the N-terminal R residue is deleted.

[0037] In other embodiments, the peptide comprises or consists of: MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M207) (SEQ ID NO:204); or a subsequence or fragment thereof.

[0038] In some embodiments, the peptide is a variant peptide designated M139. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:193. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:193. In some embodiments, the peptide is a variant peptide designated M140. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:194. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:194. In some embodiments, the peptide is a variant peptide designated M141. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:195. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:195. In some embodiments, the peptide is a variant peptide designated M160. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:196. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:196. In some embodiments, the peptide is a variant peptide designated M200. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:197. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:197. In some embodiments, the peptide is a variant peptide designated M201. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:198. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:198. In other embodiments, the peptide is a variant peptide designated M202. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:199. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:199. In certain embodiments, the peptide is a variant peptide designated M203. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:200. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:200. In some embodiments, the peptide is a variant peptide designated M204. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:201. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:201. In another embodiment, the peptide is a variant peptide designated M205. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:202. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:202. In other embodiments, the peptide is a variant peptide designated M206. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:203. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:203. In yet other embodiments, the peptide is a variant peptide designated M207. In some embodiments, the peptide comprises an amino acid sequence set forth in SEQ ID NO:204. In other embodiments, the peptide consists of an amino acid sequence set forth in SEQ ID NO:204.

[0039] In various additional particular aspects, the N-terminus of the peptide sequence includes or consists of any of:

HPIPDSSPLLQFGGQVRLRHLYTSG (M5-R) (amino acids 1-25 of SEQ ID NO:160);
DSSPLLQFGGQVRLRHLYTSG (M6-R) (amino acids 2-22 of SEQ ID NO:6);
RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7) (amino acids 1-27 of SEQ ID NO:7);
HPIPDSSPLLQWGDPIRLRHLYTSG (M8-R) (amino acids 2-26 of SEQ ID NO:8);
HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9-R) (amino acids 2-28 of SEQ ID NO:9);
HPIPDSSPHVHYGWGDPIRLRHLYTSG (M10-R) (amino acids 2-28 of SEQ ID NO:10);
RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11) (amino acids 1-27 of SEQ ID NO:11);
RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);
RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);
HPIPDSSPHVHYGGQVRLRHLYTSG (M14-R) (amino acids 2-26 of SEQ ID NO:14);
RPLAFSDAGPHVHYGGQVRLRHLYTSG (M15) (amino acids 1-27 of SEQ ID NO:15);
RPLAFSDAGPHVHWGDPIRLRHLYTSG (M16) (amino acids 1-27 of SEQ ID NO:16);
RPLAFSDAGPHVGWGDPIRLRHLYTSG (M17) (amino acids 1-27 of SEQ ID NO:17);
RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18) (amino acids 1-27 of SEQ ID NO:18);

RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19) (amino acids 1-27 of SEQ ID NO:19);
RPLAFSDAGPVHGWGDPIRLRHLYTSG (M20) (amino acids 1-27 of SEQ ID NO:20);
RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21) (amino acids 1-27 of SEQ ID NO:21);
RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22) (amino acids 1-27 of SEQ ID NO:22);
RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23) (amino acids 1-27 of SEQ ID NO:23);
RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24) (amino acids 1-27 of SEQ ID NO:24);
RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25) (amino acids 1-27 of SEQ ID NO:25);
RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26) (amino acids 1-27 of SEQ ID NO:26);
RPLAFSDSSPHVHWGDPIRLRHLYTSG (M27) (amino acids 1-27 of SEQ ID NO:27);
RPLAFSDAGPHVWGDPIRLRHLYTSG (M28) (amino acids 1-26 of SEQ ID NO:28);
RPLAFSDAGPHVHYWGDPIRLRHLYTSG (M29) (amino acids 1-28 of SEQ ID NO:29);
RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30) (amino acids 1-29 of SEQ ID NO:30);
RHPIPDSSPLLQFGAQVRLRHLYTSG (M31) (amino acids 1-26 of SEQ ID NO:31);
RHPIPDSSPLLQFGDQVRLRHLYTSG (M32) (amino acids 1-26 of SEQ ID NO:32);
RHPIPDSSPLLQFGPQVRLRHLYTSG (M33) (amino acids 1-26 of SEQ ID NO:33);
RHPIPDSSPLLQFGGAVRLRHLYTSG (M34) (amino acids 1-26 of SEQ ID NO:34);
RHPIPDSSPLLQFGGEVRLRHLYTSG (M35) (amino acids 1-26 of SEQ ID NO:35);
RHPIPDSSPLLQFGGNVRLRHLYTSG (M36) (amino acids 1-26 of SEQ ID NO:36);
RHPIPDSSPLLQFGGQARLRHLYTSG (M37) (amino acids 1-26 of SEQ ID NO:37);
RHPIPDSSPLLQFGGQIRLRHLYTSG (M38) (amino acids 1-26 of SEQ ID NO:38);
RHPIPDSSPLLQFGGQTRLRHLYTSG (M39) (amino acids 1-26 of SEQ ID NO:39);
RHPIPDSSPLLQFGWGQPVRLRHLYTSG (M40) (amino acids 1-28 of SEQ ID NO:40);
DAGPHVHYGWGDPIRLRHLYTSG (M74-R) (amino acids 2-24 of SEQ ID NO:74);
VHYGWGDPIRLRHLYTSG (M75-R) (amino acids 2-19 of SEQ ID NO:75);
RLRHLYTSG (M77-R) (amino acids 2-10 of SEQ ID NO:77);
RHPIPDSSPLLQFGWGDPIRLRHLYTSG (M9) (amino acids 1-28 of SEQ ID NO:9);
RHPIPDSSPLLQWGDPIRLRHLYTSG (M8) (amino acids 1-26 of SEQ ID NO:8);
RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);
RHPIPDSSPHVHYGWGDPIRLRHLYTSG (M10) (amino acids 1-28 of SEQ ID NO:10);
RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);
RHPIPDSSPHVHYGGQVRLRHLYTSG (M14) (amino acids 1-26 of SEQ ID NO:14);

RPLAFSDAGPHVHYGGDIRLRHLYTSG (M43) amino acids 1-27 of SEQ ID NO:43); or
RDSSPLLQFGGQVRLRHLYTSG (M6) (amino acids 1-22 of SEQ ID NO:6);
or any of the foregoing peptide sequences where the amino terminal R residue is deleted.

[0040] In certain embodiments, the peptide comprises or consists of any of:
HPIPDSSPLLQFGGQVRLRHLYTSG (M5-R) (amino acids 1-25 of SEQ ID NO:160);
DSSPLLQFGGQVRLRHLYTSG (M6-R) (amino acids 2-22 of SEQ ID NO:6);
RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7) (amino acids 1-27 of SEQ ID NO:7);
HPIPDSSPLLQWGDPIRLRHLYTSG (M8-R) (amino acids 2-26 of SEQ ID NO:8);
HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9-R) (amino acids 2-28 of SEQ ID NO:9);
HPIPDSSPHVHYGWGDPIRLRHLYTSG (M10-R) (amino acids 2-28 of SEQ ID NO:10);
RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11) (amino acids 1-27 of SEQ ID NO:11);
RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);
RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);
HPIPDSSPHVHYGGQVRLRHLYTSG (M14-R) (amino acids 2-26 of SEQ ID NO:14);
RPLAFSDAGPHVHYGGQVRLRHLYTSG (M15) (amino acids 1-27 of SEQ ID NO:15);
RPLAFSDAGPHVHWGDPIRLRHLYTSG (M16) (amino acids 1-27 of SEQ ID NO:16);
RPLAFSDAGPHVGWGDPIRLRHLYTSG (M17) (amino acids 1-27 of SEQ ID NO:17);
RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18) (amino acids 1-27 of SEQ ID NO:18);
RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19) (amino acids 1-27 of SEQ ID NO:19);
RPLAFSDAGPVHGWGDPIRLRHLYTSG (M20) (amino acids 1-27 of SEQ ID NO:20);
RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21) (amino acids 1-27 of SEQ ID NO:21);
RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22) (amino acids 1-27 of SEQ ID NO:22);
RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23) (amino acids 1-27 of SEQ ID NO:23);
RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24) (amino acids 1-27 of SEQ ID NO:24);
RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25) (amino acids 1-27 of SEQ ID NO:25);
RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26) (amino acids 1-27 of SEQ ID NO:26);
RPLAFSDSSPHVHWGDPIRLRHLYTSG (M27) (amino acids 1-27 of SEQ ID NO:27);
RPLAFSDAGPHVWGDPIRLRHLYTSG (M28) (amino acids 1-26 of SEQ ID NO:28);
RPLAFSDAGPHVHYWGDPIRLRHLYTSG (M29) (amino acids 1-28 of SEQ ID NO:29);
RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30) (amino acids 1-29 of SEQ ID NO:30);
RHPIPDSSPLLQFGAQVRLRHLYTSG (M31) (amino acids 1-26 of SEQ ID NO:31);
RHPIPDSSPLLQFGDQVRLRHLYTSG (M32) (amino acids 1-26 of SEQ ID NO:32);

RHPIPDSSPLLQFGPQVRLRHLYTSG (M33) (amino acids 1-26 of SEQ ID NO:33);
RHPIPDSSPLLQFGGAVRLRHLYTSG (M34) (amino acids 1-26 of SEQ ID NO:34);
RHPIPDSSPLLQFGGEVRLRHLYTSG (M35) (amino acids 1-26 of SEQ ID NO:35);
RHPIPDSSPLLQFGGNVRLRHLYTSG (M36) (amino acids 1-26 of SEQ ID NO:36);
RHPIPDSSPLLQFGGQARLRHLYTSG (M37) (amino acids 1-26 of SEQ ID NO:37);
RHPIPDSSPLLQFGGQIRLRHLYTSG (M38) (amino acids 1-26 of SEQ ID NO:38);
RHPIPDSSPLLQFGGQTRLRHLYTSG (M39) (amino acids 1-26 of SEQ ID NO:39);
RHPIPDSSPLLQFGWGQPVRLRHLYTSG (M40) (amino acids 1-28 of SEQ ID NO:40);
DAGPHVHYGWGDPIRLRHLYTSG (M74-R) (amino acids 2-24 of SEQ ID NO:74);
VHYGWGDPIRLRHLYTSG (M75-R) (amino acids 2-19 of SEQ ID NO:75);
RLRHLYTSG (M77-R) (amino acids 2-10 of SEQ ID NO:77);
RHPIPDSSPLLQFGWGDPIRLRHLYTSG (M9) (amino acids 1-28 of SEQ ID NO:9);
RHPIPDSSPLLQWGDPIRLRHLYTSG (M8) (amino acids 1-26 of SEQ ID NO:8);
RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);
RHPIPDSSPHVHYGWGDPIRLRHLYTSG (M10) (amino acids 1-28 of SEQ ID NO:10);
RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);
RHPIPDSSPHVHYGGQVRLRHLYTSG (M14) (amino acids 1-26 of SEQ ID NO:14);
RPLAFSDAGPHVHYGGDIRLRHLYTSG (M43) amino acids 1-27 of SEQ ID NO:43); or
RDSSPLLQFGGQVRLRHLYTSG (M6) (amino acids 1-22 of SEQ ID NO:6). In some embodiments, the peptide comprise one of the foregoing sequences. In another embodiment, the peptide consists of one of the foregoing sequences. In some embodiments, the peptide comprises 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 (SEQ ID NO:169), wherein the W residue corresponds to the first amino acid position of the C-terminal region.

[0041] In various further particular aspects, a peptide sequence includes or consists of:
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA
LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS
LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT
GLEAVRSPSFEK (SEQ ID NO:160);

DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTV AIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE AVRSPSFEK (SEQ ID NO:138 or 161);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK(SEQ ID NO:2 or 140); or

DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT GLEAVRSPSFEK (SEQ ID NO:141);

or a subsequence or fragment thereof of any of the foregoing peptide sequences. In certain embodiments of any of the foregoing peptide sequences, the R terminal residue is deleted.

[0042] In further embodiments, a peptide sequence comprises or consists of: MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV TGLEAVRSPSFEK (M70) (SEQ ID NO:70), or a subsequence or fragment thereof.
In certain embodiments, a peptide sequence includes the addition of amino acid residues 30-194 of SEQ ID NO:99 (FGF19) at the C-terminus, resulting in a chimeric polypeptide.

[0043] In some embodiments, a peptide sequence has at least one amino acid substitution to amino acid residues 125-129 of SEQ ID NO:99 (FGF19), EIRPD. In other embodiments, the peptide sequence has at least one amino acid substitution to amino acid residues 126-128 of SEQ ID NO:99 (FGF19), IRP. In other embodiments, the peptide sequence has at least one amino acid substitution to amino acid residues 127-128 of SEQ ID NO:99 (FGF19), RP. In other embodiments, the peptide sequence has at least one amino acid substitution to amino acid residues 1-124 of SEQ ID NO:99 (FGF19) and/or to amino acid residues 130-194 of SEQ ID NO:99 (FGF19). For example, in certain embodiments, a peptide sequence comprises substitution to one of amino acid residues 127-128 of SEQ ID NO:99 (FGF19), RP, wherein at least one amino acid substitution is R127L or P128E. Said substitutions within a corresponding FGF19 sequence (e.g., EIRPD, IRP or RP) of a peptide variant provided herein is also contemplated. In certain embodiments, the peptide comprises both a R127L and P128E substitution to amino acid residues 127-128 of SEQ ID NO:99 (FGF19), RP, or the corresponding FGF19 sequence thereof in a variant peptide provided herein. In certain embodiments, the amino acid sequence of the peptide comprises at least one amino acid substitution in the Loop-8 region of FGF19, or the corresponding FGF19 sequence thereof in a variant peptide provided herein. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In other embodiments, the amino acid sequence of the peptide comprises three amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises four amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises five amino acid substitutions to the EIRPD (amino acids 2-6 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In other embodiments, the amino acid sequence of the peptide comprises three amino acid substitutions to the IRP (amino acids 3-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid sequence of the peptide comprises one amino acid substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the

Loop-8 region of FGF19. In some embodiments, the amino acid sequence of the peptide comprises two amino acid substitutions to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19. In certain embodiments, the amino acid substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is an Arg (R) to Leu (L) substitution. In other embodiments, the substitution to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is a Pro (P) to Glu (E) substitution. In some embodiments, the substitutions to the RP (amino acids 4-5 of SEQ ID NO:190) amino acid sequence in the Loop-8 region of FGF19 is an Arg (R) to Leu (L) substitution and a Pro (P) to Glu (E) substitution. In specific embodiments, the foregoing substitution(s) in the Loop-8 region of FGF19 is in the corresponding FGF19 sequence thereof in a variant peptide provided herein. That is, said substitutions within a corresponding FGF19 sequence (e.g., EIRPD, IRP or RP) of a peptide variant provided herein is also contemplated.

[0044] Peptide or chimeric sequences provided herein can be of any suitable length. In particular embodiments, the N-terminal or C-terminal region of the peptide or chimeric sequence is 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 other particular aspects, a peptide or chimeric sequence 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 one embodiment, the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI) (SEQ ID NO:187). In further particular embodiments, a peptide or chimeric sequence has an N-terminal region, or a C-terminal region that 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. In additional more particular embodiments, a peptide or chimeric sequence has an FGF19 sequence portion, or an FGF21 sequence portion that 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.

[0045] In various further embodiments, a peptide or chimeric sequence has an amino acid substitution, an addition, insertion or is a subsequence that has at least one amino acid deleted. Such amino acid substitutions, additions, insertions and deletions of a peptide sequence can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid residues (10-20, 20-30, 30-40, 40-50, *etc.*), for example, at the N- or C-terminus, or internal. For example, a subsequence that 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 aspect, the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI) (SEQ ID NO:187).

[0046] In various still more particular aspects, a peptide or chimeric sequence includes all or a portion of an FGF19 sequence set forth as:
PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKM
QGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPML
PMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:188)
positioned at the C-terminus of the peptide, or the amino terminal "R" residue is deleted from the sequence.

[0047] In various embodiments, a peptide or chimeric sequence has a function or activity greater or less than a comparison sequence. 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 a fibroblast growth factor receptor 4 (FGFR4) mediated activity. In additional aspects, a chimeric peptide sequence or peptide sequence binds to FGFR4 or activates FGFR4, or does not detectably bind to 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 some embodiments, a chimeric peptide sequence or peptide sequence provided herein activates FGFR4 to an extent or amount less than the extent or amount that FGF19 activates FGFR4. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein activates FGFR4 to an extent or amount comparable to the extent or amount that FGF19 activates FGFR4. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein activates FGFR4 to an extent or amount greater than the extent or amount that FGF19 activates FGFR4.

[0048] In one embodiment, a chimeric peptide sequence or peptide sequence provided herein maintains an FGFR4 mediated activity. In one embodiment, a chimeric peptide sequence or peptide sequence provided herein increases an FGFR4 mediated activity. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein binds to FGFR4 with an affinity less than FGF19 binding affinity for FGFR4. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein binds to FGFR4 with an affinity comparable to FGF19 binding affinity for FGFR4. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein binds to FGFR4 with an affinity greater than FGF19 binding affinity for FGFR4. In some embodiments, a chimeric peptide sequence or peptide sequence provided herein does not detectably bind to FGFR4.

[0049] In further aspects, a chimeric peptide sequence or peptide sequence has reduced HCC formation compared to FGF19, or an FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19; or has greater glucose lowering activity compared to FGF19, or an FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19; has less lipid increasing activity compared to FGF19, or an FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19; or has less triglyceride, cholesterol, non-HDL or HDL increasing activity compared to FGF19, or an FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI

(SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19; or the peptide sequence 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.

[0050] In one embodiment, a peptide or chimeric sequence has a function or activity greater or less than a comparison sequence. In some embodiments, the comparison sequence is FGF19. In another embodiment, the comparison sequence is FGF19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19. In one embodiment, a peptide or chimeric peptide sequence provided herein has greater glucose lowering activity compared to a comparison sequence. In another embodiment, a peptide or chimeric peptide sequence provided herein has less lipid increasing activity compared to a comparison sequence. In other embodiment, a peptide or chimeric peptide sequence provided herein has lower or reduced lipid (*e.g.,* triglyceride, cholesterol, non-HDL) activity compared to a comparison sequence. In other embodiments, a peptide or chimeric peptide sequence provided herein has more HDL increasing activity as compared to a comparison sequence. In other embodiment, a peptide or chimeric peptide sequence provided herein has less lean mass reducing activity compared to a comparison sequence or FGF21.

[0051] In further additional various embodiments, a peptide or chimeric sequence includes one or more L-amino acids, D-amino acids, non-naturally occurring amino acids, or amino acid mimetic, derivative or analogue. In still further various embodiments, a peptide or chimeric sequence has an N-terminal region, or a C-terminal region, or a FGF19 sequence portion, or an FGF21 sequence portion, joined by a linker or spacer.

[0052] Non-limiting exemplary bile acid related or associated disorders treatable according to the methods and uses provided herein include: cholestasis, including, for example diseases of intrahepatic cholestasis (*e.g.*, primary biliary cirrhosis (PBC), primary familial intrahepatic cholestasis (PFIC) (*e.g.*, progressive PFIC), primary sclerosing choangitis (PSC), pregnancy intrahepatic cholestasis (PIC), neonatal cholestasis, and drug-induced cholestasis (*e.g.*, estrogen)), and diseases of extrahepatic cholestasis (*e.g.*, bile cut compression from tumor, bile duct blockade by gall stones); bile acid malabsorption and other disorders involving the distal small intestine, including ileal resection, inflammatory bowel diseases (*e.g.*, Crohn's disease and ulcerative colitis), short bowel syndrome, disorders impairing absorption of bile acids not otherwise characterized (idiopathic)) leading to diarrhea (*e.g.*, bile acid diarrhea (BAD)) and GI symptoms, and GI, liver, and/or biliary cancers (*e.g.*, colon cancer and hepatocellular cancer); and/or bile acid synthesis abnormalities, such as those contributing to non-alcoholic steatohepatitis (NASH), cirrhosis and portal hypertension; *e.g.*, in mammals, such as humans. Additional bile acid-related disorders include metabolic syndrome; a lipid or glucose disorder; cholesterol or triglyceride metabolism; type 2 diabetes.

[0053] In one particular embodiment, the bile acid related or associated disorder is bile acid malabsorption. In another particular embodiment, the bile acid related or associated disorder is diarrhea. In a still further particular embodiment, the bile acid related or associated disorder is cholestasis (*e.g.*, intrahepatic or extrahepatic cholestasis), and in another further particular embodiment, the bile acid related or associated disorder is primary billiary cirrhosis (PBC). In other particular embodiments, the bile acid related or associated disorder is primary sclerosing cholangitis. In another embodiment, the bile acid related or associated disorder is PFIC (*e.g.*, progressive PFIC).

[0054] In still further embodiments, the at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder is: a glucocorticoid; CDCA; UDCA; insulin, an insulin secretagogues, an insulin mimetic, a sulfonylurea and a meglitinide; a biguanide; an alpha-glucosidase inhibitors; a DPP-IV inhibitor, GLP-1, a GLP-1 agonists and a GLP-1 analog; a DPP-IV-resistant analogue; a PPAR gamma agonist, a dual-acting PPAR agonist, a pan-acting PPAR agonist; a PTP1B inhibitor; an SGLT inhibitor; an RXR agonist; a glycogen synthase kinase-3 inhibitor; an immune modulator; a beta-3 adrenergic receptor agonist; an 11beta-HSD1 inhibitor; amylin and an amylin analogue; a bile acid sequestrant; or an SGLT-2 inhibitor.

[0055] In certain embodiments, the at least one additional agent effective in modulating PBC is UDCA, an FXR agonist, OCA, an ASBT inhibitor, an autoimmune agent, an anti-IL-12 agent, an anti-CD80 agent, an anti-CD20 agent, a CXCL10 neutralizing antibody, a ligand for CXCR3, a fibrate, fish oil, colchicine, methotrexate, azathioprine, cyclosporine, or an anti-retroviral therapy. In particular embodiments, the at least one additional agent effective in modulating PBC is UDCA, OCA, an ASBT inhibitor, an anti-IL-12 agent, an anti-CD20 agent, or a fibrate.

[0056] In some embodiments, the combination of a chimeric peptide sequence or a peptide sequence described herein and at least one additional therapeutic agent or treatment modality is assessed to ensure that it does not cause untoward adverse effects in the subject. In a particular aspect, the combination of a chimeric peptide sequence or a peptide sequence described herein and at least one additional therapeutic agent or treatment modality is assessed to ensure that it does not induce HCC in the subject. Such assessments may be performed before initiation of therapy (*e.g.*, in a dose escalation study), during therapy, (*e.g.*, by evaluating a marker correlating with HCC activity), or subsequent to termination of therapy (*e.g.*, by performing a liver biopsy). In some aspects, the assessment is performed in a suitable test environment (*e.g.*, a validated animal model). One of ordinary skill in the art is familiar with additional means for ensuring that the combination therapy described herein is suitable for the particular subject, or a subject population representative of the particular subject, taking into consideration all relevant factors including, for example, the severity of the subject's bile acid-related disorder (*e.g.*, PBC) and the other medications be taken by the subject.

[0057] A detailed description of PBC, including its diagnosis and treatment, are described elsewhere herein. Absent effective therapy, the median time to develop extensive fibrosis is around 2 years. The median survival of untreated patients with PBC is approximately 9–10 years from presentation, with 26% developing liver failure during this time (Trivedi, P. *et al.*, Ther. Adv. Chronic Dis. 4(3):119-41 (2013)). Thus, alternative treatment regimens such as those described herein have the potential of dramatically delaying disease progression and improving patient survival.

Detailed Description

[0058] Provided herein, in certain embodiments, are uses of chimeric and peptide sequences that modulate bile acid homeostasis in combination with one or more additional therapeutic agents or treatment modalities that are useful in the treatment and/or prevention of bile acid-related or associated disorders. The invention is based, in part, on the use of variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of a bile acid-related disorder (*e.g.*, PBC), in combination with other therapeutic agents and/or treatment modalities. Such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences include sequences that do not substantially increase or induce HCC formation or HCC tumorigenesis and/or do not induce a substantial elevation or increase in lipid profile.

[0059] 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 (SEQ ID NO:121) or DASPH (SEQ ID NO:122) 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; SEQ ID NO:169) and the W residue corresponds to the first amino acid position of the C-terminal region. In particular embodiments, the variant is M70: MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDS16MDPFG LVTGLEAVRSPSFEK (SEQ ID NO:70).

[0060] 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; SEQ ID NO: 185) and the R residue corresponds to the first position of the C-terminal region.

[0061] In particular aspects, modifications to the Loop-8 region of FGF19 are disclosed herein that possess favorable metabolic parameters without exhibiting substantial tumorigenicity. Herein, FGF19 residues 127-129 are defined as constituting the Loop-8 region, although in the literature the Loop-8 region is sometimes defined as including or consisting of other residues (*e.g.*, residues 125-129). Certain combinations of R127L and P128E substitutions to the FGF19 framework had an unexpectedly positive effect on HCC formation. Even more surprisingly, a combination of R127L and P128E substitutions and a substitution of Gln (Q) for Leu (L) in the FGF19 core region had an even more significant effect on preventing HCC formation. Accordingly, variants of FGF19 Loop-8 region are included since they can reduce or eliminate substantial, measurable or detectable HCC formation. Furthermore, the effect of reducing HCC formation may be enhanced by modifications to amino acid residues outside of the Loop 8 region (*e.g.*, substitutions of amino acid residues in the core region).

[0062] In further embodiments, a peptide sequence includes or consists of a FGF19 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 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. Examples of such sequences are disclosed in PCT Pub. No. WO 2013/006486 and US Pub. No. 2013/0023474, as well as PCT Publ. No. WO 2014/085365, published June 5, 2014. Table 1 and the Sequence Listing also sets forth representative sequences that may be used in the methods provided herein.

Peptide Molecules

[0063] 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 abbreviations and their common three-letter abbreviation. In the peptide sequences provided herein, conventional amino acid residues have their conventional meaning. Thus, "Leu" is leucine, "Ile" is isoleucine, "Nle" is norleucine, and so on. To assist the reader, conventional 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)

[0064] In various particular aspects, a peptide or chimeric sequence provided herein has at the N-terminal region first amino acid position an “M” residue, an “R” residue, a “S” residue, a “H” residue, a “P” residue, a “L” residue or an “D” residue. In various alternative particular aspects, a peptide or chimeric sequence peptide sequence does not have a “M” residue or an “R” residue at the first amino acid position of the N-terminal region.

[0065] Typically, the number of amino acids or residues in a peptide sequence provided herein 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.

[0066] 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 provided herein includes a portion of an FGF19 sequence and a portion of an FGF21 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.

[0067] Also provided herein are subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in the Sequence Listing, or Table 1), so long as the foregoing retains at least a detectable or measureable activity or function. 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 (SEQ ID NO:115), DSS, MDSS (SEQ ID NO:116) or MRDSS (SEQ ID NO:117). Furthermore, 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 (SEQ ID NO:119), MSDSSPL (SEQ ID NO:120) (cleaved to SDSSPL (SEQ ID NO:112)) and MSSPL (SEQ ID NO:113) (cleaved to SSPL (SEQ ID NO:114)).

[0068] 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 provided herein can be modified to increase serum half-life, to increase *in vitro* and/or *in vivo* stability of the protein, *etc.*

[0069] Particular examples of such subsequences, variants and modified forms of the peptide sequences exemplified herein (*e.g.*, a peptide sequence listed in the Sequence Listing or Table 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.

[0070] 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.

[0071] 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 provided herein are included, unless a D-isomer leads to a sequence that has no detectable or measurable function.

[0072] 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.*, activity that improves PBC and/or the manifestations thereof. 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.*, activity that improves PBC and/or the manifestations thereof.

[0073] Particular examples of subsequences, variants and modified forms of the peptide sequences exemplified herein 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. 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 those regions.

[0074] 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)).

[0075] In the peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein, 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 provided herein (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)).

[0076] 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.

[0077] 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, such as 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, *e.g.*, 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.*, activity that improves PBC and/or the manifestations thereof).

[0078] 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 (CH_3--$(CH_2)_5$--C(=O)--), hexanoyl (CH_3--$(CH_2)_4$--C(=O)--), homoarginine, homocysteine, homolysine, homophenylalanine, homoserine, methyl, methionine sulfoxide, methionine sulfone, norvaline (NVA), phenylglycine, propyl, isopropyl, sarcosine (SAR), tert-butylalanine, and benzyloxycarbonyl.

[0079] 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 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 C_1 to C_6 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.

[0080] 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.

[0081] In certain embodiments, covalent modifications of the peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein are provided. An exemplary 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.

[0082] 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.*

[0083] Exemplified peptide sequences, and subsequences, variants and modified forms of the peptide sequences exemplified herein 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 a peptide sequence provided herein 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.

[0084] 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.

[0085] The term “bind,” or “binding,” when used in reference to a peptide sequence, means that the peptide sequence interacts at the molecular level. 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).

[0086] 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 peptide sequences, variants, fusions and chimeras provided herein, and variations, derivatives, substitutions and modifications thereof.

[0087] 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.

[0088] Peptide sequences provided herein including subsequences, sequence variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 1), can also be modified to form a chimeric molecule. In certain embodiments, provided herein are 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.

[0089] The term "peptide" also includes dimers or multimers (oligomers) of peptides. In certain embodiments, dimers or multimers (oligomers) of the exemplified peptide sequences are provided herein, as well as subsequences, variants and modified forms of the exemplified peptide sequences, including sequences listed in the Sequence Listing or Table 1.

[0090] In certain embodiments, a peptide sequence provided herein comprises an amino acid sequence set forth in Table 1. In other embodiments, a peptide sequence provided herein consists of an amino acid sequence set forth in Table 1.

Table 1

SEQ ID NO.	Amino Acid Sequence
1.	RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
2.	RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
3.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
4.	RPLAFSDAGPHVHYAWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
5.	RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
6.	RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
7.	RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
8.	RHPIPDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
9.	RHPIPDSSPLLQFGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
10.	RHPIPDSSPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
11.	RPLAFSDAGPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
12.	RPLAFSDAGPLLQFGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS

	LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
13.	RPLAFSDAGPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
14.	RHPIPDSSPHVHYGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
15.	RPLAFSDAGPHVHYGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
16.	RPLAFSDAGPHVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
17.	RPLAFSDAGPHVGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
18.	RPLAFSDAGPHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
19.	RPLAFSDAGPVYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
20.	RPLAFSDAGPVHGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
21.	RPLAFSDAGPVHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
22.	RPLAFSDAGPHVHGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
23.	RPLAFSDAGPHHGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
24.	RPLAFSDAGPHHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS

	PLETDSMDPFGLVTGLEAVRSPSFEK
25.	RPLAFSDAGPHVYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
26.	RPLAFSDSSPLVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
27.	RPLAFSDSSPHVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
28.	RPLAFSDAGPHVWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
29.	RPLAFSDAGPHVHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
30.	RPLAFSDAGPHVHYAWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
31.	RHPIPDSSPLLQFGAQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
32.	RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
33.	RHPIPDSSPLLQFGPQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
34.	RHPIPDSSPLLQFGGAVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
35.	RHPIPDSSPLLQFGGEVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
36.	RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
37.	RHPIPDSSPLLQFGGQARLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI

	KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
38.	RHPIPDSSPLLQFGGQIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
39.	RHPIPDSSPLLQFGGQTRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
40.	RHPIPDSSPLLQFGWGQPVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
41.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPEPPGILAPQPPDVGSSDPL SMVGPSQGRSPSYAS
42.	HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPEPPGILAPQPPDVGSSDPLSMVGP SQGRSPSYAS
43.	RPLAFSDAGPHVHYGGDIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
44.	RPLAFSDAGPHVHYGWGDPIRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPES LLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVY QSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDP LSMVGPSQGRSPSYAS
45.	HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLK ALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAH GLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
46.	RPLAFSDAGPHVHYGWGDPIRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPES LLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVY QSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDP LSMVGPSQGRSPSYASPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAV RSPSFEK
47.	HPIPDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
48.	RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
49.	RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY

	RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
50.	RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
51.	RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
52.	RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
53.	MDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
54.	RPLAFSDAGPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
55.	RPLAFSDAGPHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
56.	RPLAFSDAGPVYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
57.	RPLAFSDAGPVHGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
58.	RPLAFSDAGPVHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
59.	RPLAFSDAGPHHGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
60.	RPLAFSDAGPHHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
61.	RPLAFSDAGPHVGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK

62.	RPLAFSDAGPHVYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
63.	RPLAFSDAGPHVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
64.	RPLAFSDSSPLVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
65.	RPLAFSDSSPHVHWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
66.	RPLAFSDAGPHLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
67.	RPLAFSDAGPHVWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
68.	RPLAFSDAGPHVHYWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
69.	RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
70.	MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
71.	HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLK ALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAH SLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVG PSQGRSPSYAS
72.	HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLK ALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAH GLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMV GPSQGRSPSYAS
73.	HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLK ALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAH GLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMV VQDELQGVGGEGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE
74.	RDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS

	EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
75.	RVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRL PVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSM DPFGLVTGLEAVRSPSFEK
76.	RGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIK GVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT GLEAVRSPSFEK
77.	RRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHS VRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQR QLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE AVRSPSFEK
78.	RAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
79.	RGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLET DSMDPFGLVTGLEAVRSPSFEK
80.	RPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
81.	RHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHR LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDS MDPFGLVTGLEAVRSPSFEK
82.	RPLAFSAAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
83.	RPLAFSDAAPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
84.	RPLAFSDAGAHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
85.	RPLAFSDAGPHVHYGAGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
86.	RPLAFSDAGPHVHYGWGAPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK

87.	RPLAFSDAGPHVHYGWGDAICARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCM GADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRG FLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE K
88.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPAGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLAHFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
89.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPAGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSAFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
90.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQAQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
91.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQRQLYKNRGFLPLAHFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
92.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQRQLYKNRGFLPLSAFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
93.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQAQLYKNRGFLPLAHFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
94.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLAAFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
95.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQRQLYKNRGFLPLSAFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
96.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQAQLYKNRGFLPLAHFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
97.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQAQLYKNRGFLPLSAFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
98.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN VYRSEKHRLPVSLSSAAQAQLYKNRGFLPLAAFLPMLPMVPEEPEDLRGHLESDM FSSPLETDSMDPFGLVTGLEAVRSPSFEK
138.	DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHR

	LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDS MDPFGLVTGLEAVRSPSFEK
139.	RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
140.	RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
141.	DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLET DSMDPFGLVTGLEAVRSPSFEK
142.	RHPIPDSSPLLQFGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
143.	RHPIPDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
144.	RPLAFSDAGPLLQFGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
145.	RHPIPDSSPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
146.	RPLAFSDAGPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
147.	RHPIPDSSPHVHYGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
148.	RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
149.	RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
150.	RHPIPDSSPLLQFGAQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK

151.	RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
152.	RHPIPDSSPLLQFGPQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
153.	RHPIPDSSPLLQFGGAVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
154.	RHPIPDSSPLLQFGGEVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
155.	RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
156.	RHPIPDSSPLLQFGGQARLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
157.	RHPIPDSSPLLQFGGQIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
158.	RHPIPDSSPLLQFGGQTRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
159.	RHPIPDSSPLLQFGWGQPVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
160.	HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
161.	DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHR LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDS MDPFGLVTGLEAVRSPSFEK
162.	HPIPDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
163.	HPIPDSSPLLQFGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS

	EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
164.	HPIPDSSPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK
165.	HPIPDSSPHVHYGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
166.	DAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
167.	VHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP FGLVTGLEAVRSPSFEK
168.	RLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSV RYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQL YKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAV RSPSFEK
188.	PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGAD GKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLP LSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK
192.	MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
193.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
194.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
195.	RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
196.	RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYN VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK
197.	RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK
198.	RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS

	LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
199.	RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK
200.	RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
201.	RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
202.	RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKH RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETD SMDPFGLVTGLEAVRSPSFEK
203.	RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK
204.	MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK

[0091] In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:1. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:2. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:3. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:4. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:5. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:6. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:7. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:8. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:9. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:10. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:11. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:12. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:13. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:14. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:15. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:16. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:17. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:18. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:19. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:20. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:21. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:22. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:23. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:24. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:25. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:26. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:27. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:28. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:29. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:30. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:31. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:32. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:33. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:34. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:35. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:36. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:37. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:38. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:39. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:40. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:41. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:42. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:43. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:44. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:45. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:46. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:47. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:48. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:49. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:50. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:51. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:52. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:53. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:54. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:55. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:56. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:57. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:58. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:59. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:60. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:61. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:62. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:63. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:64. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:65. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:66. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:67. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:68. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:69. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:70. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:71. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:72. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:73. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:74. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:75. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:76. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:77. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:78. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:79. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:80. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:81. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:82. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:83. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:84. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:85. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:86. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:87. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:88. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:89. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:90. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID

NO:91. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:92. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:93. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:94. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:95. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:96. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:97. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:98. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:138. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:139. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:140. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:141. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:142. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:143. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:144. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:145. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:146. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:147. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:148. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:149. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:150. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:151. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:152. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:153. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:154. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:155. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:156. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:157. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:158. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:159. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:160. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:161. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:162. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:163. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:164. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:165. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:166. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:167. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:168. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:192. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:193. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:194. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:195. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:196. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:197. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:198. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:199. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:200. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:201. In other embodiments, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:202. In one embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:203. In another embodiment, the peptide sequence comprises an amino acid sequence set forth in SEQ ID NO:204. In certain embodiments of the various peptide sequences provided herein, the R residue at the N-terminus is deleted.

[0092] In yet other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:1. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:2. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:3. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:4. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:5. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:6. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:7. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:8. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:9. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:10. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:11. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:12. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:13. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:14. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:15. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:16. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:17. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:18. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:19. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:20. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:21. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:22. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:23. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:24. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:25. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:26. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:27. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:28. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:29. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:30. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:31. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:32. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:33. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:34. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:35. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:36. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:37. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:38. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:39. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:40. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:41. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:42. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:43. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:44. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:45. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:46. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:47. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:48. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:49. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:50. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:51. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:52. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:53. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:54. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:55. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:56. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:57. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:58. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:59. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:60. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:61. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:62. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:63. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:64. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:65. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:66. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:67. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:68. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:69. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:70. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:71. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:72. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:73. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:74. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:75. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:76. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:77. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:78. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:79. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:80. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:81. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:82. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:83. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:84. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:85. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:86. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:87. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:88. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:89. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:90. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:91. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:92. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:93. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:94. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:95. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:96. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:97. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:98. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:138. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:139. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:140. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:141. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:142. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:143. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:144. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:145. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:146. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:147. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:148. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:149. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:150. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:151. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:152. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:153. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:154. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:155. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:156. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:157. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:158. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:159. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:160. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:161. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:162. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:163. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:164. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:165. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:166. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:167. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:168. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:192. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:193. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:194. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID

NO:195. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:196. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:197. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:198. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:199. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:200. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:201. In other embodiments, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:202. In one embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:203. In another embodiment, the peptide sequence consists of an amino acid sequence set forth in SEQ ID NO:204. In certain embodiments of the various peptide sequences provided herein, the R residue at the N-terminus is deleted.

Nucleic Acid Molecules

[0093] Also provided are nucleic acid molecules encoding peptide sequences provided herein, including subsequences, sequence variants and modified forms of the sequences listed in the Sequence Listing (and in PCT Pub. No. WO 2013/006486 and US Pub. No. 2013/0023474, as well as PCT Publ. No. WO 2014/085365) or Table 1, and vectors that include nucleic acid encoding the peptides used in the methods described herein. 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 useful in the treatment or prevention of a bile acid-related disorder (*e.g.*, PBC).

[0094] 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 analogs and derivatives.

[0095] As a result of the degeneracy of the genetic code, the nucleic acid molecules provided herein include sequences degenerate with respect to nucleic acid molecules encoding the peptide sequences useful in the methods provided herein. Thus, degenerate nucleic acid sequences encoding peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (*e.g.*, in the Sequence Listing or Table 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.

[0096] 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, for example, sequencing, gel electrophoresis, and UV spectrometry.

[0097] 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.*

[0098] 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.

[0099] 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 provided herein 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' or 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 provided herein. A "promoter" typically means a minimal sequence element sufficient to direct transcription.

[0100] 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, or producing peptide sequences, for example.

[0101] As used herein, the term "transgene" means a polynucleotide that has been introduced into a cell or organism by artifice. For example, in 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.

[0102] 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.

[0103] As methods and uses provided herein 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.

[0104] 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).

[0105] 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).

Cell Lines and Animal Models

[0106] In certain embodiments, also provided is a 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. 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. Transformed and host cells that express peptide sequences provided herein typically include a nucleic acid that encodes the 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.

[0107] 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.

[0108] 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 a 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.

[0109] 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 provided herein.

[0110] 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.

[0111] 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.

[0112] Nucleic acids encoding peptide sequences provided herein 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.

[0113] 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 certain embodiments, 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.

[0114] 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. Transgenic animals provided herein 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.

[0115] 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 a composition provided herein, 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. 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.

[0116] 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 provided herein is expressed by a cell transfected with a nucleic acid encoding the peptide sequence. A particular example of a recombinant nucleic acid would be 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 within 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.

Particular Modifications to Enhance Peptide Function

[0117] It is frequently beneficial, and sometimes imperative, to improve one of more physical properties of the treatment modalities disclosed herein and/or the manner in which they are administered. Improvements of physical properties include, for example, modulating immunogenicity; methods of increasing solubility, bioavailability, serum half-life, and/or therapeutic half-life; and/or modulating biological activity. Certain modifications may also be useful to, for example, raise of antibodies for use in detection assays (*e.g.*, epitope tags) and to provide for ease of protein purification. Such improvements must generally be imparted without adversely impacting the bioactivity of the treatment modality and/or increasing its immunogenicity.

[0118] Pegylation of is one particular modification contemplated herein, while other modifications include, but are not limited to, glycosylation (N- and O-linked); polysialylation; albumin fusion molecules comprising serum albumin (*e.g.*, human serum albumin (HSA), cyno serum albumin, or bovine serum albumin (BSA)); albumin binding through, for example a conjugated fatty acid chain (acylation); and Fc-fusion proteins.

[0119] Pegylation: The clinical effectiveness of protein therapeutics is often limited by short plasma half-life and susceptibility to protease degradation. Studies of various therapeutic proteins (*e.g.*, filgrastim) have shown that such difficulties may be overcome by, for example, conjugating or linking the protein to any of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes. This is frequently effected by a linking moiety covalently bound to both the protein and the nonproteinaceous polymer, *e.g.*, a PEG. 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. In addition to the beneficial effects of pegylation on pharmacokinetic parameters, pegylation itself may enhance activity.

[0120] PEGs suitable for conjugation to a polypeptide sequence are generally soluble in water at room temperature, and have the general formula $R(O\text{-}CH_2\text{-}CH_2)_nO\text{-}R$, 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 polypeptide sequence can be linear or branched. Branched PEG derivatives, “star-PEGs” and multi-armed PEGs are contemplated by the present disclosure. A molecular weight of the PEG used in embodiments provided herein is not restricted to any particular range, and examples are set forth elsewhere herein; by way of example, certain embodiments have molecular weights between 5kDa and 20kDa, while other embodiments have molecular weights between 4kDa and 10kDa.

[0121] In other embodiments, provided herein are 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. Cation exchange chromatography may be used to separate conjugates, and a fraction is then identified which contains the conjugate having, for example, the desired number of PEGs attached, purified free from unmodified protein sequences and from conjugates having other numbers of PEGs attached.

[0122] Pegylation most frequently occurs at the alpha amino group at the N-terminus of the polypeptide, the epsilon amino group on the side chain of lysine residues, and the imidazole group on the side chain of histidine residues. Since most recombinant polypeptides possess a single alpha and a number of epsilon amino and imidazole groups, numerous positional isomers can be generated depending on the linker chemistry.

[0123] General pegylation strategies known in the art can be applied herein. PEG may be bound to a polypeptide provided herein via a terminal reactive group (a "spacer" or "linker") which mediates a bond between the free amino or carboxyl groups of one or more of the polypeptide 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 a 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.

[0124] Conjugation of one or more of the polypeptide sequences provided herein 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 means 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. Pegylation of various molecules is discussed in, for example, U.S. Pat. Nos. 5,252,714; 5,643,575; 5,919,455; 5,932,462; and 5,985,263.

[0125] In some embodiments, also provided herein are uses of PEG mimetics. Recombinant PEG mimetics have been developed that retain the attributes of PEG (*e.g.*, enhanced serum half-life) while conferring several additional advantageous properties. By way of example, simple polypeptide chains (comprising, for example, Ala, Glu, Gly, Pro, Ser and Thr) capable of forming an extended conformation similar to PEG can be produced recombinantly already fused to the peptide or protein drug of interest (*e.g.*, XTEN technology; Amunix; Mountain View, CA). This obviates the need for an additional conjugation step during the manufacturing process. Moreover, established molecular biology techniques enable control of the side chain composition of the polypeptide chains, allowing optimization of immunogenicity and manufacturing properties.

[0126] Glycosylation: As used herein, "glycosylation" is meant to broadly refer to the enzymatic process by which glycans are attached to proteins, lipids or other organic molecules. The use of the term "glycosylation" herein is generally intended to mean adding or deleting one or more carbohydrate moieties (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that may or may not be present in the native sequence. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins involving a change in the nature and proportions of the various carbohydrate moieties present.

[0127] Glycosylation can dramatically affect the physical properties (*e.g.*, solubility) of polypeptides and can also be important in protein stability, secretion, and subcellular localization. Glycosylated polypeptides may also exhibit enhanced stability or may improve one or more pharmacokinetic properties, such as half-life. In addition, solubility improvements can, for example, enable the generation of formulations more suitable for pharmaceutical administration than formulations comprising the non-glycosylated polypeptide.

[0128] Addition of glycosylation sites can be accomplished by altering the amino acid sequence. The alteration to the polypeptide 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. A particular embodiment comprises the generation and use of N-glycosylation variants.

[0129] The polypeptide sequences provided herein may optionally be altered through changes at the nucleic acid level, particularly by mutating the nucleic acid encoding the polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0130] Polysialylation: In certain embodiments, also provided herein is the use of polysialylation, the conjugation of polypeptides to the naturally occurring, biodegradable α-(2→8) linked polysialic acid ("PSA") in order to improve the polypeptides' stability and in vivo pharmacokinetics.

[0131] Albumin Fusion: Additional suitable components and molecules for conjugation include albumins such as human serum albumin (HSA), cyno serum albumin, and bovine serum albumin (BSA).

[0132] In some embodiments, albumin is conjugated to a drug molecule (*e.g.*, a polypeptide described herein) at the carboxyl terminus, the amino terminus, both the carboxyl and amino termini, and internally (see, *e.g.*, US Pat Nos. 5,876,969 and 7,056,701).

[0133] In the HSA–drug molecule conjugates embodiments provided herein, various forms of albumin may be used, such as albumin secretion pre-sequences and variants thereof, fragments and variants thereof, and HSA variants. Such forms generally possess one or more desired albumin activities. In additional embodiments, fusion proteins are provided herein comprising a polypeptide drug molecule fused directly or indirectly to albumin, an albumin fragment, an albumin variant, *etc.,* wherein the fusion protein has a higher plasma stability than the unfused drug molecule and/or the fusion protein retains the therapeutic activity of the unfused drug molecule. In some embodiments, the indirect fusion is effected by a linker, such as a peptide linker or modified version thereof.

[0134] As alluded to above, fusion of albumin to one or more polypeptides provided herein can, for example, be achieved by genetic manipulation, such that the nucleic acid coding for

HSA, or a fragment thereof, is joined to the nucleic acid coding for the one or more polypeptide sequences.

[0135] Alternative Albumin Binding Strategies: Several albumin – binding strategies have been developed as alternatives to direct fusion and may be used with the agents described herein. By way of example, in certain embodiments, provided herein is albumin binding through a conjugated fatty acid chain (acylation) and fusion proteins which comprise an albumin binding domain (ABD) polypeptide sequence and the sequence of one or more of the polypeptides described herein.

[0136] Conjugation with Other Molecules: Additional suitable components and molecules for conjugation include, for example, thyroglobulin; tetanus toxoid; Diphtheria toxoid; polyamino acids such as poly(D-lysine:D-glutamic acid); VP6 polypeptides of rotaviruses; influenza virus hemagglutinin, influenza virus nucleoprotein; Keyhole Limpet Hemocyanin (KLH); and hepatitis B virus core protein and surface antigen; or any combination of the foregoing.

[0137] Thus, in certain embodiments, conjugation of one or more additional components or molecules at the N- and/or C-terminus of a polypeptide sequence, such as another polypeptide (*e.g.*, a polypeptide having an amino acid sequence heterologous to the subject polypeptide), or a carrier molecule is also contemplated. Thus, an exemplary polypeptide sequence can be provided as a conjugate with another component or molecule.

[0138] A polypeptide may also be conjugated to large, slowly metabolized macromolecules such as proteins; polysaccharides, such as sepharose, agarose, cellulose, or cellulose beads; polymeric amino acids such as polyglutamic acid, or polylysine; amino acid copolymers; inactivated virus particles; inactivated bacterial toxins such as toxoid from diphtheria, tetanus, cholera, or leukotoxin molecules; inactivated bacteria; and dendritic cells. Such conjugated forms, if desired, can be used to produce antibodies against a polypeptide provided herein.

[0139] Fc-fusion Molecules: In certain embodiments, the amino- or carboxyl- terminus of a polypeptide sequence provided herein can be fused with an immunoglobulin Fc region (*e.g.*, human Fc) to form a fusion conjugate (or fusion molecule). Fc fusion conjugates have been shown to increase the systemic half-life of biopharmaceuticals, and thus the biopharmaceutical product may require less frequent administration.

[0140] 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. More recent Fc-fusion technology links a single copy of a biopharmaceutical to the Fc region of an antibody to optimize the pharmacokinetic and pharmacodynamic properties of the biopharmaceutical as compared to traditional Fc-fusion conjugates.

[0141] Purification: 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.

[0142] 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 (0 M to 0.5 M) NaCl gradient buffered at a pH from 3 to 5.5, such as 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 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.

[0143] Other Modifications: In certain embodiments, also provided herein is the use of other modifications, currently known or developed in the future, to improve one or more properties. Examples include hesylation, various aspects of which are described in, for example, U.S. Patent Appln. Nos. 2007/0134197 and 2006/0258607, and fusion molecules comprising SUMO as a fusion tag (LifeSensors, Inc.; Malvern, PA).

[0144] In still other embodiments, a peptide sequence provided herein 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 provided herein using linker technology known in the art and described herein.

[0145] 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.

[0146] In certain embodiments, a peptide sequence provided herein 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 ^{131}, indium^{111}, 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.

[0147] Linkers: Linkers and their use have been described above. Any of the foregoing components and molecules used to modify the polypeptide sequences provided herein 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 polypeptide 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 amino acid (*e.g.*, Gly), 2, 3, 4, 5, 6, 7, 8, 9, 10, 10-20, 20-30, 30-50 or more than 50 amino acids.

[0148] Exemplary flexible linkers include glycine polymers $(G)_n$, glycine-serine polymers (for example, $(GS)_n$, $GSGGS_n$ (SEQ ID NO:206) and $GGGS_n$ (SEQ ID NO:207), 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 neutral tethers between components. Exemplary flexible linkers include, but are not limited to, GGSG (SEQ ID NO:208), GGSGG (SEQ ID NO:209), GSGSG (SEQ ID NO:210), GSGGG (SEQ ID NO:211), GGGSG (SEQ ID NO:189), and GSSSG (SEQ ID NO:212).

Bile Acid-related Disorders and the Treatment or Prevention Thereof

[0149] As used herein, the phrases "bile acid-related disorder," "bile acid-related or associated disorder," and the like, when used in reference to a condition of a subject, means a disruption of bile acid homeostasis, which may manifest itself as, for example, an acute, transient or chronic abnormal level of a bile acid or one or more bile acids. The condition can be caused by inhibition, reduction or a delay in bile acid synthesis, metabolism or absorption such that the subject exhibits a bile acid level not typically found in normal subjects.

[0150] Also provided herein are *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 set forth herein in combination with one or more additional therapeutic agents and/or treatment modalities. In various embodiments, the methods include administering a peptide sequence, such as an FGF19 or FGF21 variant, fusion or chimera disclosed herein (*e.g.*, in the Sequence Listing or Table 1), or a subsequence, a variant or modified form of an FGF19 or FGF21 variant, fusion or chimera disclosed herein (*e.g.*, the Sequence Listing or Table 1), to a subject in an amount effective for treating a bile acid-related disorder, in combination with an additional therapeutic agent(s) and/or treatment modalities (*e.g.*, an agent useful in the treatment and/or prevention of PBC). As set forth herein, the additional therapeutic agent(s) can be administered before, with, or following administration of the peptides described herein.

[0151] Also provided here are 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) a bile-acid related or associated disorder relative to an appropriate matched subject of comparable age, gender, race, *etc.*). Thus, in various embodiments, a method provided herein for, for example, modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes contacting or administering i) one or more peptides provided herein (*e.g.*, a variant or fusion of FGF19 and/or FGF21 as set forth in the Sequence Listing or Table 1) in an amount effective to modulate bile acid homeostasis or treat a bile-acid related or associated disorder, and ii) at least one additional therapeutic agent or treatment modality that is useful in the treatment or prevention of a bile acid related disorder (*e.g.*, PBC).

[0152] The term "subject" refers to an animal. Typically, the animal is a mammal that would benefit from treatment with a peptide sequence provided herein. Particular examples include primates (*e.g.*, humans), dogs, cats, horses, cows, pigs, and sheep.

[0153] Subjects include those having a disorder, *e.g.*, a bile acid related or associated disorder, such as cholestasis, including, for example diseases of intrahepatic cholestasis (*e.g.*, PBC, PFIC, PSC, PIC, neonatal cholestasis, and drug induced cholestasis (*e.g.*, estrogen)), and diseases of extrahepatic cholestasis (*e.g.*, bile cut compression from tumor, bile duct blockade by gall stones); bile acid malabsorption and other disorders involving the distal small intestine, including ileal resection, inflammatory bowel diseases (*e.g.*, Crohn's disease and ulcerative colitis), short bowel syndrome, disorders impairing absorption of bile acids not otherwise characterized (idiopathic)) leading to diarrhea (*e.g.*, BAD) and GI symptoms, and GI, liver, and/or biliary cancers (*e.g.*, colon cancer and hepatocellular cancer); and/or bile acid synthesis abnormalities, such as those contributing to NASH, cirrhosis and portal hypertension; or subjects that do not have a disorder but may be at risk of developing the disorder.

[0154] Additional bile acid-related disorders that may be treated or prevented with the peptide sequences provided herein in combination with one or more additional therapeutic agents or treatment modalities include metabolic syndrome, a lipid or glucose disorder, cholesterol or triglyceride metabolism, diabetes (*e.g.*, type 2 diabetes), 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, and dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary artery disease, cerebrovascular disorders and the like.

[0155] Other conditions which may be associated with 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 (including portal hypertension (defined as a hepatic venous pressure gradient (HVPG) greater than 5 mm Hg), cardiovascular disease, stroke and heart failure; 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; Disorders of cell cycle or cell differentiation processes such as adipose cell tumors, lipomatous carcinomas including, for example, liposarcomas, solid tumors, and neoplasms; 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; Skin and dermatological disorders and/or disorders of wound healing processes, including erythemato-squamous dermatoses; and Other Disorders such as syndrome X, osteoarthritis, and acute respiratory distress syndrome.

[0156] Treatment of a bile acid-related disorder (*e.g.*, NASH) may have the benefit of alleviating or abolishing a disorder secondary thereto. By way of example, a subject suffering from NASH may also have depression or anxiety due to NASH; thus, treating the subject's NASH may also indirectly treat the depression or anxiety. The use of the therapies disclosed herein to target such secondary disorders is also contemplated in certain embodiments.

[0157] In particular embodiments, the subject has or is at risk of having PBC. In other particular embodiments, the subject has or is at risk of having NASH. In one embodiment, the subject has PBC. In one embodiment, the subject is at risk of having PBC. In other embodiments, the subject has NASH. In other embodiments, the subject is at risk of having NASH.

[0158] Subjects at risk of developing a bile acid-related or associated disorder (such as the disorders described above) include, for example, those who may have a family history or genetic predisposition toward such disorder, as well those whose diet may contribute to development of such disorders.

[0159] As disclosed herein, treatment methods include contacting or administering a peptide as set forth herein (*e.g.*, a variant or fusion of FGF19 and/or FGF21 as set forth in the Sequence Listing or Table 1) 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 the 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 bile acid related or associated disorder, treatment can lower or reduce one or more symptoms or effects of the bile acid-related or associated disorders described above.

[0160] Treatment methods also include contacting or administering one or more additional agents or therapeutic modalities useful in the treatment or prevention of a bile acid related disorder, such as those agents or therapeutic modalities described herein, 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 the 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 bile acid related or associated disorder, treatment with a peptide provided herein in combination with another therapeutic agent can lower or reduce one or more symptoms or effects of the bile acid-related or associated disorders described above.

[0161] An "effective amount" or a "sufficient amount" for use and/or for treating a subject refers to an amount that provides, in single or multiple doses, alone, or in combination with one or more other agents, treatments, protocols, or therapeutic regimens, 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, in remission 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.

[0162] 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 bile acid-related or associated disorder such as those described above, including cholestasis (*e.g.*, PBC), disorders impairing absorption of bile acids leading to diarrhea (*e.g.*, BAD) and bile acid synthesis abnormalities (*e.g.*, NASH), an improvement can be a lowering or a reduction in one or more symptoms or effects of the disorder.

[0163] 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.*).

[0164] Thus, in the case of a disorder treatable by a peptide sequence provided herein in combination with an additional agent, the amount of the peptide and the additional agent 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 bile acid homeostasis in a subject can reduce the dosage amount or frequency of the peptides and agents described herein in order to treat the bile acid-related or associated disorders described previously even though complete freedom from treatment has not resulted. An effective amount can be ascertained, for example, by measuring one or more relevant physiological effects.

[0165] Methods and uses provided herein for treating a subject are applicable for prophylaxis to prevent or reduce the likelihood of a disorder in a subject, such as a bile acid-related or associated disorder. Accordingly, methods and uses provided herein for treating a subject having, or at risk of developing, a bile acid-related disorder or associated disorder can be practiced prior to, substantially contemporaneously with, or following administration or application of another agent useful for the treatment or prevention of a bile acid-related or associated disorder, and/or 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 provided herein 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.

[0166] PBC and Combination Therapy with Agents Effective in the Treatment or Prevention Thereof. Primary biliary cirrhosis (PBC), the most common cholestatic liver disease, is a progressive hepatic disease that primarily results from autoimmune destruction of the bile ducts that transport bile acids out of the liver. As the disease progresses, persistent toxic build-up of bile acids causes progressive liver damage marked by chronic inflammation and fibrosis. Because patients with PBC have an increased risk of HCC, combination therapy with the variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences described herein is of particular import, as such sequences do not induce, or do not substantially increase, HCC formation or HCC tumorigenesis.

[0167] Although patients with PBC are often asymptomatic at the time of initial diagnosis, most present, or subsequently develop, one or more of the following: pruritus; fatigue; jaundice; xanthoma; disorders associated with an extrahepatic autoimmune disorder (*e.g.*, Sjögren's Syndrome and rheumatoid arthritis); and complications that result from cirrhosis or portal hypertension (*e.g.*, ascites, esophageal varices and hepatic encephalopathy).

[0168] While a definitive cause of PBC has not been identified, most research suggests that it is an autoimmune disorder. There appears to be a genetic predisposition, and genetic studies have indicated that part of the IL-12 signaling cascade, including IL-12A and I-12RB2 polymorphisms, is important in the etiology of the disease.

[0169] There is no definitive means of diagnosing PBC; rather, assessment of a number of factors is generally required. Moreover, diagnosis of PBC requires that other conditions with similar symptoms (*e.g.*, autoimmune hepatitis and primary sclerosing cholangitis) by ruled out; by way of example, abdominal ultrasound or CT scan is usually performed to rule out blockage of the bile ducts.

[0170] Diagnostic blood tests include deranged liver function tests (gamma-glutamyl transferase and alkaline phosphatase) and the presence of particular antibodies (antimitochondrial antibody (AMA) an antinuclear antibody (ANA)). Antinuclear antibodies are believed to be prognostic indicators of PBC. When other tests and procedures are indicative of PBC, a liver biopsy is frequently performed to confirm disease. Endoscopic retrograde cholangiopancreatography (ERCP), an endoscopic evaluation of the bile duct, may also be employed to confirm disease.

[0171] PBC is classified into four stages marking the progression of disease. Stage 1 (Portal Stage) is characterized by portal inflammation and mild bile duct damage; Stage 2 (Periportal Stage) is characterized by enlarged triads, periportal fibrosis or inflammation; Stage 3 (Septal Stage) is characterized by active and/or passive fibrous septa; and Stage 4 (Biliary Cirrhosis) is characterized by the presence of hepatic nodules. Liver biopsy is required to determine the stage of disease.

[0172] Serum bilirubin is an indicator of PBC progression and prognosis. Patients with a serum bilirubin level of 2–6 mg/dL have a mean survival time of 4.1 years, patients with a serum bilirubin level of 6–10 mg/dL have a mean survival time of 2.1 years, and patients with a serum bilirubin level above 10 mg/dL have a mean survival time of 1.4 years. Liver transplantation is an option in advanced cases of PBC, although the recurrence rate may be as high as 18% at 5 years, and up to 30% at 10 years.

[0173] Although disease progression may be slowed, pharmaceutical intervention with currently used therapies is neither curative nor effective in all patient populations. In order to improve the therapeutic outcome of pharmacological therapy, one aspect pertains to the use of one or more current therapies in combination with variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of PBC and associated diseases, disorders and conditions. The most commonly used and/or promising agents for combination therapy are set forth hereafter, although it is to be understood that these agents are illustrative, and not exclusionary.

[0174] PBC treatment most frequently involves the bile acid ursodeoxycholic acid (Urosdiol, UDCA). UDCA therapy is helpful in reducing the cholestasis and improving the liver function tests in PBC patients; however, it does not demonstrably improve symptoms and has a questionable impact on prognosis. UDCA has been shown to reduce mortality, adverse events and the need for transplantation in PBC. Although UDCA is considered the first-line therapy, approximately one-third of patients may be non-responsive and remain at risk of progressive liver disease and are candidates for alternative or additive therapy.

[0175] There are several alternative and adjuvant therapies, some of which are currently in clinical development, that can be used in combination with variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of PBC and associated diseases, disorders and conditions.

[0176] Farnesoid-X-receptor agonists represent a promising class of agents that may be used in combination therapy. One of the primary functions of agonists of FXR, a nuclear receptor expressed at high levels in the liver and intestine, is the suppression of cholesterol 7α hydroxylase-1 (CYP7A1), the rate-limiting enzyme in the synthesis of bile acids from cholesterol. Obeticholic acid (OCA; Intercept Pharmaceuticals, NY) is a bile acid analog and FXR agonist derived from the primary human bile acid chenodeoxycholic acid, or CDCA. OCA is currently being evaluated for patients having an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol.

[0177] Inhibitors of the apical sodium-dependent bile acid transporter (ASBT) represent another class of agents that may be used in combination with the variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences described herein for the treatment and/or prevention of PBC and associated diseases. ASBT, a member of the sodium/bile-salt co-transport family coded by gene SLC10A2, is currently thought to be the primary mechanism for bile acid reabsorption in the intestine. Examples of ABST inhibitors include LUM001 and SC-435, both of which are being developed by Lumena Pharmaceuticals (San Diego, CA).

[0178] Bile acid sequestrants also find use in the treatment of PBC. Cholestyramine and colestipol are the best known bile acid sequestrants. However, their use is sometimes limited because they are only available in powder form and are not tolerated by many patients, often because of the poor texture and taste of the resin powder. The bile acid sequestrant colesevelam is available in tablet form and is often better tolerated. All bile acid sequestrants are capable of binding other compounds, including the fat-soluble vitamins A, D, E and K, and deficiencies of these vitamins many necessitate supplementation. Importantly, the PBC patient population inherently has poor lipid-dependent absorption of vitamins A, D, E and K, and thus patients taking bile acid sequestrants are at particular risk for deficiency of those vitamins.

[0179] Agents associated with immune and inflammatory function are candidates for combination therapy with the variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of PBC and associated diseases, disorders and conditions.

[0180] The interleukin IL-12 is linked with autoimmunity. Data indicate that the IL-12 signaling pathway plays a key role in the effector mechanisms that lead to biliary destruction. Targeting the p40 subunit of IL-12 has also been shown to ameliorate experimental immune-mediated cholangiopathy. Thus, anti-IL-12 agents (*e.g.*, monoclonal Ab inhibitors) provide a promising treatment. Furthermore, because polymorphisms in CD80 have been identified as conferring an increased susceptibility to PBC, blockade of co-stimulation between T cells and antigen-presenting cells through CD80 by use of an anti-CD80 agent could represent an important therapeutic approach for the treatment of PBC. In addition, improvement in IgM titre and an increase in intrahepatic regulatory T-cell number using the anti-CD20 antibody rituximab (RITUXAN) have shown promise.

[0181] The immune-mediated destruction of small-sized bile ducts in PBC is predominantly cell-mediated, characterized by Th1 cells, CD8+ T cells, NK cells and NKT cells which express CXCR3. Therefore, neutralizing antibodies to CXCL10, a ligand for CXCR3, may offer the possibility to interfere with one of the key inflammatory processes and contribute to immune-mediated biliary destruction in PBC. Similarly, blockade of co-stimulatory signals between T cells expressing CD28 and antigen-presenting cells expressing CD80 (*e.g.* cholangiocytes, antibody-secreting B cells) might represent an important approach for the treatment of autoimmune diseases.

[0182] The variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences described herein can be used in combination with other agents for the treatment and/or prevention of those bile acid-related disorders referenced herein that have an immune and/or inflammatory component, including, but not limited to, PBC and associated diseases, disorders and conditions. Examples of such other agents include, for example, non-steroidal anti-inflammatory drugs (NSAID); steroids; cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to, or antagonists of, other human cytokines or growth factors (*e.g.*, IL-2, IL-6, or PDGF); TNF antagonists (*e.g.*, agents such as REMICADE, p75TNFRIgG (ENBREL) or p55TNFR1gG (LENERCEPT)); interferon-β1a (AVONEX); interferon-β1b (BETASERON); and immune checkpoint inhibitors, including PD1 (associated agents include the antibodies nivolumab and lambrolizumab), PDL1, BTLA, CTLA4 (associated agents include the fully humanized CTLA4 monoclonal antibody ipilimumab (YERVOY), TIM3, LAG3, and A2aR.

[0183] Fibrates have been shown to improve various aspects of PBC, including liver function tests, both as monotherapy and in combination with UDCA non-responders. In certain embodiments, a fibrate is a member selected from the group of bezafibrate (BEZALIP), ciprofibrate (MODALIM), gemfibrozil (LOPID), clofibrate, and fenofibrate (TRICOR). Fish oil has exhibited similar benefits.

[0184] In PBC patients demonstrating certain characteristics of hepatitis on biopsy, corticosteroids such as budesonide may improve liver histology and biochemistry, particularly when used in combination with UDCA. Colchicine has been shown to improve liver function tests (*e.g.*, AST and ALP) and represents another alternative treatment for PBC.

[0185] Though not an exhaustive list, other drugs that have shown promise include methotrexate as an immunomodulatory treatment, azathioprine, cyclosporine, and certain agents used in anti-retroviral therapy (*e.g.*, combivir).

[0186] Various treatments exist for the sequelae associated with PBC. For example, itching can be relieved by the bile acid sequestrant cholestyramine, or alternatively naltrexone and rifampicin. The fatigue associated with PBC may effectively be treated with modafinil (Provigil; Teva (formerly Cephalon)) without damaging the liver. As patients with PBC have increased risk of developing osteoporosis and esophageal varices compared to the general population (and others with liver disease), screening and treatment of these complications is an important part of the management of PBC. Combination therapy with the variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of PBC and associated diseases, disorders and conditions, as taught herein, offer novel, promising alternatives to the management of such sequelae.

[0187] NASH and NAFLD and Combination Therapy with Agents Effective in the Treatment or Prevention Thereof. Non-alcoholic steatohepatitis (NASH), considered part of a spectrum of non-alcoholic fatty liver diseases (NAFLD), causes inflammation and accumulation of fat and fibrous tissue in the liver. Although the exact cause of NASH is unknown, risk factors include central obesity, type-2 diabetes mellitus, insulin resistance (IR) and dyslipidemia; combinations of the foregoing are frequently described as the metabolic syndrome. In addition, certain drugs have been linked to NASH, including tamoxifen, amiodarone and steroids (*e.g.*, prednisone and hydrocortisone). Non-alcoholic fatty liver disease is the most common cause of chronic liver disease in the United States, and the estimated prevalence of NAFLD is 20-30% and for NASH it is estimated at 3.5-5%. (See, *e.g.*, Abrams, G.A., *et al.*, Hepatology, 2004. 40(2):475-83; Moreira, R.K., Arch Pathol Lab Med, 2007. 131(11):1728-34).

[0188] NASH frequently presents with no overt symptoms, complicating its diagnosis. Liver function tests generally begin the diagnostic process, with levels of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) elevated in about 90% percent of individuals with NASH. Other blood tests are often used for ruling out other causes of liver disease, such as hepatitis. Imaging tests (*e.g.*, ultrasound, CT scan, or MRI) may reveal fat accumulation in the liver but frequently cannot differentiate NASH from other causes of liver disease that have a similar appearance. A liver biopsy is required to confirm NASH.

[0189] The prognosis for individuals suffering from NASH is difficult to predict, although features in the liver biopsy can be helpful. The most serious complication of NASH is cirrhosis, which occurs when the liver becomes severely scarred. It has been reported that between 8 and 26 percent of individuals with NASH develop cirrhosis, and it is predicted that NASH will be the leading indication for liver transplantation by 2020.

[0190] At the present time, treatment of NASH focuses primarily on pharmacological and non-pharmacological management of those medical conditions associated with it, including hyperlipidemia, diabetes and obesity. Although not curative, pharmacological intervention of NASH itself includes treatment with vitamin E, pioglitazone, metformin, statins, omega-3 fatty acids, and ursodeoxycholic acid (UDCA (ursodiol)). Other agents being evaluated, currently approved for different indications, include losartan and telisartan, exenatide, GLP-1 agonists, DPP IV inhibitors, and carbamazepine.

[0191] In view of the deficiencies of the aforementioned current therapies, combination therapy with agents having distinct mechanisms of action offers a promising new avenue for the treatment and prevention of NASH and NAFLD. Addressing such deficiencies is also contemplated, for example, by using the current therapies in combination with the variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences as taught herein. Also provided herein is the prophylactic and/or therapeutic use of these variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences in combination with therapies developed in the future for the treatment or prevention of NASH and NAFLD.

[0192] Combination Therapy for the Treatment or Prevention of Other Bile acid-related Disorders and Associated Diseses, Disorders and Conditions. Also provided herein is the use of variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences and variants of fusions (chimeras) of FGF19 and/or FGF21 peptide sequences having one or more activities associated with the treatment and/or prevention of other bile acid-related disorders and associated diseases, disorders and conditions besides PBC, in combination with other therapeutic agents and/or treatment modalities.

[0193] By way of example, patients with bile acid diarrhea secondary to Crohn's ileitis will be helped with glucocorticoid treatment. Microscopic colitis is also helped by steroids. In patients with a short-bowel syndrome (a bile acid deficiency occurs in the proximal intestine that leads to impaired micellar solubilization), cholylsarcosine (cholyl-N-methylglycine), a synthetic bile acid analogue, has been shown to increase lipid absorption.

[0194] Administration of the primary bile acid chenodeoxycholic Acid (CDCA) has been shown to decrease biliary cholesterol secretion and gradual dissolution of gallstones. Because

CDCA is slightly hepatotoxic, it was gradually replaced by UDCA. Despite the efficacy and safety of UDCA administration for cholesterol gallstone dissolution, it is not frequently used today because of the success of laparoscopic cholecystectomy, which provides a rapid cure for symptomatic disease. Medical therapy, in contrast, requires months of therapy, does not always dissolve stones, and is followed by gradual recurrence in some patients.

[0195] Bile acid replacement is used in inborn errors of bile acid biosynthesis, usually with a mixture of chenodeoxycholic Acid (CDCA) or Ursodeoxycholic Acid (UDCA) and cholic acid, to suppress the synthesis of cytotoxic bile acid precursors and restore the input of primary bile acids into the enterohepatic circulation.

[0196] In addition to the agents and therapeutic modalities set forth above, combination therapy with numerous additional agents (and classes thereof) is also contemplated, including. but not limited to, 1) insulin *e.g.*, bolus and basal analogs), insulin mimetics and agents that entail stimulation of insulin secretion, including sulfonylureas (*e.g.*, chlorpropamide, tolazamide, acetohexamide, tolbutamide, glyburide, glimepiride, glipizide) and meglitinides (*e.g.*, repaglinide (PRANDIN) and nateglinide (STARLIX)); 2) biguanides (*e.g.*, metformin (GLUCOPHAGE)) and other agents that act by promoting glucose utilization, reducing hepatic glucose production and/or diminishing intestinal glucose output; 3) alpha-glucosidase inhibitors (*e.g.*, acarbose and miglitol) and other agents that slow down carbohydrate digestion and consequently absorption from the gut and reduce postprandial hyperglycemia; 4) thiazolidinediones (*e.g.*, rosiglitazone (AVANDIA), troglitazone (REZULIN), pioglitazone (ACTOS), glipizide, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, ciglitazone, adaglitazone, darglitazone that enhance insulin action (*e.g.*, by insulin sensitization), thus promoting glucose utilization in peripheral tissues; 5) glucagon-like-peptides including DPP-IV inhibitors (*e.g.*, vildagliptin (GALVUS) and sitagliptin (JANUVIA)) and Glucagon-Like Peptide-1 (GLP-1) and GLP-1 agonists and analogs (*e.g.*, exenatide (BYETTA and ITCA 650 (an osmotic pump inserted subcutaneously that delivers an exenatide analog over a 12-month period; Intarcia, Boston, MA)); 6) and DPP-IV-resistant analogues (incretin mimetics), PPAR gamma agonists, dual-acting PPAR agonists, pan-acting PPAR agonists, PTP1B inhibitors, SGLT inhibitors, insulin secretagogues, RXR agonists, glycogen synthase kinase-3 inhibitors, immune modulators, beta-3 adrenergic receptor agonists, 11beta-HSD1 inhibitors, and amylin analogues.

[0197] Other exemplary agents that can be used, in certain embodiments, in combination with the chimeric peptides and methods provided herein include dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine formulations (*e.g.* and bile acid sequestrants (*e.g.*, colesevelam), and SGLT-2 inhibitors. Appetite suppression drugs are also well known and can be used in combination with the compositions and methods provided herein. Supplementary therapies can be administered prior to, contemporaneously with or following methods and uses provided herein.

Dosing and Administration

[0198] Peptide sequences provided herein including subsequences, sequence variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 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 abnormal or aberrant bile acid homeostasis, such as metabolic syndrome; a lipid- or glucose-related disorder; cholesterol or triglyceride metabolism; type 2 diabetes; cholestasis, including, for example diseases of intrahepatic cholestasis (*e.g.*, PBC, PFIC, PSC, PIC, neonatal cholestasis, and drug induced cholestasis (*e.g.*, estrogen)), and diseases of extrahepatic cholestasis (*e.g.*, bile cut compression from tumor, bile duct blockade by gall stones); bile acid malabsorption and other disorders involving the distal small intestine, including ileal resection, inflammatory bowel diseases (*e.g.*, Crohn's disease and ulcerative colitis), disorders impairing absorption of bile acids not otherwise characterized (idiopathic)) leading to diarrhea (*e.g.*, BAD) and GI symptoms, and GI, liver, and/or biliary cancers (*e.g.*, colon cancer and hepatocellular cancer); and/or bile acid synthesis abnormalities, such as those contributing to NASH, cirrhosis and portal hypertension. 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.

[0199] Peptide sequences provided herein including subsequences, sequence variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 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).

[0200] Peptide sequences provided herein including subsequences, variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 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 provided herein including subsequences, variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 1) and methods provided herein including pharmaceutical compositions can be administered via a (micro)encapsulated delivery system or packaged into an implant for administration.

[0201] A particular non-limiting example of parenteral (*e.g.*, subcutaneous) administration entails the use of Intarcia's subcutaneous delivery system (Intarcia Therapeutics, Inc.; Hayward, CA). The system comprises a miniature osmotic pump that delivers a consistent amount of a therapeutic agent over a desired period of time. In addition to maintaining drug levels within an appropriate therapeutic range, the system can be used with formulations that maintain the stability of proteinaceous therapeutic agents at human body temperature for extended periods of time.

Compositions

[0202] Also provided herein are "pharmaceutical compositions," which include a peptide sequence (or sequences) provided herein, including subsequences, variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 1), and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients; in combination with, or separate from, one or more additional agents for the treatment of a bile acid-related disease, disorder or condition, or a composition comprising such one or more additional agents and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In particular embodiments, a peptide sequence or sequences and an additional agent(s) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in accordance with the methods and uses provided herein. 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 provided herein. Pharmaceutical compositions provided herein can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0203] In some aspects, the pharmaceutical compositions may further comprise other therapeutically active agents or compounds disclosed herein (*e.g.*, bile acid stabilizing agents or drugs) or known to the skilled artisan which can be used in the treatment or prevention of various bile acid diseases and disorders as set forth herein. As set forth above, the additional therapeutically active agents or compounds may be present in a separate pharmaceutical composition(s). Exemplary dosing parameters and regimens are described herein.

[0204] Pharmaceutical compositions typically comprise a therapeutically effective amount of at least one of the peptide sequences provided herein, including subsequences, variants and modified forms of the exemplified peptide sequences (*e.g.*, sequences listed in the Sequence Listing or Table 1) and/or one or more additional agents described herein, 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 herein. 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.

[0205] 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.

[0206] Pharmaceutical compositions provided herein may contain still other pharmaceutically-acceptable formulation agents for modifying or maintaining the rate of release of a peptide and/or an additional agent, as described herein. 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 provided herein.

[0207] 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 peptides and the other agents described herein, 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 peptides and/or other agents described herein 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.

[0208] 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).

[0209] 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).

[0210] 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 a peptide provided herein 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.

[0211] 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 of preparing liposomes are described in, for example, U.S. Patent Nos. 4,235,871, 4,501,728, and 4,837,028. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0212] 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.

[0213] 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.

[0214] 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.

[0215] 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.

[0216] Pharmaceutical compositions provided herein 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.

[0217] 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.

[0218] Also provided herein are peptides and/or one or more additional agents described herein in the form of suppositories for rectal administration. The suppositories can be prepared by mixing a peptide and/or one or more additional agents described herein 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.

Methods of Identifying Modulators of Bile Acid-related Disorders

[0219] Also provided herein are methods of identifying a peptide (or a subsequence, variant or modified form as set forth herein) that modulates bile acid homeostasis without having substantial HCC activity. In one embodiment, a method includes: providing a candidate peptide sequence; administering the candidate peptide sequence to a test animal; measuring bile acid levels of the animal after administration of the candidate peptide sequence, to determine if the candidate peptide sequence favorably modulates bile acid homeostasis; and analyzing the candidate peptide sequence for induction of HCC in the animal, or expression of a marker correlating with HCC activity. A candidate peptide that modulates bile acid homeostasis but does not have substantial HCC activity thereby identifies a peptide sequence that modulates bile acid homeostasis without substantial HCC activity.

[0220] 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, bile acids and precursors, such as 7 alpha-hydroxy-4-cholesten-3-one, can be assayed or measured in a sample (*e.g.*, serum) from a subject. Another non-limiting examples is a two reaction method (Randox Laboratories, Ltd.) using serum or heparinized plasma. In the first reaction bile acids are oxidized by 3-α-hydroxysteroid dehydrogenase with the subsequent reduction of Thio-NAD to Thio-NADH. In the second reaction, oxidized bile acids are reduced by the same enzyme with the subsequent oxidation of NADH to NAD. The rate of formation of Thio-NADH is determined by measuring the specific absorbance change at 405 nm.

[0221] 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.

[0222] 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 certain embodiments, 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.

[0223] 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 provided herein 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).

[0224] It is to be understood that the techniques, assays and the like described in this section are applicable to identifying an additional agent described herein having desired properties and/or characteristics. Moreover, the techniques, assays and the like described in this section are applicable to identifying a peptide in combination with an additional agent described herein, for example, a composition comprising a peptide in combination with an additional agent described herein that has at least one favorable characteristic; or a treatment regimen comprising a peptide provided herein in combination with an additional agent described herein that has at least one favorable characteristic.

Antibodies

[0225] Also provided herein is the generation and use of antibodies, and fragments thereof, that bind the peptide sequences provided herein, including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in the Sequence Listing or Table 1), and/or one or more additional agents as described herein.

[0226] 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.

[0227] 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.

[0228] 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.

[0229] 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.

[0230] 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.

[0231] 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.

[0232] 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.

[0233] 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.

[0234] The terms "complementarity determining regions" or "CDRs" refer 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".

[0235] 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, such as ≤ 100 nM or ≤ 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.

[0236] 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.

[0237] 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.

[0238] 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.

[0239] 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.

[0240] 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 provided herein 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 provided herein and/or one or more additional agents described herein, thereby having an effect on a condition or disorder.

Kits

[0241] Also provided herein are kits including, but not limited to, peptide sequences provided herein and/or one or more additional agents for the treatment of a bile acid-related disease, disorder or condition, or a composition comprising the foregoing, and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients, optionally in further combination with one or more therapeutic agents distinct from those described above, compositions and pharmaceutical compositions thereof, packaged into suitable packaging material. A kit may include 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 treatment and/or prevention of a bile acid related or associated disorder, such as cholestasis, including, for example diseases of intrahepatic cholestasis (*e.g.*, PBC, PFIC, PSC, PIC, neonatal cholestasis, and drug induced cholestasis (*e.g.*, estrogen)), and diseases of extrahepatic cholestasis (*e.g.*, bile cut compression from tumor, bile duct blockade by gall stones); bile acid malabsorption and other disorders involving the distal small intestine, including ileal resection, inflammatory bowel diseases (*e.g.*, Crohn's disease and ulcerative colitis), disorders impairing absorption of bile acids not otherwise characterized (idiopathic)) leading to diarrhea (*e.g.*, BAD) and GI symptoms, and GI, liver, and/or biliary cancers (*e.g.*, colon cancer and hepatocellular cancer); and/or bile acid synthesis abnormalities, such as those contributing to NASH, cirrhosis and portal hypertension, *etc.*

[0242] 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.*).

[0243] Kits provided herein 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.

[0244] Labels or inserts can include, among other things, identifying information of one or more components therein, dosing parameters, and/or information on the 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.

[0245] 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 regimens set forth herein. Exemplary instructions include instructions for treatment or use of a peptide sequence as set forth herein and/or the use of an additional agent or treatment modality useful in treating a bile acid-related or associated disorder or a disorder of bile acid homeostasis. Kits provided herein therefore can additionally include labels or instructions for practicing any of the methods and uses provided herein, including treatment methods and uses.

[0246] 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 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.

[0247] Kits provided herein 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. In certain embodiments, kits are designed for cold storage. Kits provided herein can further be designed to contain peptide sequences provided herein, or that contain nucleic acids encoding peptide sequences. Kits provided herein can also be designed to contain, either separately or in combination with the peptide sequences provided herein, one or more additional agents useful in the treatment or prevention of a bile acid-related disease or disorder. Any cells in the kit can be maintained under appropriate storage conditions until ready to use.

[0248] 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.

[0249] 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.

[0250] 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%, 96%, 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.

[0251] 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, 2500-5000, 5000-25,000, or 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.*

[0252] A series of ranges are disclosed throughout this document. The use of a series of ranges includes 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.

[0253] 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.

[0254] 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 descriptions in the Experimental section are intended to illustrate but not limit the scope of invention described in the claims.

Experimental

[0255] The following descriptions are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below were performed and are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate the data and the like associated with the teachings of the present invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, *etc.*), but some experimental errors and deviations should be accounted for.

[0256] Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: bp = base pair(s); kb = kilobase(s); s or sec = second(s); min = minute(s); h or hr = hour(s); aa = amino acid(s); kb = kilobase(s); nt = nucleotide(s); pg = picogram; ng = nanogram; μg = microgram; mg = milligram; g = gram; kg = kilogram; pl or pL = picoliter(s); dl or dL = deciliter; μl or μL = microliter; ml or mL = milliliter; l or L = liter; μM = micromolar; mM = millimolar; M = molar; kDa = kilodalton; i.m. = intramuscular(ly); i.p. = intraperitoneal(ly); SC or SQ = subcutaneous(ly); QD = daily; BID = twice daily; QW = weekly; TIW = three times a week; QM = monthly; HPLC = high performance liquid chromatography; BW = body weight; U = unit; ns = not statistically significant; PBS = phosphate-buffered saline; PCR = polymerase chain reaction; NHS = N-Hydroxysuccinimide; HSA = human serum albumin; BSA = bovine serum albumin; DMEM = Dulbeco's Modification of Eagle's Medium; GC = genome copy; EDTA = ethylenediaminetetraacetic acid.

Materials and Methods

[0257] The following general materials and methods can be used.

[0258] **Standard Molecular Biology Techniques.** Standard methods in molecular biology are described in the scientific literature (see, *e.g.*, Sambrook and Russell (2001) Molecular Cloning, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; and Ausubel, *et al.* (2001) Current Protocols in Molecular Biology, Vols. 1-4, John Wiley and Sons, Inc. New York, N.Y., which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4)).

[0259] The scientific literature describes methods for protein purification, including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization, as well as chemical analysis, chemical modification, post-translational modification, production of fusion proteins, and glycosylation of proteins (see, *e.g.*, Coligan, *et al.* (2000) Current Protocols in Protein Science, Vols. 1-2, John Wiley and Sons, Inc., NY).

[0260] Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (*e.g.*, Harlow and Lane (1999) Using Antibodies, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY); standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan *et al.* (2001) Current Protocols in Immunology, Vol. 4, John Wiley, Inc., NY); methods for flow cytometry, including fluorescence-activated cell sorting (FACS), are available (see, *e.g.*, Shapiro (2003) Practical Flow Cytometry, John Wiley and Sons, Hoboken, NJ); and fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, for example, as diagnostic reagents, are available (Molecular Probes (2003) Catalogue, Molecular Probes, Inc., Eugene, OR.; Sigma-Aldrich (2003) Catalogue, St. Louis, MO).

[0261] **Software.** Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GCG Wisconsin Package™ (Accelrys, Inc., San Diego, CA); and DeCypher™ (TimeLogic Corp., Crystal Bay, NV).

[0262] **Animals.** Mice can be purchased from The Jackson Laboratory (Bar Harbor, ME) and used in various models, assays and the like familiar to the skilled artisan. By way of example, *db/db* mice (The Jackson Laboratory) can be 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. Mice can have free access to water (autoclaved distilled water) and can be 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. All animal studies can be approved by the NGM Institutional Animal Care and Use Committee.

[0263] **DNA and Amino Acid Sequences.** cDNA of ORF encoding human FGF19 (Homo sapiens FGF19, GenBank Accession No. NM_005117.2) and protein sequence encoded by the cDNA (GenBank Accession No. NP_005108.1) can be used herein.

[0264] **PCR**. FGF19 ORF can be amplified with polymerase chain reaction (PCR) using recombinant DNA (cDNA) prepared from human small intestinal tissue. PCR reagent kits with Phusion® high-fidelity DNA polymerase can be purchased from New England BioLabs (F-530L, Ipswich, MA). The following primers can be used: forward PCR primer:

[0265] 5' CCGACTAGTCACCatgcggagcgggtgtgtgg (SEQ ID NO:136) and reverse PCR primer:

[0266] 5' ATAAGAATGCGGCCGCTTACTTCTCAAAGCTGGGACTCCTC (SEQ ID NO:137). Amplified DNA fragment can be digested with restriction enzymes Spe I and Not I (the restriction sites are frequently not included in the 5' or 3' PCR primers, respectively) and then ligated with AAV transgene vectors that have been digested with the same restriction enzymes. The vector that can be used for expression can contain a selectable marker and an expression cassette comprising a strong eukaryotic promoter 5' of a site for insertion of the cloned coding sequence, followed by a 3' untranslated region and a bovine growth hormone polyadenylation tail. The expression construct can also be flanked by internal terminal repeats at the 5' and 3' ends.

[0267] CYP7A1 Repression Assay in Primary Human Hepatocytes. Primary human hepatocytes can be plated on collagen-coated plates (Becton Dickinson Biosciences) in Williams E media (Invitrogen) supplemented with 100 nM dexamethasone (Sigma) and 0.25 mg/ml MatriGel™ (Becton Dickinson Biosciences). Cells can be treated with FGF19 or variants at 37°C for 6 hours. CYP7A1 expression can be evaluated in triplicate by quantitative RT-PCR (TaqMan® ABI PRISM 7700, Applied Biosystems) and normalized to GAPDH expression.

[0268] CYP7A1 *In vivo* Repression Assay. Nine-week-old male db/db mice (Jackson Laboratories) can be injected intraperitoneally with recombinant proteins FGF19 or FGF21 at 0.1 mg/kg, 1 mg/kg, and 10 mg/kg. Animals can be euthanized 5 hours post-injection. Livers can be harvested and homogenized in TRIzol® reagent (Invitrogen). Total RNA can be extracted and treated with DNase (Ambion) followed by quantitative RT-PCR analysis and normalized to GAPDH expression.

[0269] Production and Purification of AAV. AAV293 cells (which can be obtained from Agilent Technologies, Santa Clara, CA) can be 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 can be plated at 50% density on day 1 in 150 mm cell culture plates and can be 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 AAV2/9 plasmid (Gao *et al.*, J. Virol. 78:6381 (2004)). Forty-eight (48) hours after transfection, the cells can be 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 can be frozen in an alcohol dry ice bath and then thawed in a 37°C water bath. The freeze and thaw cycles can be repeated three times; Benzonase® (Sigma-aldrich, St. Louis, MO) can be added to 50 units/ml;

deoxycholate can be added to a final concentration of 0.25%. After incubation at 37°C for 30 min, cell debris can be pelleted by centrifugation at 5000 x g for 20 min. Viral particles in the supernatant can be purified using a gradient comparable to discontinued iodixanal (Sigma-aldrich, St. Louis, MO) gradient as previously described (Zolotukhin S. et al (1999) Gene Ther. 6:973). The viral stock can be 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 can be 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.

[0270] Afterwards, 15 μl of the solution containing 2 mg/ml of Proteinase K, 0.5% SDS and 25 mM EDTA can be added and the mixture can be incubated for an additional 20 min at 55°C to release viral DNA. Viral DNA can be cleaned with mini DNeasy® Kit (Qiagen, Valencia, CA) and eluted with 40 μl of water. Viral genome copy (GC) can be determined by using quantitative PCR. Viral stock can be diluted with PBS to desirable GC/ml, and viral working solution (200 μl) can be delivered into mice via tail vein injection.

[0271] **HCC Assay.** Liver specimens can be harvested from db/db mice 24 weeks after AAV injection. HCC scores can be 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.

[0272] **Serum FGF19/FGF21/Variants Exposure Level Assay**. Whole blood (about 50 μl/mouse) from mouse tail snips can be collected into plain capillary tubes (BD Clay Adams SurePrep™, Becton Dickenson and Co. Sparks, MD). Serum and blood cells can be separated by spinning the tubes in an Autocrit™ Ultra 3 (Becton Dickinson and Co. Sparks, MD). FGF19, FGF21, and variant exposure levels in serum can be determined using EIA kits (Biovendor) by following the manufacturer's instructions.

[0273] **FGFR4 Binding and Activity Assays**. Solid phase ELISA (binding) and ERK phosphorylation assay can be performed using purified recombinant proteins. FGFR binding assay can be conducted using solid phase ELISA. Briefly, a 96-well plate can be coated with 2 μg/ml anti-hFc antibody and can be incubated with 1 μg/ml FGFR1-hFc or FGFR4-hFc. Binding to FGF19 variants in the presence of 1 μg/ ml soluble β-klotho and 20 μg/ml heparin can be detected by biotinylated anti- FGF19 antibodies (0.2 μg/mL), followed by streptavidin-

HRP incubation (100 ng/mL). For FGFR4 activation assay, Hep3B cells can be stimulated with FGF19 variants for 10 minutes at 37°C, then can be immediately lysed and assayed for ERK phosphorylation using a commercially available kit from Cis-Bio.

[0274] In the examples that follow, wild-type FGF19, wild-type FGF21, variants of FGF19 peptide sequences, fusions of FGF19 and/or FGF21 peptide sequences, and variants of fusions (chimeras) of FGF19 (for purposes of the Experimental section, collectively "Invention Peptides") can be used to illustrate the procedures, methodologies and the like useful in evaluating other Invention Peptides, as well as in evaluating the one or more additional agents or therapeutic modalities having a desired effect on one or more bile acid-related or associated diseases, disorders or conditions (for purposes of the Experimental section, "Additional Agents") useful in combination with the Invention Peptides.

[0275] **Example 1**: Through assessment of wild-type FGF19 and FGF21, this example illustrates how the peptides (*e.g.*, M70) provided herein can be evaluated for inhibition of CYP7A1 expression.

[0276] Briefly, at time0 *db/db* mice can be dosed intraperitoneally with either recombinant FGF19 (0.1 mg/kg; 1 mg/kg; 10 mg/kg) or recombinant FGF21 (0.1 mg/kg; 1 mg/kg; 10 mg/kg). Five hours after dosing, livers can be harvested, RNA extracted, and CYP7A1 expression determined by real-time PCR (QPCR) using GADPH as a normalization control. In each group of mice containing the desired number of animals (*e.g.*, n = 3), CYP7A1 expression values for the various FGF19 and FGF21 concentrations can be compared to mice dosed with PBS vehicle control.

[0277] **Example 2**: Using the assays described above (*e.g.*, *in vitro* cell-based assay (primary human hepatocyte) and *in vivo* assay (protein dosing in *db/db* mice)), repression of CYP7A1 in primary human hepatocytes can be determined for Invention Peptides. Invention Peptides that retain Cyp7a1 repression activity can be further evaluated in the HCC assay (or other relevant assay or model) described above to identify variants that can be useful for modulating bile acid metabolism and/or for treating bile acid-related diseases (*e.g.*, PBC, NASH, and bile acid diarrhea) without causing induction of HCC.

[0278] **Example 3**: Invention Peptides can be analyzed for lipid elevating activity and tumorigenesis using the above-described methods or any methods familiar to the skilled artisan. If a positive correlation is observed between lipid elevation and tumorigenesis, as determined by

HCC formation in *db/db* mice, lipid elevating activity can be used as an indicator and/or predictor of HCC formation in animals.

[0279] **Example 4**: The teachings of this example can be used to determine whether administration of Invention Peptides to human patients can result in suppression of 7a-hydroxy-4-cholsten-3-one (C4), a marker of bile acid synthesis.

[0280] Study Subjects: Healthy adults in the age range 18–65 years and with normal body weight (body mass index, BMI 20-35) can be enrolled in the study. The study protocol can be approved by the Human Research Ethics Committee in Australia, and written informed consent can be obtained from each subject. For inclusion in the study, each subject can be required to be in good health as determined by no clinically significant findings from medical history, physical exam, 12-lead ECG, clinical laboratory findings, and vital signs at screening. Subjects with a history or clinical manifestation of any significant metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, GI, neurological, or psychiatric disorder can be excluded from enrollment.

[0281] Study Design: The study can be a randomized, double-blind, placebo-controlled design. Prescreening of subjects can be performed 7–30 days prior to entry, and baseline evaluations can be performed before treatment. Each subject can be given a SC injection of 3 mg/day in a single bolus dose daily for 7 days of one or more Invention Peptides. Blood samples can be collected into heparinized tubes through an indwelling catheter. Blood samples taken on Day 1 and Day 7 at 4.5 hrs or 24 hrs after administration of one or more Invention Peptides or placebo can be analyzed. Serum levels of 7a-hydroxy-4-cholesten-3-one (C4) can be used to monitor CYP7A1 enzymatic activity (bile acid synthesis). They can be analyzed from individual serum samples after sample extraction followed by high-pressure liquid chromatography (HPLC) as described previously (Galman *et al.* (2003) J Lipid Res. 2003; 44(4):859-66).

[0282] **Example 5**: The previously described assays for FGFR4 binding and activity can be used to assess whether Invention Peptides show activation of mouse FGFR4-β-klotho signaling in a rat myoblast cell line

[0283] Methods: An ELK luciferase assay can be performed in L6 cells transiently transfected with mouse FGFR4, b-klotho, and reporter constructs containing 5xUAS luciferase and GAL4-DNA-binding domain (DBD) fused to ELK1. In this system, luciferase activity is regulated by the endogenous phosphorylated extracellular signal-regulated kinase (ERK). Cells can be incubated with ligands for 6 hours before being lysed for luciferase activity measurements.

[0284] Thereafter, a cell-based receptor activation assay can be used to evaluate the ability of mouse FGFR4 to mediate ligand-dependent signaling in the presence of β-klotho. To this end, a rat L6 myoblast cell line, which lacks endogenous expression of these proteins, can be transfected with DNAs encoding FGFR4 and β-klotho from mouse, as well as plasmids containing an Elk1-dependent chimeric transcription factor–based reporter system. Following transfection, concentration response of ligand-dependent luciferase expression can be analyzed in whole-cell lysates in the presence of luciferin substrate.

[0285] The resulting data can suggest that the formation of a ternary complex between the FGFR4-β-klotho co-receptors and cognate ligands is important for potent activation of intracellular signaling.

Sequence Listing

[0286] The present specification is being filed with a computer readable form (CRF) copy of the Sequence Listing. The CRF entitled 13370-016-228_SEQLIST.txt, which was created on June 15, 2015 and is 256,662 bytes in size, is identical to the paper copy of the Sequence Listing and is incorporated herein by reference in its entirety.

What is Claimed is:

1. A method of modulating bile acid homeostasis or treating a bile-acid related or associated disorder, comprising:

a) administering a chimeric peptide sequence, comprising:

i) 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 (SEQ ID NO:121) or DASPH (SEQ ID NO:122), and

ii) 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 (SEQ ID NO:169), wherein the W residue corresponds to the first amino acid position of the C-terminal region; and

b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder,

thereby modulating bile acid homeostasis or treating the bile-acid related or associated disorder.

2. A method of modulating bile acid homeostasis or treating a bile-acid related or associated disorder, comprising:

a) administering a chimeric peptide sequence, comprising:

i) 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

ii) 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 (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region; and

b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder,

thereby modulating bile acid homeostasis or treating the bile-acid related or associated disorder.

3. A method of modulating bile acid homeostasis or treating a bile-acid related or associated disorder, comprising:

a) administering a chimeric peptide sequence, comprising:

i) 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

ii) 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 (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region; and

b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder,

thereby modulating bile acid homeostasis or treating the bile-acid related or associated disorder.

4. The method 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 method 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 method of modulating bile acid homeostasis or treating a bile-acid related or associated disorder, comprising:

a) administering a peptide sequence, comprising or consisting of any of:

i) a FGF19 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19;

ii) a FGF21 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21;

iii) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence; or

iv) 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; and

b) administering at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder, thereby modulating bile acid homeostasis or treating the bile-acid related or associated disorder.

7. The method 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 acids 17-146 of SEQ ID NO:100 (FGF21) fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 (FGF19) (M46).

8. The method of claim 6, wherein the peptide sequence comprises at least one amino acid substitution to amino acid residues 125-129 of SEQ ID NO:99 (FGF19), EIRPD; at least one amino acid substitution to amino acid residues 126-128 of SEQ ID NO:99 (FGF19), IRP; or at least one amino acid substitution to amino acid residues 127-128 of SEQ ID NO:99 (FGF19), RP.

9. The method of claim 8, wherein the peptide sequence comprises a substitution to one of amino acid residues 127-128 of SEQ ID NO:99 (FGF19), IRP, wherein at least one amino acid substitution is R127L or P128E.

10. The method of claim 9, wherein the peptide sequence comprises
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDG
YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES
DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M3) (SEQ ID NO:3); or
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDG

YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M140) (SEQ ID NO:194).

11. The method of claim 8, wherein the peptide sequence further comprises at least one amino acid substitution to amino acid residues 1-124 of SEQ ID NO:99 (FGF19) and/or to amino acid residues 130-194 of SEQ ID NO:99 (FGF19).

12. The method of claim 11, wherein the peptide sequence is RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M160) (SEQ ID NO:196).

13. The method of claims 1, 2, 3 or 6, wherein the peptide sequence comprises or consists of any sequence set forth herein as M1 to M98, M101 to M160 or M200 to M207, or SEQ ID NOs:1 to 98, 101 to 135, or 138 to 212.

14. The method of claims 1, 2, 3 or 6, wherein the peptide sequence comprises or consists of any sequence set forth in the Sequence Listing or Table 1 herein.

15. The method of claims 1, 2 or 6, wherein the peptide sequence has a WGDPI (SEQ ID NO:170) sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of SEQ ID NO:99 (FGF19).

16. The method of claim 15, wherein the peptide sequence maintains or increases an FGFR4 mediated activity.

17. The method of claims 1, 2 or 6, wherein the peptide sequence has a substituted, mutated or absent WGDPI (SEQ ID NO:170) sequence motif corresponding to FGF19 WGDPI sequence of amino acids 16-20 of FGF19.

18. The method of claim 17, wherein the WGDPI (SEQ ID NO:170) sequence has one or more amino acids substituted, mutated or absent.

19. The method of claims 1, 2 or 6, wherein the peptide sequence is distinct from an FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the FGF19 WGDPI (SEQ ID NO:170) sequence at amino acids 16-20.

20. The method 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.

21. The method of claim 1, wherein the N-terminal region comprises amino acid residues VHYG (SEQ ID NO:101), wherein the N-terminal region comprises amino acid residues DASPHVHYG (SEQ ID NO:102), or wherein the N-terminal region comprises amino acid residues DSSPLVHYG (SEQ ID NO:103).

22. The method of claim 21, wherein the G corresponds to the last position of the N-terminal region.

23. The method of claims 1 or 6, wherein the N-terminal region comprises amino acid residues DSSPLLQ (SEQ ID NO:104), and wherein the Q residue is the last amino acid position of the N-terminal region.

24. The method of claim 22 or 23, wherein the N-terminal region further comprises: RHPIP (SEQ ID NO:106), where R is the first amino acid position of the N-terminal region; or HPIP (SEQ ID NO:107), where H is the first amino acid position of the N-terminal region; or RPLAF (SEQ ID NO:108), where R is the first amino acid position of the N-terminal region; or PLAF (SEQ ID NO:109), 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.

25. The method of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of any of M1 to M98, M101 to M160, or M200 to M207 variant peptide sequences, or a subsequence or fragment of any of the M1 to M98, M101 to M160, or M200 to M207 variant peptide sequences.

26. The method of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of any of:
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK (M69) (SEQ ID NO: 69);

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK (M52) (SEQ ID NO:52);

RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK (M5) (SEQ ID NO:5);

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK (M5-R) (SEQ ID NO:160);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE AHSLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLS MVGPSQGRSPSYAS (M71) (SEQ ID NO:71);
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE

AHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLS MVGPSQGRSPSYAS (M72) (SEQ ID NO:72);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQL KALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSE AHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLS MVVQDELQGVGGEGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE (M73) (SEQ ID NO:73);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M1) (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGY NVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD MFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M2) (SEQ ID NO:2 or 140);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M3) (SEQ ID NO:3);

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK (M48) (SEQ ID NO:48 or 6 or 148);

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSL LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNV YRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMF SSPLETDSMDPFGLVTGLEAVRSPSFEK (M49) (SEQ ID NO:49 or 7 or 149);

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK (M50) (SEQ ID NO:50);

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLE IKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDSMDPFGLVTGLEAVRSPSFEK (M51) (SEQ ID NO:51 or 36 or 155);

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSE KHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPL ETDSMDPFGLVTGLEAVRSPSFEK (M53) (SEQ ID NO:192);

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVY RSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFS SPLETDS16MDPFGLVTGLEAVRSPSFEK (M70) (SEQ ID NO:70);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M139) (SEQ ID NO:193);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M140) (SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDG

YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M141) (SEQ ID NO:195); or

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M160) (SEQ ID NO:196);

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.

27. The method of claims 1 or 2, wherein the N-terminal region comprises amino acid residues DSSPLLQFGGQV (SEQ ID NO:105), and wherein the V residue corresponds to the last position of the N-terminal region.

28. The method of any of claims 1 to 3 or 6, wherein amino acid residues HPIP (SEQ ID NO:107) are the first 4 amino acid residues of the N-terminal region.

29. The method of any of claims 1 to 3, 6 or 26, 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 (SEQ ID NO:115) sequence, or the first through fourth positions of the N-terminal

region is an MDSS (SEQ ID NO:116) sequence, or the first through fifth positions of the N-terminal region is an MRDSS (SEQ ID NO:117) sequence, or the first through fifth positions of the N-terminal region is an MSSPL (SEQ ID NO:118) sequence, or the first through sixth positions of the N-terminal region is an MDSSPL (SEQ ID NO:119) sequence, or the first through seventh positions of the N-terminal region is an MSDSSPL (SEQ ID NO:120) sequence.

30. The chimeric method 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).

31. The method of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of:

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYR SEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSS PLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:160);

DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEK HRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLE TDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:138 or 161);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDG YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAH SLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGY NVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD MFSSPLETDSMDPFGLVTGLEAVRSPSFEK(SEQ ID NO:2 or 140); or

DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIK AVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRS EKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSP LETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:141);

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.

32. The method of claim 25, 26 or 31, 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.

33. The method 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.

34. The method 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.

35. The method 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.

36. The method of any of claims 1 to 3 or 6, wherein the peptide sequence at comprises or consists of any of:

HPIPDSSPLLQFGGQVRLRHLYTSG (M5-R) (amino acids 1-25 of SEQ ID NO:160);
DSSPLLQFGGQVRLRHLYTSG (M6-R) (amino acids 2-22 of SEQ ID NO:6);
RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7) (amino acids 1-27 of SEQ ID NO:7);
HPIPDSSPLLQWGDPIRLRHLYTSG (M8-R) (amino acids 2-26 of SEQ ID NO:8);
HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9-R) (amino acids 2-28 of SEQ ID NO:9);
HPIPDSSPHVHYGWGDPIRLRHLYTSG (M10-R) (amino acids 2-28 of SEQ ID

NO:10);
RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11) (amino acids 1-27 of SEQ ID NO:11);
RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);
RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);
HPIPDSSPHVHYGGQVRLRHLYTSG (M14-R) (amino acids 2-26 of SEQ ID NO:14);
RPLAFSDAGPHVHYGGQVRLRHLYTSG (M15) (amino acids 1-27 of SEQ ID NO:15); RPLAFSDAGPHVHWGDPIRLRHLYTSG (M16) (amino acids 1-27 of SEQ ID NO:16);
RPLAFSDAGPHVGWGDPIRLRHLYTSG (M17) (amino acids 1-27 of SEQ ID NO:17);
RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18) (amino acids 1-27 of SEQ ID NO:18);
RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19) (amino acids 1-27 of SEQ ID NO:19);
RPLAFSDAGPVHGWGDPIRLRHLYTSG (M20) (amino acids 1-27 of SEQ ID NO:20);
RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21) (amino acids 1-27 of SEQ ID NO:21);
RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22) (amino acids 1-27 of SEQ ID NO:22);
RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23) (amino acids 1-27 of SEQ ID NO:23);
RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24) (amino acids 1-27 of SEQ ID NO:24);
RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25) (amino acids 1-27 of SEQ ID NO:25);
RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26) (amino acids 1-27 of SEQ ID NO:26);
RPLAFSDSSPHVHWGDPIRLRHLYTSG (M27) (amino acids 1-27 of SEQ ID NO:27);
RPLAFSDAGPHVWGDPIRLRHLYTSG (M28) (amino acids 1-26 of SEQ ID NO:28);

RPLAFSDAGPHVHYWGDPIRLRHLYTSG (M29) (amino acids 1-28 of SEQ ID NO:29); RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30) (amino acids 1-29 of SEQ ID NO:30);
RHPIPDSSPLLQFGAQVRLRHLYTSG (M31) (amino acids 1-26 of SEQ ID NO:31);
RHPIPDSSPLLQFGDQVRLRHLYTSG (M32) (amino acids 1-26 of SEQ ID NO:32);
RHPIPDSSPLLQFGPQVRLRHLYTSG (M33) (amino acids 1-26 of SEQ ID NO:33);
RHPIPDSSPLLQFGGAVRLRHLYTSG (M34) (amino acids 1-26 of SEQ ID NO:34);
RHPIPDSSPLLQFGGEVRLRHLYTSG (M35) (amino acids 1-26 of SEQ ID NO:35);
RHPIPDSSPLLQFGGNVRLRHLYTSG (M36) (amino acids 1-26 of SEQ ID NO:36);
RHPIPDSSPLLQFGGQARLRHLYTSG (M37) (amino acids 1-26 of SEQ ID NO:37);
RHPIPDSSPLLQFGGQIRLRHLYTSG (M38) (amino acids 1-26 of SEQ ID NO:38);
RHPIPDSSPLLQFGGQTRLRHLYTSG (M39) (amino acids 1-26 of SEQ ID NO:39);
RHPIPDSSPLLQFGWGQPVRLRHLYTSG (M40) (amino acids 1-28 of SEQ ID NO:40);
DAGPHVHYGWGDPIRLRHLYTSG (M74-R) (amino acids 2-24 of SEQ ID NO:74);
VHYGWGDPIRLRHLYTSG (M75-R) (amino acids 2-19 of SEQ ID NO:75);
RLRHLYTSG (M77-R) (amino acids 2-10 of SEQ ID NO:77);
or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted.

37. The method of any of claims 1 to 3 or 6, wherein the peptide sequence comprises or consists of any of:

RHPIPDSSPLLQFGWGDPIRLRHLYTSG (M9) (amino acids 1-28 of SEQ ID NO:9);

RHPIPDSSPLLQWGDPIRLRHLYTSG (M8) (amino acids 1-26 of SEQ ID NO:8);

RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);

RHPIPDSSPHVHYGWGDPIRLRHLYTSG (M10) (amino acids 1-28 of SEQ ID NO:10);

RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);

RHPIPDSSPHVHYGGQVRLRHLYTSG (M14) (amino acids 1-26 of SEQ ID NO:14);

RPLAFSDAGPHVHYGGDIRLRHLYTSG (M43) amino acids 1-27 of SEQ ID NO:43); or

RDSSPLLQFGGQVRLRHLYTSG (M6) (amino acids 1-22 of SEQ ID NO:6);

or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted.

38. The method of claims 36 or 37, 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.

39. The method of any of claims 36 or 37, wherein the peptide sequence further comprises all or a portion of an FGF19 sequence set forth as:
PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGA
DGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGF
LPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (SEQ ID NO:188) positioned at the C-terminus of the peptide, or wherein the amino terminal "R" residue is deleted from the peptide.

40. The method of any of claims 1 to 3 or 6, wherein a subsequence of a chimeric peptide sequence or peptide sequence is administered, wherein the subsequence has at least one amino acid deletion.

41. The method of claim 40, 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.

42. The method of claim 6, wherein the reference or wild type FGF19 sequence is set forth as:

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDG
YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES
DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:99).

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

44. The method 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.

45. The method of any of claims 1 to 3 or 6, wherein the N-terminal region comprises any one of the following sequences: MDSSPL (SEQ ID NO:119), MSDSSPL (SEQ ID NO:120), SDSSPL(SEQ ID NO:112), MSSPL (SEQ ID NO:113), or SSPL (SEQ ID NO:114).

46. The method 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 (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19.

47. The method 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 (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19.

48. The method 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 (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19.

49. The method 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 (SEQ ID NO:171), WGDPV (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDP (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) substituted for the WGDPI sequence at amino acids 16-20 of FGF19.

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

51. The method of any of claims 46 to 50, wherein the HCC formation, glucose lowering activity, lipid increasing activity, or lean mass reducing activity is ascertained in a db/db mouse.

52. The method 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 FGFR4 or activate FGFR4.

53. The method 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.

54. The method 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.

55. The method 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.

56. The method of claim 55, wherein the amino acid deletions are at the N- or C-terminus, or internal.

57. The method of claim 55, wherein the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI) (SEQ ID NO:187).

58. The method 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.

59. The method of any of claims 1 to 3 or 6, wherein the chimeric peptide sequence or peptide sequence comprises a pharmaceutical composition.

60. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises a metabolic syndrome; a lipid or glucose disorder; cholesterol or triglyceride metabolism; type 2 diabetes; cholestasis, intrahepatic cholestasis, primary biliary cirrhosis (PBC), primary familial intrahepatic cholestasis (PFIC), progressive

PFIC, primary sclerosing choangitis (PSC), pregnancy intrahepatic cholestasis (PIC), neonatal cholestasis, and drug induced cholestasis, diseases of extrahepatic cholestasis, bile cut compression from tumor, bile duct blockade by gall stones, bile acid malabsorption and other disorders involving the distal small intestine, ileal resection, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, idiopathic disorders impairing absorption of bile acids, diarrhea, bile acid diarrhea (BAD), GI symptoms, GI cancers, liver cancers, biliary cancers, colon cancer, hepatocellular cancer, bile acid synthesis abnormalities, non-alcoholic steatohepatitis (NASH), cirrhosis, portal hypertension, or any combination thereof.

61. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises a lipid- or glucose-related disorder.

62. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises bile acid malabsorption or diarrhea.

63. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises cholestasis or primary biliary cirrhosis.

64. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises primary sclerosing cholangitis.

65. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder comprises PBC, NASH, or BAD.

66. The method of any of claims 1 to 3 or 6, wherein the bile acid associated or related disorder is PBC.

67. The method of any one of claims 1-66, wherein the at least one additional agent effective in modulating bile acid homeostasis or treating a bile-acid related or associated disorder is: a glucocorticoid; CDCA; UDCA; insulin, an insulin secretagogues, an insulin mimetic, a sulfonylurea and a meglitinide; a biguanide; an alpha-glucosidase inhibitors; a DPP-IV inhibitor, GLP-1, a GLP-1 agonists and a GLP-1 analog; a DPP-IV-resistant analogue; a PPAR gamma agonist, a dual-acting PPAR agonist, a pan-acting PPAR

agonist; a PTP1B inhibitor; an SGLT inhibitor; an RXR agonist; a glycogen synthase kinase-3 inhibitor; an immune modulator; a beta-3 adrenergic receptor agonist; an 11beta-HSD1 inhibitor; amylin and an amylin analogue; a bile acid sequestrant; or an SGLT-2 inhibitor.

68. The method of claim 66, wherein the at least one additional agent effective in modulating PBC is UDCA, an FXR agonist, OCA, an ASBT inhibitor, an autoimmune agent, an IL-12 agent, an anti-CD80 agent, an anti-CD20 agent, a CXCL10 neutralizing antibody, a ligand for CXCR3, a fibrate, fish oil, colchicine, methotrexate, azathioprine, cyclosporine, or an anti-retroviral therapy.

69. The method of claim 66, wherein the at least one additional agent effective in modulating PBC is UDCA, OCA, an ASBT inhibitor, an IL-12 agent, an anti-CD20 agent, or a fibrate.