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Ai-Luen Wu ET AL: "FGF19 Regulates Cell Proliferation, Glucose and Bile Acid Metabolism via FGFR4-Dependent and Independent Pathways", PLoS ONE, vol. 6, no. 3, 1 January 2011 (2011-01-01) , page e17868, XP055059113, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0017868

DESCRIPTION

Field of the Invention

[0001] The invention relates to 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) that modulate bile acid homeostasis, and uses of the variants and fusions in treatment of bile acid related and associated disorders.

Introduction

[0002] Bile acids are 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. Emulsification of lipids and fat-soluble vitamins in the intestine allows the formation of micelles that can then be transported via the lacteal system. Other functions of bile acids include driving the flow of bile to eliminate catabolites from the liver and aiding in the reduction of the bacterial flora found in the small intestine and biliary tract. Bile acids are also involved in the regulation of their own synthesis and enterohepatic circulation. See, *e.g.,* Staels et al., Diabetes Care (2009) vol. 32 no. suppl 2 S237-S245.

[0003] 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. 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 in the classical bile acid synthesis pathway. (See, *e.g.,* Inagaki et al., Cell Metabolism 2:217-25 (Oct 2005)).

[0004] As described further herein, activity of cyp7a1 is down-regulated by cholic acid and upregulated by cholesterol; thus, cyp7a1 is regulated by bile acids themselves. The conversion of cholesterol to bile acids is primarily effected by this pathway. 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 themselves.

[0005] 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). Hepatic cells may conjugate these four bile with one of two amino acids, glycine or taurine, to form a total of eight possible conjugated bile acids, referred to as bile salts. Thus, in total the principal bile acids are cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, deoxycholic acid and lithocholic acid. All four of these bile acids can be transported back into the blood stream, be returned to the liver, and be re-secreted through enterohepatic circulation. See, *e.g.,* Staels et al., Diabetes Care (2009) vol. 32 suppl 2 S237-S245.

[0006] The primary bile acids (cholic acid and chenodeoxycholic acid) are synthesized in the liver), while

the secondary bile acids (deoxycholic acid and lithocholic acid) are made by bacteria. The four bile acids are secreted into the bile canalicular lumen for storage in the gallbladder as mixed micelles with phospholipids and cholesterol. Upon ingestion of a meal, cholecystokinin stimulates gallbladder contraction resulting in its release of micellar bile acids into the intestinal lumen to aid digestion. Enterohepatic circulation enables ~90-95% of bile acids to be reabsorbed from the distal ileum and transported back to the liver; this bile acid uptake and transportation occurs primarily by pericentral hepatocytes. 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).

[0007] The primary bile acids (chenodeoxycholic acid and cholic acid) are physiological ligands/activators of farnesoid-X-receptor (FXR), pregnane-X-receptor (PXR) and constitutive androstane receptor (CAR), and litocholic acid is a ligand for the Vitamin D receptor (VDR) and the G-protein coupled receptor TGR5. FXR demonstrates a high selectivity for bile acids; conversely, PXR and CAR act upon a number of receptors integrating lipid homeostasis with xenobiotic metabolism. FXR, PXR, CAR and TGR5 exert synergistic activities in regulating lipid and glucose homeostasis and energy expenditure, as well as in regulating liver and peripheral insulin sensitivity. 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.

[0008] The synthesis of bile acids in the liver is negatively regulated by the hormone FGF19. FGF19 is secreted from the intestine and signals to the liver to repress Cyp7a1. In comparison, intestinal FXR activation due to transintestinal bile acid flux after a meal also induces the expression of FGF19, which is released by small intestine 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. Repression of CYP7A1 results in decreased synthesis of bile acids from intrahepatic cholesterol in response to the daily feeding-fasting cycle. US 2011/0104152 A1 discloses FGF19v, a variant FGF19, that shows Cyp7a1 and Cyp8ab1 supressive activity, lowering of blood glucose and lipid levels, and reduced induction of hepatocyte proliferation.

Therapeutic Implications

[0009] As described herein, abnormal bile acid homeostasis can result in, or exacerbate, a number of disorders, including cholestasis, portosystemic shunt, Crohn's disease, and hepatic microvascular dysplasia. In addition, bile acids play a role in modulating the metabolic syndrome, a cluster of cardiovascular disease risk factors that include visceral obesity, insulin resistance, dyslipidemia, increased blood pressure, and hypercoagulability. Thus, modulation of bile acid activity can provide a number of beneficial therapeutic effects.

Lipid- and Glucose-related Disorders

[0010] Activation of FXR by bile acids (or nonsteroidal synthetic FXR agonists) lowers plasma

triglycerides and has been shown to improve hyperglycemia in diabetic mice. Bile acids may also regulate energy expenditure in an FXR-independent manner in mice through activation of the G protein-coupled receptor TGR5. Thus, modulation of FXR activity and bile acid metabolism may provide a therapeutic approach for the treatment of, for example, the metabolic syndrome and diabetes type 2. See, *e.g.,* Lefebvre et al., Physiol Rev. 2009 Jan;89(1):147-91.

[0011] Bile acid synthesis (along with ileal resection) disrupts the enterohepatic circulation of bile acids, decreases plasma total and LDL cholesterol, and increases levels of HDL cholesterol, apolipoprotein (apo)-AI, and triglycerides. As a direct consequence of interrupting the return of bile acids to the liver, cyp7a1 expression becomes de-repressed, and conversion of cholesterol into bile acids is stimulated. Thus, agents that sequester bile acids in the gut (e.g., cholestyramine) prevent their reabsorption, resulting in, as a compensatory mechanism, more endogenous cholesterol being shunted into the production of bile acids, leading to reduced cholesterol levels.

[0012] The depletion of hepatic cholesterol due to increased diversion to bile acid synthesis leads to increased hepatic LDL receptor expression, which results in LDL receptor expression that accounts for the decline in total and LDL cholesterol produced by bile acid synthesis or ileal resection. There is thought to be an independent regulatory role for FXR in both HDL cholesterol and triglyceride metabolism.

[0013] As noted, bile acid synthesis has also been found to be associated with type 2 diabetes. A number of factors may contribute to glucose regulation, including effects on bile acid pool size and composition, FXR-mediated alterations in hepatic glucose production and intestinal glucose absorption, influences on peripheral insulin sensitivity, incretin effects, and energy use. Not only is modulation of bile acid synthesis useful in the treatment of diabetes, it may also find clinical utility in the treatment of pre-diabetes.

Bile Acid Malabsorption and Diarrhea

[0014] Excess concentrations of bile acids in the colon, resulting from, for example, bile acid malabsorption, are a cause of chronic diarrhea. When large amounts of bile acids enter the colon, they stimulate water secretion and intestinal motility causing chronic diarrhea, a condition referred to as a bile acid diarrhea (BAD). More particularly, when intestinal expression of the bile acid transporters is reduced, the intestine is less efficient at bile acid reabsorption (Type 1 bile acid malabsorption). Similarly, if intestinal motility is affected by gastro-intestinal surgery, or bile acids are deconjugated by small intestinal bacterial overgrowth, absorption is less efficient (Type 3 bile acid malabsorption). There is also a very small group of patients which do not exhibit any obvious signs of disease (Type 2 bile acid malabsorption). (See generally, Walters et al., Clin. Gastroenterol Hepatol. 7:1189-94 (Nov 2009)).

Cholestasis and Primary Biliary Cirrhosis

[0015] The condition of cholestasis is caused by acute or chronic interruption in the excretion of bile (through, for example, obstruction) within or outside the liver. Failure to form bile results in progressive cholestatic liver injury and death. Obstruction causes bile salts, the bile pigment bilirubin, and lipids to accumulate in the blood stream instead of being eliminated normally. Symptoms of chronic cholestasis include skin discoloration, scars or skin injuries caused by scratching, bone pain, xanthoma, or

xanthelasma. Patients with advanced cholestasis feel ill, tire easily, and are often nauseated. Abdominal pain and such systemic symptoms as anorexia, vomiting, and fever are usually due to the underlying condition that causes cholestasis.

[0016] Intrahepatic cholestasis is usually caused by hepatitis or by medications that produce symptoms resembling hepatitis. Phenothiazine-derivative agents, including chlorpromazine, can cause sudden fever and inflammation, although symptoms usually disappear after cessation of the agents. In rare cases, a condition resembling chronic biliary cirrhosis, discussed further below, persists even after the medication is stopped. Some patients experience a similar reaction in response to, for example, tricyclic antidepressants (e.g., amitriptyline and imipramine) and phenylbutazone. Intrahepatic cholestasis may also have other causes, including alcoholic liver disease, primary biliary cirrhosis, and cancer that has metastasized.

[0017] In comparison, there are several origins of extrahepatic cholestasis, including as an adverse effect of certain medications, a complication of surgery, serious injury, tissue-destroying infection, or intravenous feeding. Extrahepatic cholestasis can be caused by conditions such as tumors and gallstones that block the flow of bile from the gallbladder to the duodenum (e.g., by a stone obstructing the common bile duct). Extrahepatic cholestasis may also be caused by pancreatic cancer and, less frequently, as a result of non-cancerous narrowing of the common duct, ductal carcinoma, or disorders of the pancreas.

[0018] Symptoms of both intrahepatic and extrahepatic cholestasis include jaundice, dark urine, and pale stools. Itching over the skin may be severe if the condition is advanced.

[0019] Intrahepatic cholestasis of pregnancy (ICP) frequently develops during the second and third trimesters of pregnancy, and it is the second most common cause of jaundice during pregnancy. Although symptoms usually disappear within two-to-four weeks after the baby's birth, they may reappear if the mother subsequently becomes again. A similar condition affects some women who take oral contraceptives, but symptoms disappear upon cessation of the use of oral contraceptives.

[0020] Inborn errors of bile acid synthesis are rare genetic disorders that sometimes present as neonatal cholestasis. It is characterized by a failure to produce normal bile acids and an accumulation of unusual bile acids and bile acid intermediates. If not diagnosed or if diagnosed improperly, such inborn errors can result in liver failure or progressive chronic liver disease.

[0021] Drug-induced cholestasis may be a complication of chemotherapy or other medications. The two major types of drug-induced cholestasis are idiosyncratic reactions and direct toxic injury. Idiosyncratic reactions may occur at the onset of treatment or thereafter. Allergic responses are varied and are not related to the amount of medication being taken.

[0022] In direct toxic injury, the severity of symptoms parallels the amount of medication involved. This condition develops a short time after treatment begins, follows a predictable pattern, and usually causes liver damage. Direct toxic reactions develop in 1% of all patients who take chlorpromazine.

[0023] The rare condition of benign familial recurrent cholestasis is characterized by brief, repeated episodes of itching and jaundice, although the symptoms frequently disappear and the condition does not cause cirrhosis. (See generally, Rose et al., Cell Metabolism 14(1):123-30 (July 2011).

[0024] Primary Biliary Cirrhosis (PBC) is a progressive hepatic disease that primarily results from

autoimmune destruction of the bile ducts that transport bile acids out of the liver, resulting in cholestasis. As the disease progresses, persistent toxic build-up of bile acids causes progressive liver damage marked by chronic inflammation and fibrosis.

[0025] While PBC is rare, it is the most common cholestatic liver disease and is the fifth most common cause of liver transplant in the United States. 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. Though not required, a liver biopsy can be used to confirm the diagnosis of PBC, and bilirubin is frequently monitored to provide an indication of liver function. Elevated serum levels of ALP, an enzyme released by hepatic cells in response to bile acidmediated toxicity, is generally closely monitored in patients as an indicator of treatment response and prognosis.

[0026] Despite receiving ursodiol, the standard of care therapy for PBC, a significant portion of patients at advanced stated PBC will progress to liver failure, transplant or death within five-ten years. As a result, alternative therapies are currently being evaluated. One potentially promising agent is OCA, is a bile acid analog and FXR agonist derived from the primary human bile acid chenodeoxycholic acid, or CDCA. OCA is being evaluated for patients having an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol (Intercept Pharmaceuticals, New York).

Primary Sclerosing Cholangitis

[0027] Primary sclerosing cholangitis is a chronic fibrosing inflammatory process that results in the destruction of the biliary tree and biliary cirrhosis. The strictures are located in both the intrahepatic and extrahepatic ducts in more than 80% of the patients, but about 10% of these patients have only intrahepatic strictures, while less than 5% will have only extrahepatic strictures. Remissions and relapses characterize the disease course. Although the cause of primary sclerosing cholangitis is unknown, it is believed that damage to the bile duct occurs through one or more of genetic abnormalities of immune regulation, viral infection, toxins from intestinal bacteria, bacteria in the portal venous system, ischemic vascular damage, and toxic bile acids from intestinal bacteria.

[0028] The majority of patients with primary sclerosing cholangitis have underlying inflammatory bowel disease (ulcerative colitis or Crohn's disease). Patients are more likely to have ulcerative colitis than Crohn's disease (85% versus 15%), with approximately 2.5-7.5% of all ulcerative colitis patients having primary sclerosing cholangitis. Primary sclerosing cholangitis may remain quiescent for long periods of time in some patients; in most cases, however, it is progressive.

[0029] The prevalence of primary sclerosing cholangitis in the United States is approximately 1-6 cases per 100,000 population, and the vast majority are Caucasian. Approximately 75% of patients with primary sclerosing cholangitis are men having an average age of approximately 40 years at the time of diagnosis. Management of this disease in the early stages involves the use of drugs to prevent disease progression. Endoscopic and surgical approaches are reserved for the time when symptoms develop. Liver transplantation may ultimately be required and offers the only chance for a complete cure. Patients with primary sclerosing cholangitis are at an increased risk for cholangiocarcinoma (10-15%).

[0030] Most patients with primary sclerosing cholangitis do not exhibit symptoms and are usually diagnosed by the detection of abnormal biochemical tests of liver function on routine blood testing. When symptoms develop they are a result of obstruction to bile flow and include jaundice, itching, right upper

quadrant abdominal pain, fever, and chills. Symptoms may also include weight loss and fatigue. Patients may remain asymptomatic for many years despite the presence of advanced disease, and the development of symptoms usually suggests the presence of advanced disease.

Diagnosis

[0031] Bile acid malabsorption is readily diagnosed by the SeHCAT (23-seleno-25-homo-taurocholic acid (selenium homocholic acid taurine or tauroselcholic acid)) nuclear medicine test. An alternative diagnostic test involves measurement in the serum of 7 alpha-hydroxy-4-cholesten-3-one, a bile acid precursor.

Treatment

[0032] Bile acid sequestrants (e.g., cholestyramine and colestipol which are in powder form) are the main agents used to treat bile acid malabsorption. Unfortunately, many patients do not tolerate cholestyramine and colestipol, often because of the poor texture and taste of the resin powder. Fortunately, the bile acid sequestrant colesevelam is available in tablet form and is often better tolerated.

[0033] All bile acid sequestrants are capable of binding other compounds, and it is also possible that deficiencies of fat-soluble vitamins (A, D, E and K) may occur, requiring administration of vitamin supplements.

[0034] Displacement and replacement therapy have also proven useful in certain disorders associated with bile acid homeostasis. In displacement therapy, the composition of the circulating bile acids is changed, either to decrease the cytotoxicity of endogenous bile acids or to modulate cholesterol metabolism to decrease biliary cholesterol secretion. Conversely, bile acid replacement aims to correct a bile acid deficiency.

Displacement Therapy

[0035] Administration of the primary bile acid chenodeoxycholic Acid (CDCA) has been shown to decrease in biliary cholesterol secretion and gradual dissolution of gallstones. CDCA was gradually replaced by ursodeoxycholic acid (UDCA) because the later did not result in any hepatotoxicity. Chenodeoxycholic acid is slightly hepatotoxic in humans, but in certain animals, it is highly hepatotoxic. 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.

[0036] UDCA therapy has been shown to improve liver test results in patients with primary biliary cirrhosis, an effect that likely involves multiple mechanisms. UDCA therapy has also shown favorable effects in other cholestatic conditions, such as cholestasis associated with pregnancy and cholestasis associated with total parenteral nutrition.

Replacement Therapy

[0037] 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.

[0038] In patients with a short-bowel syndrome, a bile acid deficiency occurs in the proximal intestine, leading to impaired micellar solubilization. This, plus the decreased surface area and rapid transit time, leads to severe fat malabsorption. Cholylsarcosine (cholyl-*N*-methylglycine), a synthetic bile acid analogue, has been shown to increase lipid absorption in a patient with short-bowel syndrome, and it is resistant to deconjugation and dehydroxylation.

[0039] Patients with bile acid diarrhea secondary to Crohn's ileitis will be helped with glucocorticoid treatment, and microscopic colitis is also helped by steroids. Administration of budesonide and other agents, including antibiotics, are useful in certain situations.

[0040] As detailed above, treatment of PBC generally entails administration of ursodiol, though alternative therapies are being evaluated for patients having an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol.

[0041] Accordingly, there is a need for treatment of bile acid disorders, such as the foregoing disorders and including, but not limited to: metabolic syndrome; a lipid or glucose disorder; cholesterol or triglyceride metabolism; type 2 diabetes; 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), 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. The invention satisfies this need and provides related benefits.

Summary

[0042] The invention is based, in part, on 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, such as bile acid homeostasis modulating activity. Such fusions (chimeras) of FGF19 and/or FGF21 peptide sequences include sequences that are used for treating a bile-acid related or associated disorder. Such fusions (chimeras) of FGF19 and/or FGF21 peptide sequences also include sequences that do not substantially or significantly increase or induce hepatocellular carcinoma (HCC) formation or HCC tumorigenesis. Such variants and fusions (chimeras) of FGF19 and/or FGF21 peptide sequences further include sequences that do not induce a substantial elevation or increase in lipid profile.

[0043] In one embodiment, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: administering a chimeric peptide sequence, In a first aspect, the invention provides a chimeric peptide having an amino acid sequence consisting of:
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTV
AIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQR
QLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M69) (SEQ ID NO:69), or
MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M70) (SEQ ID NO:70)
for use in a method of treating a bile-acid-related or associated disorder (BARD); wherein said disorder is cholestasis, intrahepatic cholestasis, primary familial intrahepatic cholestasis (PFIC), progressive PFIC, pregnancy intrahepatic cholestasis (PIC), neonatal cholestasis, drug induced cholestasis, extrahepatic cholestasis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), bile cut compression from tumor, bile duct blockade by gall stones, bile acid malabsorption, bile acid diarrhea (BAD), or bile acid synthesis abnormalities.

[0044] In one embodiment, the amino- or carboxy- terminus of said peptide is fused with an immunoglobulin Fc region.

[0045] In a second aspect, the invention provides a pharmaceutical composition comprising a chimeric peptide as defined in the first aspect, for use in a method of treating a bile-acid-related or associated disorder (BARD); wherein said disorder is cholestasis, intrahepatic cholestasis, primary familial intrahepatic cholestasis (PFIC), progressive PFIC, pregnancy intrahepatic cholestasis (PIC), neonatal cholestasis, drug induced cholestasis, extrahepatic cholestasis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), bile cut compression from tumor, bile duct blockade by gall stones, bile acid malabsorption, bile acid diarrhea (BAD), or bile acid synthesis abnormalities, wherein said pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

[0046] The ambit of the claimed invention is as described in the first and second aspects above. Parts of the disclosure herein that do not pertain to the specific chimeric peptides or pharmaceutical compositions of these aspects for use in the treatment of the specific BARDs of these aspects, are for illustrative purposes only.

[0047] comprising: a) an N-terminal region comprising at least seven amino acid residues, the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises DSSPL or DASPH; and b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 16-29 of SEQ ID NO:99 [FGF19] (WGDPIRLRHLYTSG; SEQ ID NO:169), wherein the W residue corresponds to the first amino acid position of the C-terminal region, to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0048] Also disclosed herein, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: administering a chimeric peptide sequence, comprising: a) an N-terminal region comprising a portion of SEQ ID NO:100 [FGF21], the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal

region; and b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 [FGF19], RLRHLYTSG (SEQ ID NO: 185), and wherein the R residue corresponds to the first position of the C-terminal region, to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0049] Disclosed herein, a method or use of modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes: administering a chimeric peptide sequence, comprising: a) an N-terminal region comprising a portion of SEQ ID NO:100 [FGF21], the N-terminal region having a first amino acid position and a last amino acid position,
wherein the N-terminal region comprises at least 5 contiguous amino acids of SEQ ID NO: 100 [FGF21] including the amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region; and b) a C-terminal region comprising a portion of SEQ ID NO:99 [FGF19], the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 [FGF19], RLRHLYTSG (SEQ ID NO: 185), and wherein the R residue corresponds to the first position of the C-terminal region, to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0050] Disclosed herein, 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: a) a FGF19 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19; b) a FGF21 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21; c) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence; or d) a portion of an FGF19 sequence fused to a portion of an FGF21 sequence, wherein the FGF19 and/or FGF21 sequence portion(s) have one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19 and/or FGF21, to modulate bile acid homeostasis or treat the bile-acid related or associated disorder.

[0051] In various particular instances 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.

[0052] In various additional instances, 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).

[0053] In various further instances, 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.

[0054] Methods and uses disclosed 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 to M98, or M101 to M160, or SEQ ID NOs:1 to 98, 101 to 135, or 138 to 196, a peptide sequence that includes or consists of any sequence set forth in Tables 1-10, or a peptide sequence that includes or consists of any sequence set forth in the Sequence Listing herein.

[0055] Methods and uses disclosed herein can be practiced using a peptide or chimeric sequence of any suitable length. In particular instances, 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 instances, 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 instances, 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 instances 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.

[0056] In various instances, a 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]; 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 instances, 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.

[0057] In various further instances, 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 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.

[0058] In various additional instances, 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.

[0059] More particularly, an N-terminal region may further include: 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.

[0060] In various other instances, 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 instances, 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.

[0061] In various other particular instances, 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 instances, 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.

[0062] In further various other instances, 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).

[0063] In various still additional instances, 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].

[0064] In various more particular instances, a peptide sequence has or consists of any one of the following sequences:

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M3) (SEQ ID NO:3);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M140) (SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL

VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M160) (SEQ ID NO:196);

RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M69) (SEQ ID NO: 69);

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (M52) (SEQ ID NO:52);

RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK (M5) (SEQ ID NO:5);

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M5-R) (SEQ ID NO:160);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M71) (SEQ
ID NO:71);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M72) (SEQ
ID NO:72);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGGEGCHMHPE
NCKTLLTDIDRTHTEKPVWDGITGE (M73) (SEQ ID NO:73);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M1) (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS
SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA
VRSPSFEK (M2) (SEQ ID NO:2 or 140);

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (M48) (SEQ ID NO:48 or 6 or 148);

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL
RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA

KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVR
SPSFEK (M49) (SEQ ID NO:49 or 7 or 149);

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK (M50) (SEQ ID NO:50);

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK (M51) (SEQ ID NO:51 or 36 or 155);

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVA
IKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (M53) (SEQ ID NO:192);

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDS16MDPFGLVTGLEAV
RSPSFEK (M70) (SEQ ID NO:70);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M139) (SEQ ID NO:193); or

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M141) (SEQ ID NO:195);
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.

[0065] In various additional particular instances, 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).

[0066] In various further particular instances, a peptide sequence includes or consists of:
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (SEQ ID NO:160);

DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (SEQ ID NO:138 or 161);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS
SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA
VRSPSFEK(SEQ ID NO:2 or 140); or

DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTV
AIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQR
QLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF
EK (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.

[0067] In various still additional particular instances, 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.

[0068] In various further instances, 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 instance, the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI) (SEQ ID NO:187).

[0069] In various still more particular instances, a peptide or chimeric sequence includes all or a portion of an FGF19 sequence set forth as:
PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGL
LQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPE
EPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:188) positioned at the C-terminus of the peptide, or the amino terminal "R" residue is deleted from the sequence.

[0070] A peptide or chimeric sequence may have a function or activity greater or less than a comparison sequence. A peptide of the invention has reduced 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; or 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; 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; or has less triglyceride, cholesterol, non-HDL or HDL increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI (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.

[0071] A peptide or chimeric sequence disclosed herein may have an effect on function or activity of other molecules. In one embodiment, a peptide sequence maintains or increases an FGFR4 mediated activity. In another embodiment, a peptide sequence binds to fibroblast growth factor In one instance, a peptide sequence receptor 4 (FGFR4) or activates FGFR4. In one instance, a peptide sequence does not detectably bind to FGFR4 or activate FGFR4. A peptide sequence may bind to FGFR4 with an affinity less than, comparable to or greater than FGF19 binding affinity for FGFR4. A peptide sequence may activate FGFR4 to an extent or amount less than, comparable to or greater than FGF19 activates FGFR4.

[0072] A peptide or chimeric sequence may include one or more L-amino acids, D-amino acids, non-naturally occurring amino acids, or amino acid mimetic, some instances derivative or analogue. In some instances, 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.

[0073] A chimeric peptide or peptide sequence may be included in a pharmaceutical composition, which in turn can be used for practicing the methods and uses. disclosed herein Such compositions include combinations of inactive or other active ingredients. A composition, such as a pharmaceutical composition may include a chimeric peptide sequence or peptide sequence and an agent that improves bile acid homeostasis.

[0074] Uses and methods of treatment that include administration or delivery of a chimeric A peptide or peptide sequence are also provided. A use or method of treatment of a subject includes administering an invention chimeric peptide or peptide sequence to a subject, such as a subject having, or at risk of having, a disorder treatable by an invention peptide sequence, in an amount effective for treating the disorder. A method or use includes administering an invention chimeric peptide or peptide sequence to a subject, such as a subject having a bile acid related or associated disorder.

[0075] A chimeric peptide sequence or peptide sequence is administered to a subject in an amount effective to improve or provide bile acid homeostasis. Non-limiting exemplary bile acid related or associated disorders treatable according to the invention methods and uses include: 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. In one embodiment, the bile acid related or associated disorder is bile acid malabsorption. In another embodiment, the bile acid related or associated disorder is diarrhea. In another embodiment, the bile acid related or associated disorder is cholestasis (e.g., intrahepatic or extrahepatic cholestasis). In

another embodiment, the bile acid related or associated disorder is primary billiary cirrhosis. In another embodiment, 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).

[0076] Methods and uses of analyzing and/or identifying a chimeric peptide sequence or peptide sequence are also disclosed, such as chimeric peptide sequences and peptide sequences that modulate bile acid homeostasis, optionally without having substantial or significant HCC activity. In one embodiment, a method or use includes: a) providing a candidate peptide sequence; b) administering the candidate peptide sequence to a test animal; c) measuring bile acid levels of the animal after administration of the candidate peptide sequence, to determine if the candidate peptide sequence modulates bile acid homeostasis; and d) 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 the candidate peptide sequence as a peptide sequence having that modulates bile acid homeostasis without substantial HCC activity.

[0077] The chimeric peptide sequence or peptide sequence is also analyzed for induction of HCC in the animal (e.g., assessing a hepatic tissue sample from the test animal), or expression of a marker correlating with HCC activity. Such methods and uses identify the candidate as having bile acid homeostasis modulating activity, optionally also without substantial or significant HCC activity.

Description of Drawings

[0078]

FIG. 1 shows cyp7a1 expression in *db*/*db* mice dosed intraperitoneally with the indicated concentrations of FGF19 and FGF21 (SEQ ID NOs:99 and 100).

FIG. 2A-2D show cyp7a1 expression in human primary hepatocytes following dosing of A) variant M1 (SEQ ID NO:1); B) variant M2 (SEQ ID NO:2); C) variant M5 (SEQ ID NO:5); and D) variant M32 (SEQ ID NO:32).

FIG. 3A-3D show cyp7a1 expression in human primary hepatocytes following dosing of A) variant M69 (SEQ ID NO:69); B) variant M75 (SEQ ID NO:75); C) variant M70 (SEQ ID NO:70); and D) variant M76 (SEQ ID NO:76).

FIG. 4A-4D show cyp7a1 expression in human primary hepatocytes following dosing of A) variant M85 (SEQ ID NO:85); B) variant M96 (SEQ ID NO:96); C) variant M90 (SEQ ID NO:90); and D) variant M98 (SEQ ID NO:98).

FIG. 5 is a table showing the cyp7a1 IC_{50} (pM), relative cyp7a1 expression and HCC core of the indicated variants: M1, M2, M5, M32, M69, M70, M75, M76, M85, M90, M96 and M98.

FIG. 6 depicts the results of a human clinical trial, showing administration of M70 is able to suppress 7a-hydroxy-4-cholsten-3-one (C4), a marker of bile acid synthesis, as compared to a placebo.

FIG. 7 depicts that the expression of FGFR4/β-klotho complex in L6 cells potentiates activation of intracellular signaling pathways by FGF19, M3 and M70.

Detailed Description

[0079] Provided herein are chimeric and peptide sequences that modulate bile acid homeostasis and are able to treat a bile-acid related or associated disorder. In one instance, 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.

[0080] In another instance, 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.

[0081] In further instances, a peptide sequence includes or consists of a FGF19 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19. In additional instances, 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 instances, a peptide sequence includes or consists of a portion of an FGF19 sequence fused to a portion of an FGF21 sequence. In still additional instances, 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.

[0082] Provided herein are methods and uses of treating a subject having or at risk of having a disorder treatable using variants and fusions of FGF19 and FGF21 peptide sequences. A method or use disclosed herein includes contacting or administering to a subject one or more variant or fusion FGF19 and/or FGF21 peptide sequences in an amount effective for treating a bileacid related or associated disorder. In another instance, a method or use includes contacting or administering to a subject one or more nucleic acid molecules encoding a variant or fusion FGF19 and/or FGF21 peptide sequence (for example, an expression control element in operable linkage with the nucleic acid encoding the peptide sequence, optionally including a vector), in an amount effective for treating a bile-acid related or associated disorder.

[0083] A representative reference or wild type FGF19 sequence is set forth as:
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (SEQ ID NO:99).

[0084] A representative reference or wild type FGF21 sequence is set forth as: HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (SEQ ID NO:100). FGF21 allelic variants include, e.g., M70, M71 and M72.

[0085] The terms "peptide," "protein," and "polypeptide" sequence are used interchangeably herein to refer to two or more amino acids, or "residues," including chemical modifications and derivatives of amino acids, covalently linked by an amide bond or equivalent. The amino acids forming all or a part of a peptide may be from among the known 21 naturally occurring amino acids, which are referred to by both their single letter abbreviation or common three-letter abbreviation. In the peptide sequences of the invention, conventional amino acid residues have their conventional meaning. Thus, "Leu" is leucine, "Ile" is isoleucine, "Nle" is norleucine, and so on.

[0086] Exemplified herein are peptide sequences, distinct from reference FGF19 and FGF21 polypeptides set forth herein, that modulate bile acid homeostasis, *in vivo* (*e.g.,* Tables 1-10 and the Sequence Listing). Non-limiting particular examples are a peptide sequence with amino-terminal amino acids 1-16 of FGF21 fused to carboxy-terminal amino acids 21-194 of FGF19; a peptide sequence with amino-terminal amino acids 1-147 of FGF19 fused to carboxy-terminal amino acids 147-181 of FGF21; a peptide sequence with amino-terminal amino acids 1-20 of FGF19 fused to carboxy-terminal amino acids 17-181 of FGF21; a peptide sequence with amino-terminal amino acids 1-146 of FGF21 fused to carboxy-terminal amino acids 148-194 of FGF19; and a peptide sequence with amino-terminal amino acids 1-20 of FGF19 fused to internal amino acids 17-146 of FGF21 fused to carboxy-terminal amino acids 148-194 of FGF19.

[0087] Additional particular peptides sequences have a WGDPI (SEQ ID NO:170) sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of FGF19 (SEQ ID NO:99), lack a WGDPI (SEQ ID NO:170) sequence motif corresponding to the WGDPI sequence of amino acids 16-20 of FGF19 (SEQ ID NO:99), or have a substituted (*i.e.*, mutated) WGDPI (SEQ ID NO:170) sequence motif corresponding to FGF19 WGDPI sequence of amino acids 16-20 of FGF19 (SEQ ID NO:99).

[0088] Particular peptide sequences also include sequences distinct from FGF19 and FGF21 *(e.g.,* as set forth herein), and FGF 19 variant sequences having any 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 FGF19 WGDPI(SEQ ID NO:170) sequence at amino acids 16-20. Accordingly, the wild-type FGF19 and FGF21 *(e.g.,* as set forth herein as SEQ ID NOS:99 and 100, respectively) may be excluded sequences, and FGF19 having any of GQV, GDI, WGPI(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 may also be excluded. This exclusion, however, does not apply to where a sequence has, for example, 3 FGF21 residues fused to FGF19 having, for example, any of GQV, GQV, GDI, or GPI, or 2 FGF21 residues fused to any of WGPI (SEQ ID NO:171), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), or WGDP (SEQ ID NO:183).

[0089] Particular non-limiting examples of peptide sequences include or consist of all or a part of a sequence variant specified herein as M1-M98 (SEQ ID NOs:1-52, 192, and 54-98, respectively). More particular non-limiting examples of peptide sequences include or consist of all or a part of a sequence set forth as:

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ

RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M5-R) (SEQ ID NO:160) (FGF21 sequences can also include an "R" residue at the amino terminus);

DSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (SEQ ID NO:138 and 161);

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M1) (SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS
SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA
VRSPSFEK (M2) (SEQ ID NO:2 or 140);

DSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTV
AIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQR
QLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF
EK (SEQ ID NO:141);

RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M69) (SEQ ID NO:69);

RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K (M52) (SEQ ID NO:52);

HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ

RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK (M5-R) (SEQ ID NO:160);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV

IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLPGNKSPH RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M71) (SEQ ID NO:71);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH RDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M72) (SEQ ID NO:72);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGGEGCHMHPE NCKTLLTDIDRTHTEKPVWDGITGE (M73) (SEQ ID NO:73);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE AVRSPSFEK (M3) (SEQ ID NO:3);

RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE K (M48) (SEQ ID NO:48, 6 or 148);

RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVR SPSFEK (M49) (SEQ ID NO:49, 7 or 149);

RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAK QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS PSFEK (M50) (SEQ ID NO:50);

RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS PSFEK (M51) (SEQ ID NO:51, 36 or 155);

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVA IKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE K (M53) (SEQ ID NO:192);

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS PSFEK (M70) (SEQ ID NO:70);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M139) (SEQ ID NO:193);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M140) (SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M141) (SEQ ID NO:195); or

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M160) (SEQ ID NO:196);
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.

[0090] Additional particular non-limiting examples of peptide sequences, having at the N-terminus, a peptide sequence including or consisting of all or a part of any of: HPIPDSSPLLQFGGQVRLRHLYTSG (M5-R) (amino acids 1-25 of SEQ ID NO:160); DSSPLLQFGGQVRLRHLYTSG (M6) (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);
and for any of the foregoing peptide sequences the amino terminal R residue may be deleted.

[0091] Peptide sequences disclosed herein additionally include those with reduced or absent induction or formation of HCC 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. Peptide sequences disclosed herein also include those with greater glucose lowering activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI, 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. Peptide sequences disclosed herein moreover include those with less lipid (e.g., triglyceride, cholesterol, non-HDL or HDL) increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI (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.

[0092] Typically, the number of amino acids or residues in a peptide sequence will total less than about 250 (e.g., amino acids or mimetics thereof). In various particular instances, the number of residues comprise from about 20 up to about 200 residues (e.g., amino acids or mimetics thereof). In additional instances, the number of residues comprise from about 50 up to about 200 residues (e.g., amino acids

or mimetics thereof). In further instances, the number of residues comprise from about 100 up to about 195 residues (e.g., amino acids or mimetics thereof) in length.

[0093] 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 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.

[0094] The disclosure also includes subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-10 and Sequence Listing), so long as the foregoing retain at least a detectable or measureable activity or function. For example, certain exemplified variant peptides have FGF19 C-terminal sequence, PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGL LQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPE EPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:188) at the C-terminal portion, e.g., following the "TSG" amino acid residues of the variant.

[0095] 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 instances 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, in cells when a "M" residue is adjacent to a "S" residue, the "M" residue may be cleaved such that the "M" residue is deleted from the peptide sequence, whereas when the "M" residue is adjacent to a "D" residue, the "M" residue may not be cleaved. Thus, by way of example, various 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)). disclosure

[0096] Accordingly, the "peptide," "polypeptide," and "protein" sequences of the disclosure include subsequences, variants and modified forms of the FGF19 and FGF21 variants and subsequences listed in Tables 1-10 and Sequence Listing, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and Sequence Listing, so long as the subsequence, variant or modified form *(e.g.,* fusion or chimera) retains at least a detectable activity or function, *e.g.,* modulates bile acid homeostasis.

[0097] 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 disclosed herein can be modified to increase serum half-life, to increase *in vitro* and/or *in vivo* stability of the protein, *etc.*

[0098] Particular examples of such subsequences, variants and modified forms of the peptide sequences exemplified herein *(e.g.,* a peptide sequence listed in Tables 1-10 and Sequence Listing) 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.

[0099] 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.

[0100] Specific examples of substitutions include substituting a D residue for an L-residue. Accordingly, although residues are listed in the L-isomer configuration D-amino acids at any particular or all positions of the peptide sequences of the invention are included, unless a D-isomer leads to a sequence that has no detectable or measurable function.

[0101] Additional specific examples are non-conservative and conservative substitutions. A "conservative substitution" is a replacement of one amino acid by a biologically, chemically or structurally similar residue. Biologically similar means that the substitution is compatible with a biological activity, e.g., glucose lowering activity. Structurally similar means that the amino acids have side chains with similar length, such as alanine, glycine and serine, or having similar size, or the structure of a first, second or additional peptide sequence is maintained. Chemical similarity means that the residues have the same charge or are both hydrophilic and hydrophobic. Particular examples include the substitution of one hydrophobic residue, such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, serine for threonine, *etc.* Routine assays can be used to determine whether a subsequence, variant or modified form has activity, e.g., glucose lowering activity.

[0102] Particular examples of subsequences, variants and modified forms of the peptide sequences exemplified herein *(e.g.,* a peptide sequence listed in Tables 1-10 and Sequence Listing) have 50%-60%, 60%-70%, 70%-75%, 75%-80%, 80%-85%, 85%-90%, 90%-95%, or 96%, 97%, 98%, or 99% identity to a reference peptide sequence (for example, a peptide sequence in any of Tables 1-10 Sequence Listing). The term "identity" and "homology" and grammatical variations thereof mean that two or more referenced entities are the same. Thus, where two amino acid sequences are identical, they have the identical amino acid sequence. "Areas, regions or domains of identity" mean that a portion of two or more referenced entities are the same. Thus, where two amino acid sequences are identical or homologous over one or more sequence regions, they share identity in these regions.

[0103] 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)).

[0104] In the disclosed peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-10 and Sequence Listing) an "amino acid" or "residue" includes conventional alpha-amino acids as well as beta-amino acids, alpha, alpha disubstituted amino acids and N-substituted amino acids wherein at least one side chain is an amino acid side chain moiety as defined herein. An "amino acid" further includes N-alkyl alpha-amino acids, wherein the N-terminus amino group has a C_1 to C_6 linear or branched alkyl substituent. The term "amino acid" therefore includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids *(e.g.,* by glycosylation, phosphorylation, ester or amide cleavage, *etc.),* enzymatically modified or synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, amino acids with a side chain moiety modified, derivatized from naturally occurring moieties, or synthetic, or not naturally occurring, *etc.* Modified and unusual amino acids are included in the peptide sequences of the invention (see, for example, in Synthetic Peptides: A User's Guide; Hruby et al., Biochem. J. 268:249 (1990); and Toniolo C., Int. J. Peptide Protein Res. 35:287 (1990)).

[0105] 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.

[0106] A "derivative of an amino acid side chain moiety" is included within the definition of an amino acid side chain moiety. Non-limiting examples of derivatized amino acid side chain moieties include, for example: (a) adding one or more saturated or unsaturated carbon atoms to an existing alkyl, aryl, or aralkyl chain; (b) substituting a carbon in the side chain with another atom, preferably oxygen or nitrogen; (c) adding a terminal group to a carbon atom of the side chain, including methyl (--CH_3), methoxy (--OCH_3), nitro (--NO_2), hydroxyl (--OH), or cyano (--C=N); (d) for side chain moieties including a hydroxy, thiol or amino groups, adding a suitable hydroxy, thiol or amino protecting group; or (e) for side chain moieties including a ring structure, adding one or more ring substituents, including hydroxyl, halogen, alkyl, or aryl groups attached directly or through an ether linkage. For amino groups, suitable

protecting groups are known to the skilled artisan. Provided such derivatization provides a desired activity in the final peptide sequence (e.g., glucose lowering, improved glucose or lipid metabolism, anti-diabetic activity, absence of substantial HCC formation or tumorigenesis, absence of substantial modulation of lean or fat mass, *etc.).*

[0107] 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.

[0108] A single amino acid, including stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, non-naturally occurring amino acids including derivatized amino acids, an alpha, alpha disubstituted amino acid derived from any of the foregoing (*i.e.*, an alpha, alpha disubstituted amino acid, wherein at least one side chain is the same as that of the residue from which it is derived), a beta-amino acid derived from any of the foregoing (*i.e.*, a beta-amino acid which other than for the presence of a beta-carbon is otherwise the same as the residue from which it is derived) *etc.,* including all of the foregoing can be referred to herein as a "residue." Suitable substituents, in addition to the side chain moiety of the alpha-amino acid, include C1 to C6 linear or branched alkyl. Aib is an example of an alpha, alpha disubstituted amino acid. While alpha, alpha disubstituted amino acids can be referred to using conventional L- and D-isomeric references, it is to be understood that such references are for convenience, and that where the substituents at the alpha-position are different, such amino acid can interchangeably be referred to as an alpha, alpha disubstituted amino acid derived from the L- or D-isomer, as appropriate, of a residue with the designated amino acid side chain moiety. Thus (S)-2-Amino-2-methyl-hexanoic acid can be referred to as either an alpha, alpha disubstituted amino acid derived from L-Nle (norleucine) or as an alpha, alpha disubstituted amino acid derived from D-Ala. Similarly, Aib can be referred to as an alpha, alpha disubstituted amino acid derived from Ala. Whenever an alpha, alpha disubstituted amino acid is provided, it is to be understood as including all (R) and (S) configurations thereof.

[0109] 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.

[0110] Covalent modifications of the disclosed peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-10 and Sequence Listing), are included in the invention. One type of covalent modification includes reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the peptide. Derivatization with bifunctional agents is useful, for instance, for cross linking peptide to a water-insoluble support matrix or surface for use in the method for purifying anti-peptide antibodies, and vice-versa. Commonly used cross linking agents

include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

[0111] 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.*

[0112] Exemplified peptide sequences, and subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-10 and Sequence Listing), can also include alterations of the backbone for stability, derivatives, and peptidomimetics. The term "peptidomimetic" includes a molecule that is a mimic of a residue (referred to as a "mimetic"), including but not limited to piperazine core molecules, keto-piperazine core molecules and diazepine core molecules. Unless otherwise specified, an amino acid mimetic of an invention peptide sequence includes both a carboxyl group and amino group, and a group corresponding to an amino acid side chain, or in the case of a mimetic of Glycine, no side chain other than hydrogen.

[0113] 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.

[0114] Another type of modification of the disclosed peptide sequences, including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-10 and Sequence Listing), is glycosylation. As used herein, "glycosylation" broadly refers to the presence, addition or attachment of one or more sugar (e.g., carbohydrate) moieties to proteins, lipids or other organic molecules. The use of the term "deglycosylation" herein is generally intended to mean the removal or deletion, of one or more sugar (e.g., carbohydrate) moieties. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins involving a change in the type and proportions (amount) of the various sugar (e.g., carbohydrate) moieties present.

[0115] Glycosylation can be achieved by modification of an amino acid residue, or by adding one or more glycosylation sites that may or may not be present in the native sequence. For example, a typically non-glycosylated residue can be substituted for a residue that may be glycosylated. Addition of glycosylation sites can be accomplished by altering the amino acid sequence. The alteration to the peptide sequence may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues (for O-linked glycosylation sites) or asparagine residues (for N-linked glycosylation sites). The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each

type may be different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (hereafter referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycoprotein.

[0116] Peptide sequences disclosed herein may optionally be altered through changes at the nucleotide (e.g., DNA) level, particularly by mutating the DNA encoding the peptide at preselected bases such that codons are generated that will translate into the desired amino acids. Another means of increasing the number of carbohydrate moieties on the peptide is by chemical or enzymatic coupling of glycosides to the polypeptide (see, for example, in WO 87/05330). De-glycosylation can be accomplished by removing the underlying glycosylation site, by deleting the glycosylation by chemical and/or enzymatic means, or by substitution of codons encoding amino acid residues that are glycosylated. Chemical deglycosylation techniques are known, and enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases.

[0117] Various cell lines can be used to produce proteins that are glycosylated. One non-limiting example is Dihydrofolate reductase (DHFR) - deficient Chinese Hamster Ovary (CHO) cells, which are a commonly used host cell for the production of recombinant glycoproteins. These cells do not express the enzyme beta-galactoside alpha-2,6-sialyltransferase and therefore do not add sialic acid in the alpha-2,6 linkage to N-linked oligosaccharides of glycoproteins produced in these cells.

[0118] Another type of modification is to conjugate (e.g., link) one or more additional components or molecules at the N- and/or C-terminus of an invention peptide sequence, such as another protein *(e.g.,* a protein having an amino acid sequence heterologous to the subject protein), or a carrier molecule. Thus, an exemplary peptide sequence can be a conjugate with another component or molecule.

[0119] In certain embodiments, the amino- or carboxy- terminus of an invention peptide sequence can be fused with an immunoglobulin Fc region (e.g., human Fc) to form a fusion conjugate (or fusion molecule). Fc fusion conjugates can increase the systemic half-life of biopharmaceuticals, and thus the biopharmaceutical product may have prolonged activity or require less frequent administration. Fc binds to the neonatal Fc receptor (FcRn) in endothelial cells that line the blood vessels, and, upon binding, the Fc fusion molecule is protected from degradation and re-released into the circulation, keeping the molecule in circulation longer. This Fc binding is believed to be the mechanism by which endogenous IgG retains its long plasma half-life. Well-known and validated Fc-fusion drugs consist of two copies of a biopharmaceutical linked to the Fc region of an antibody to improve pharmacokinetics, solubility, and production efficiency. More recent Fc-fusion technology links a single copy of a biopharmaceutical to Fc region of an antibody to optimize the pharmacokinetic and pharmacodynamic properties of the biopharmaceutical as compared to traditional Fc-fusion conjugates.

[0120] A conjugate modification can be used to produce a peptide sequence that retains activity with an additional or complementary function or activity of the second molecule. For example, a peptide sequence may be conjugated to a molecule, *e.g.,* to facilitate solubility, storage, *in vivo* or shelf half-life or stability, reduction in immunogenicity, delayed or controlled release *in vivo, etc.* Other functions or activities include a conjugate that reduces toxicity relative to an unconjugated peptide sequence, a conjugate that targets a type of cell or organ more efficiently than an unconjugated peptide sequence, or a drug to further counter the causes or effects associated with a disorder or disease as set forth herein (e.g., diabetes).

[0121] Clinical effectiveness of protein therapeutics may be limited by short plasma half-life and susceptibility to degradation. Studies of various therapeutic proteins have shown that various modifications, including conjugating or linking the peptide sequence to any of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes (see, for example, typically via a linking moiety covalently bound to both the protein and the nonproteinaceous polymer *(e.g.,* a PEG) can prolong half-life. Such PEG-conjugated biomolecules have been shown to possess clinically useful properties, including better physical and thermal stability, protection against susceptibility to enzymatic degradation, increased solubility, longer *in vivo* circulating half-life and decreased clearance, reduced immunogenicity and antigenicity, and reduced toxicity.

[0122] PEGs suitable for conjugation to an invention peptide sequence is 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 peptide sequence can be linear or branched. Branched PEG derivatives, "star-PEGs" and multi-armed PEGs are included in the invention. A molecular weight of the PEG used in the invention is not restricted to any particular range, but certain embodiments have a molecular weight between 500 and 20,000 while other embodiments have a molecular weight between 4,000 and 10,000.

[0123] The invention includes compositions of conjugates wherein the PEGs have different "n" values and thus the various different PEGs are present in specific ratios. For example, some compositions comprise a mixture of conjugates where n=1, 2, 3 and 4. In some compositions, the percentage of conjugates where n=1 is 18-25%, the percentage of conjugates where n=2 is 50-66%, the percentage of conjugates where n=3 is 12-16%, and the percentage of conjugates where n=4 is up to 5%. Such compositions can be produced by reaction conditions and purification methods know in the art.

[0124] PEG may directly or indirectly (e.g., through an intermediate) bind to the peptide sequences of the invention. For example, in one embodiment, PEG binds via a terminal reactive group (a "spacer"). The spacer, is, for example, a terminal reactive group which mediates a bond between the free amino or carboxyl groups of one or more of the peptide sequences and polyethylene glycol. The PEG having the spacer which may be bound to the free amino group includes N-hydroxysuccinylimide polyethylene glycol which may be prepared by activating succinic acid ester of polyethylene glycol with N-hydroxysuccinylimide. Another activated polyethylene glycol which may be bound to free amino group is 2,4-bis(O-methoxypolyethyleneglycol)-6-chloro-s-triazine which may be prepared by reacting polyethylene glycol monomethyl ether with cyanuric chloride. The activated polyethylene glycol which is bound to the free carboxyl group includes polyoxyethylenediamine.

[0125] Conjugation of one or more of invention peptide sequences to PEG having a spacer may be carried out by various conventional methods. For example, the conjugation reaction can be carried out in solution at a pH of from 5 to 10, at temperature from 4°C to room temperature, for 30 minutes to 20 hours, utilizing a molar ratio of reagent to protein of from 4:1 to 30:1. Reaction conditions may be selected to direct the reaction towards producing predominantly a desired degree of substitution. In general, low temperature, low pH *(e.g.,* pH=5), and short reaction time tend to decrease the number of PEGs attached, whereas high temperature, neutral to high pH *(e.g.,* pH≥7), and longer reaction time tend to increase the number of PEGs attached. Various methods known in the art may be used to terminate the reaction. In some embodiments the reaction is terminated by acidifying the reaction mixture and freezing at, *e.g.,* -20°C.

[0126] Peptide sequences disclosed herein including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-10 and Sequence Listing), further include conjugation to large, slowly metabolized macromolecules such as proteins; polysaccharides, such as sepharose, agarose, cellulose, cellulose beads; polymeric amino acids such as polyglutamic acid, polylysine; amino acid copolymers; inactivated virus particles; inactivated bacterial toxins such as toxoid from diphtheria, tetanus, cholera, leukotoxin molecules; inactivated bacteria; and dendritic cells. Such conjugated forms, if desired, can be used to produce antibodies against peptide sequences disclosed herein.

[0127] Additional suitable components and molecules for conjugation include, for example, thyroglobulin; albumins such as human serum albumin (HSA); tetanus toxoid; Diphtheria toxoid; polyamino acids such as poly(D-lysine:D-glutamic acid); VP6 polypeptides of rotaviruses; influenza virus hemagglutinin, influenza virus nucleoprotein; Keyhole Limpet Hemocyanin (KLH); and hepatitis B virus core protein and surface antigen; or any combination of the foregoing.

[0128] Fusion of albumin to a peptide sequence can, for example, be achieved by genetic manipulation, such that the DNA coding for HSA (human serum albumin), or a fragment joined to the DNA coding for a peptide sequence. Thereafter, a suitable host can be transformed or transfected with the fused nucleotide sequence in the form of, for example, a suitable plasmid, so as to express a fusion polypeptide. The expression may be effected *in vitro* from, for example, prokaryotic or eukaryotic cells, or *in vivo* from, for example, a transgenic organism, Expression of the fusion proteinmay be performed in mammalian cell lines, for example, CHO cell lines.

[0129] Further means for genetically fusing target proteins or peptides to albumin include a technology known as Albufuse® (Novozymes Biopharma A/S; Denmark), and the conjugated therapeutic peptide sequences frequently become much more effective with better uptake in the body. The technology has been utilized commercially to produce Albuferon® (Human Genome Sciences), a combination of albumin and interferon α-2B used to treat hepatitis C infection.

[0130] Another instance entails the use of one or more human domain antibodies (dAb). dAbs are the smallest functional binding units of human antibodies (IgGs) and have favorable stability and solubility characteristics. The technology entails a dAb(s) conjugated to HSA (thereby forming a "AlbudAb"; see, e.g., EP1517921B, WO2005/118642 and WO2006/051288) and a molecule of interest *(e.g.,* a peptide sequence of the invention). AlbudAbs are often smaller and easier to manufacture in microbial expression systems, such as bacteria or yeast, than current technologies used for extending the serum half-life of peptides. As HSA has a half-life of about three weeks, the resulting conjugated molecule improves the half-life. Use of the dAb technology may also enhance the efficacy of the molecule of interest.

[0131] 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.

[0132] 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, preferably at pH ~4.5. The content of the fractions obtained by cation exchange chromatography may be identified by molecular weight using conventional methods, for example, mass spectroscopy, SDS-PAGE, or other known methods for separating molecular entities by molecular weight. A fraction is then accordingly identified which contains the conjugate having the desired number of PEGs attached, purified free from unmodified protein sequences and from conjugates having other numbers of PEGs attached.

[0133] In still other embodiments, an invention peptide sequence is linked to a chemical agent *(e.g.,* an immunotoxin or chemotherapeutic agent), including, but are not limited to, a cytotoxic agent, including taxol, cytochalasin B, gramicidin D, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, and analogs or homologs thereof. Other chemical agents include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6- thioguanine, cytarabine, 5-fluorouracil decarbazine); alkylating agents (e.g., mechlorethamine, carmustine and lomustine, cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisplatin); antibiotics *(e.g.,* bleomycin); and anti-mitotic agents *(e.g.,* vincristine and vinblastine). Cytotoxins can be conjugated to a peptide of the invention using linker technology known in the art and described herein.

[0134] 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.

[0135] In certain embodiments, a peptide sequence of the invention is conjugated to a radioactive isotope to generate a cytotoxic radiopharmaceutical (radioimmunoconjugates) useful as a diagnostic or therapeutic agent. Examples of such radioactive isotopes include, but are not limited to, iodine ^{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.

[0136] Other means and methods for prolonging the circulation half-life, increasing stability, reducing clearance, or altering immunogenicity or allergenicity of a peptide sequence of the invention involves modification of the peptide sequence by hesylation, which utilizes hydroxyethyl starch derivatives linked to other molecules in order to modify the molecule's characteristics. Various aspects of hesylation are described in, for example, U.S. Patent Appln. Nos. 2007/0134197 and 2006/0258607.

[0137] Any of the foregoing components and molecules used to modify peptide sequences of the invention, may optionally be conjugated via a linker. Suitable linkers include "flexible linkers" which are generally of sufficient length to permit some movement between the modified peptide sequences and the linked components and molecules. The linker molecules are generally about 6-50 atoms long. The linker molecules may also be, for example, aryl acetylene, ethylene glycol oligomers containing 2-10 monomer units, diamines, diacids, amino acids, or combinations thereof. Suitable linkers can be readily selected and can be of any suitable length, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 10-20, 20-30, 30-50

amino acids *(e.g.,* Gly).

[0138] Exemplary flexible linkers include glycine polymers (G)n, glycine-serine polymers (for example, $(GS)_n$, $GSGGS_n$ (SEQ ID NO: 129) and $GGGS_n$ (SEQ ID NO:130), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Glycine and glycine-serine polymers are relatively unstructured, and therefore may serve as a neutral tether between components. Exemplary flexible linkers include, but are not limited to GGSG (SEQ ID NO:131), GGSGG (SEQ ID NO:132), GSGSG (SEQ ID NO:133), GSGGG (SEQ ID N0: 134), GGGSG (SEQ ID NO:189), and GSSSG (SEQ ID NO:135).

[0139] Peptide sequences of the disclosure, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and Sequence Listing, as well as subsequences, sequence variants and modified forms of the sequences listed in Tables 1-10 and Sequence Listing have one or more activities as set forth herein. One example of an activity is modulating bile acid homeostasis. Another example of an activity is reduced stimulation or formation of HCC, for example, as compared to FGF19. An additional example of an activity is lower or reduced lipid (e.g., triglyceride, cholesterol, non-HDL) or HDL increasing activity, for example, as compared to FGF21. A further example of an activity is a lower or reduced lean muscle mass reducing activity, for example, as compared to FGF21. Yet another example of an activity is binding to FGFR4, or activating FGFR4, for example, peptide sequences that bind to FGFR4 with an affinity comparable to or greater than FGF19 binding affinity for FGFR4; and peptide sequences that activate FGFR4 to an extent or amount comparable to or greater than FGF19 activates FGFR4. Still further examples of activities include treating a bile-acid related or associated disorder.

[0140] More particularly, peptide sequences of the disclosure, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and Sequence Listing, as well as subsequences, variants and modified forms of the sequences listed in Tables 1-10 and Sequence Listing include those with the following activities: peptide sequences modulating bile acid homeostasis or treating a bile-acid related or associated disorder while having reduced 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; peptide sequences having greater bile acid modulating activity compared to FGF19, or 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; peptide sequences having less lipid increasing activity (e.g., less triglyceride, cholesterol, non-HDL) or more HDL increasing activity compared to FGF19, or an FGF 19 variant sequence having any of GQV, GDI, WGPI (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; and peptide sequences having less lean mass reducing activity as compared to FGF21.

[0141] More particularly, peptide sequences of the disclosure, including the FGF19 and FGF21 variants and subsequences and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and Sequence Listing, as well as subsequences, variants and modified forms of the sequences listed in Tables 1-10 and the Sequence Listing include those with the following activities: peptide sequences that modulate bile acid homeostasis; peptide sequences that treat a bile-acid related or associated disorder, peptide sequences that bind to FGFR4, or activate FGFR4, such as peptide sequences that bind to FGFR4 with an affinity comparable to or greater than FGF19 binding affinity for FGFR4; peptide sequences that activate FGFR4 to an extent or amount comparable to or greater than FGF19 activates FGFR4; peptide sequences that down-regulate or reduce aldo-keto reductase gene expression, for example, compared to FGF19; and peptide sequences that up-regulate or increase solute carrier family 1, member 2 (Slcla2) gene expression as compared to FGF21.

[0142] As disclosed herein, variants include various N-terminal modifications and/or truncations of FGF19, including variants in which there has been a substitution of one or several N-terminal FGF19 amino acids with amino acids from FGF21. Such variants include variants having glucose lowering activity, as well as a favorable lipid profile and are not measurably or detectably tumorigenic.

[0143] Modifications to the Loop-8 region of FGF19 (residues 127-129 are defined as constituting the Loop-8 region) are disclosed herein that have glucose lowering activity and also 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). As set forth in Examples 8 and 9, 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 (see, *e.g.,* core region sequence denoted in Tables 1-4, 9 and 10) 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).

[0144] Activities such as, for example, modulation of bile acid homeostasis, glucose lowering activity, analysis of a bile-acid related or associated disorder, HCC formation or tumorigenesis, lipid increasing activity, or lean mass reducing activity can be ascertained in an animal, such as a *db*/*db* mouse. Measurement of binding to FGFR4 or activation of FGFR4 can be ascertained by assays disclosed herein or known to the skilled artisan.

[0145] The term "bind," or "binding," when used in reference to a peptide sequence, means that the peptide sequence interacts at the molecular level. Thus, a peptide sequence that binds to FGFR4 binds to all or a part of the FGFR4 sequence. Specific and selective binding can be distinguished from non-specific binding using assays known in the art (e.g., competition binding, immunoprecipitation, ELISA, flow cytometry, Western blotting).

[0146] Peptides and peptidomimetics can be produced and isolated using methods known in the art. Peptides can be synthesized, in whole or in part, using chemical methods (see, e.g., Caruthers (1980). Nucleic Acids Res. Symp. Ser. 215; Horn (1980); and Banga, A.K., Therapeutic Peptides and Proteins, Formulation, Processing and Delivery Systems (1995) Technomic Publishing Co., Lancaster, PA). Peptide synthesis can be performed using various solid-phase techniques (see, *e.g.,* Roberge Science

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

[0147] 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.

[0148] Peptide sequences of the disclosure including subsequences, sequence variants and modified forms of the exemplified peptide sequences (e.g., sequences listed in Tables 1-10 and the Sequence Listing), can also be modified to form a chimeric molecule. In accordance with the invention, there are provided peptide sequences that include a heterologous domain. Such domains can be added to the amino-terminus or at the carboxyl-terminus of the peptide sequence. Heterologous domains can also be positioned within the peptide sequence, and/or alternatively flanked by FGF19 and/or FGF21 derived amino acid sequences.

[0149] The term "peptide" also includes dimers or multimers (oligomers) of peptides. Disclosed herein are dimers or multimers (oligomers) of the exemplified peptide sequences as well as subsequences, variants and modified forms of the exemplified peptide sequences (e.g., sequences listed in Tables 1-10 and the Sequence Listing).

[0150] Disclosed herein are nucleic acid molecules encoding peptide sequences of the disclosure, including subsequences, sequence variants and modified forms of the sequences listed in Tables 1-10 and the Sequence Listing, and vectors that include nucleic acid that encodes the peptide. Accordingly, "nucleic acids" include those that encode the exemplified peptide sequences disclosed herein, as well as those encoding functional subsequences, sequence variants and modified forms of the exemplified peptide sequences, so long as the foregoing retain at least detectable or measureable activity or function. For example, a subsequence, a variant or modified form of an exemplified peptide sequence disclosed herein *(e.g.,* a sequence listed in Tables 1-10 and the Sequence Listing) that retains some ability to lower or reduce glucose, provide normal glucose homeostasis, or reduce the histopathological conditions associated with chronic or acute hyperglycemia *in vivo, etc.*

[0151] Nucleic acid, which can also be referred to herein as a gene, polynucleotide, nucleotide sequence, primer, oligonucleotide or probe refers to natural or modified purine- and pyrimidine-containing polymers of any length, either polyribonucleotides or polydeoxyribonucleotides or mixed polyribo-polydeoxyribo nucleotides and α-anomeric forms thereof. The two or more purine- and

pyrimidine-containing polymers are typically linked by a phosphoester bond or analog thereof. The terms can be used interchangeably to refer to all forms of nucleic acid, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The nucleic acids can be single strand, double, or triplex, linear or circular. Nucleic acids include genomic DNA and cDNA. RNA nucleic acid can be spliced or unspliced mRNA, rRNA, tRNA or antisense. Nucleic acids include naturally occurring, synthetic, as well as nucleotide analogues and derivatives.

[0152] As a result of the degeneracy of the genetic code, nucleic acid molecules include sequences degenerate with respect to nucleic acid molecules encoding the peptide sequences of the invention. Thus, degenerate nucleic acid sequences encoding peptide sequences, including subsequences, variants and modified forms of the peptide sequences exemplified herein (e.g., sequences listed in Tables 1-10 and the Sequence Listing), 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.

[0153] Nucleic acid can be produced using any of a variety of known standard cloning and chemical synthesis methods, and can be altered intentionally by site-directed mutagenesis or other recombinant techniques known to one skilled in the art. Purity of polynucleotides can be determined through sequencing, gel electrophoresis, UV spectrometry.

[0154] 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.*

[0155] 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.

[0156] Expression control elements include elements that activate transcription constitutively, that are inducible (*i.e.,* require an external signal or stimuli for activation), or derepressible (*i.e.,* require a signal to turn transcription off; when the signal is no longer present, transcription is activated or "derepressed"). Also included in the expression cassettes of the invention are control elements sufficient to render gene expression controllable for specific cell-types or tissues (*i.e.,* tissue-specific control elements). Typically, such elements are located upstream or downstream (*i.e.*, 5' and 3') of the coding sequence. Promoters are generally positioned 5' of the coding sequence. Promoters, produced by recombinant DNA or synthetic techniques, can be used to provide for transcription of the polynucleotides of the invention. A "promoter" typically means a minimal sequence element sufficient to direct transcription.

[0157] 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 disclosure, a vector is synonymous with a plasmid. Plasmids and vectors generally contain at least an origin of replication for propagation in a cell and a

promoter. Plasmids and vectors may also include an expression control element for expression in a host cell, and are therefore useful for expression and/or genetic manipulation of nucleic acids encoding peptide sequences, expressing peptide sequences in host cells and organisms *(e.g.,* a subject in need of treatment), or producing peptide sequences, for example.

[0158] As used herein, the term "transgene" means a polynucleotide that has been introduced into a cell or organism by artifice. For example, a cell having a transgene, the transgene has been introduced by genetic manipulation or "transformation" of the cell. A cell or progeny thereof into which the transgene has been introduced is referred to as a "transformed cell" or "transformant." Typically, the transgene is included in progeny of the transformant or becomes a part of the organism that develops from the cell. Transgenes may be inserted into the chromosomal DNA or maintained as a self-replicating plasmid, YAC, minichromosome, or the like.

[0159] 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.

[0160] As methods and uses disclosed 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.

[0161] 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).

[0162] 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).

[0163] Provided herein are transformed cell(s) *(in vitro, ex vivo* and *in vivo)* and host cells that produce a variant or fusion of FGF19 and/or FGF21 as set forth herein, where expression of the variant or fusion of FGF19 and/or FGF21 is conferred by a nucleic acid encoding the variant or fusion of FGF19 and/or FGF21. Transformed and host cells that express invention peptide sequences typically include a nucleic acid that encodes the invention peptide sequence. A transformed or host cell may be a prokaryotic cell or a eukaryotic cell. In some cases, the eukaryotic cell is a yeast or mammalian *(e.g.,* human, primate, *etc.)* cell.

[0164] 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.

[0165] 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.

[0166] For gene therapy uses and methods, a transformed cell can be in a subject. A cell in a subject can be transformed with a nucleic acid that encodes an invention peptide sequence as set forth herein *in vivo.* Alternatively, a cell can be transformed *in vitro* with a transgene or polynucleotide, and then transplanted into a tissue of subject in order to effect treatment. Alternatively, a primary cell isolate or an established cell line can be transformed with a transgene or polynucleotide that encodes a variant of FGF19 and/or FGF21 or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, and then optionally transplanted into a tissue of a subject.

[0167] Non-limiting target cells for expression of peptide sequences, particularly for expression *in vivo,* include pancreas cells (islet cells), muscle cells, mucosal cells and endocrine cells. Such endocrine cells can provide inducible production (secretion) of a variant of FGF19 and/or FGF21, or a fusion/chimeric

sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21. Additional cells to transform include stem cells or other multipotent or pluripotent cells, for example, progenitor cells that differentiate into the various pancreas cells (islet cells), muscle cells, mucosal cells and endocrine cells. Targeting stem cells provides longer term expression of peptide sequences of the invention.

[0168] 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.

[0169] 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.

[0170] Nucleic acids encoding invention peptide sequences can be introduced for stable expression into cells of a whole organism. Such organisms including non-human transgenic animals are useful for studying the effect of peptide expression in a whole animal and therapeutic benefit. For example, as disclosed herein, production of a variant of FGF19 and/or FGF21 or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21 as set forth herein, in mice modulated bile acid homeostasis.

[0171] Mice strains that develop or are susceptible to developing a particular disease (e.g., diabetes, degenerative disorders, cancer, *etc.)* are also useful for introducing therapeutic proteins as described herein in order to study the effect of therapeutic protein expression in the disease susceptible mouse. Transgenic and genetic animal models that are susceptible to particular disease or physiological conditions, such as streptozotocin (STZ)-induced diabetic (STZ) mice, are appropriate targets for expressing variants of FGF19 and/or FGF21, fusions/chimeric sequences (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, as set forth herein. Thus, in accordance with the invention, there are provided non-human transgenic animals that produce a variant of FGF19 and/or FGF21, or a fusion/chimeric sequence (or variant) thereof, such as a chimeric peptide sequence including all or a portion of FGF19, or including all or a portion of FGF21, the production of which is not naturally occurring in the animal which is conferred by a transgene present in somatic or germ cells of the animal.

[0172] The term "transgenic animal" refers to an animal whose somatic or germ line cells bear genetic information received, directly or indirectly, by deliberate genetic manipulation at the subcellular level, such as by microinjection or infection with recombinant virus. The term "transgenic" further includes cells or tissues (*i.e.,* "transgenic cell," "transgenic tissue") obtained from a transgenic animal genetically manipulated as described herein. In the present context, a "transgenic animal" does not encompass animals produced by classical crossbreeding or *in vitro* fertilization, but rather denotes animals in which one or more cells receive a nucleic acid molecule. Invention transgenic animals can be either heterozygous or homozygous with respect to the transgene. Methods for producing transgenic animals, including mice, sheep, pigs and frogs, are well known in the art (see, *e.g.,* U.S. Patent Nos. 5,721,367, 5,695,977, 5,650,298, and 5,614,396) and, as such, are additionally included.

[0173] Peptide sequences, nucleic acids encoding peptide sequences, vectors and transformed host

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

[0174] An "isolated" composition can also be "purified" when free of some, a substantial number of, or most or all of one or more other materials, such as a contaminant or an undesired substance or material. Peptide sequences of the invention are generally not known or believed to exist in nature. However, for a composition that does exist in nature, an isolated composition will generally be free of some, a substantial number of, or most or all other materials with which it typically associates with in nature. Thus, an isolated peptide sequence that also occurs in nature does not include polypeptides or polynucleotides present among millions of other sequences, such as proteins of a protein library or nucleic acids in a genomic or cDNA library, for example. A "purified" composition includes combinations with one or more other inactive or active molecules. For example, a peptide sequence of the invention combined with another drug or agent, such as a glucose lowering drug or therapeutic agent, for example.

[0175] As used herein, the term "recombinant," when used as a modifier of peptide sequences, nucleic acids encoding peptide sequences, *etc.,* means that the compositions have been manipulated (*i.e.*, engineered) in a fashion that generally does not occur in nature (*e.g., in vitro*). A particular example of a recombinant peptide would be where a peptide sequence of the invention is expressed by a cell transfected with a nucleic acid encoding the peptide sequence. A particular example of a recombinant nucleic acid would be where a nucleic acid (e.g., genomic or cDNA) encoding a peptide sequence cloned into a plasmid, with or without 5', 3' or intron regions that the gene is normally contiguous 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.

[0176] Provided herein are compositions and mixtures of invention peptide sequences, including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and the Sequence Listing). In one embodiment, a mixture includes one or more peptide sequences and a pharmaceutically acceptable carrier or excipient. In another embodiment, a mixture includes one or more peptide sequences and an adjunct drug or therapeutic agent, such as a bile acid homeostasis modulating or anti-diabetic, or glucose lowering, drug or therapeutic agent. Combinations, such as one or more peptide sequences in a pharmaceutically acceptable carrier or excipient, with one or more of a bile acid homeostasis modulating or a treatment for a bile-acid related or associated disorder, or anti-diabetic, or glucose lowering drug or therapeutic agent are also provided. Such combinations of peptide sequence of the invention with another drug or agent, such as a bile acid homeostasis modulating or acid related or associated disorder treating, or glucose lowering drug or therapeutic agent, for example are useful in accordance with the invention methods and uses, for example, for treatment of a subject.

[0177] Combinations also include incorporation of peptide sequences or nucleic acids of the invention

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

[0178] including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-10 and the Sequence Listing, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and the Sequence Listing) as set forth herein can be used to modulate glucose metabolism and facilitate transport of glucose from the blood to key metabolic organs such as muscle, liver and fat. Such peptide sequences can be produced in amounts sufficient or effective to restore glucose tolerance and/or to improve or provide normal glucose homeostasis.

[0179] As disclosed herein, administration of various FGF19 and/ FGF21 variants and fusion peptide sequences to mice successfully modulated bile acid homeostasis. Furthermore, in contrast to FGF19, certain peptide sequences did not stimulate or induce HCC formation or tumorigenesis in mice. Thus, administration of invention peptides and other peptides disclosed herein, including subsequences, variants and modified forms of the exemplified peptide sequences (including the FGF19 and FGF21 variants and subsequences listed in Tables 1-10 and the Sequence Listing, and the FGF19/FGF21 fusions and chimeras listed in Tables 1-10 and the Sequence Listing), into an animal, either by direct or indirect *in vivo* or by *ex vivo* methods *(e.g.,* administering the variant or fusion peptide, a nucleic acid encoding the variant or fusion peptide, or a transformed cell or gene therapy vector expressing the variant or fusion peptide), can be used to treat various disorders, such as bile-acid related or associated disorders.

[0180] Accordingly, the invention includes *in vitro, ex vivo* and *in vivo (e.g.,* on or in a subject) methods and uses. Such methods and uses can be practiced with any of the peptide sequences of the invention set forth herein.

[0181] Provided herein are methods of treating a subject having, or at risk of having, a disorder. In various embodiments, a method includes administering a peptide sequence, such as an FGF19 or FGF21 variant, fusion or chimera disclosed herein (see, *e.g.,* Tables 1-10), or a subsequence, a variant or modified form of an FGF19 or FGF21 variant, fusion or chimera disclosed herein (see, *e.g.,* Tables 1-10 and the Sequence Listing), to a subject in an amount effective for treating the disorder.

[0182] Exemplary disorders treatable, preventable, and the like with invention peptides, and methods and uses, include bile-acid related or associated disorders. Non limiting examples of diseases and disorders include: 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. For treatment, invention peptide sequences can be administered to subjects in need of modulation of bile acid homeostasis or having a bile-acid related or associated disorder. Peptide sequences of the invention may also be useful in other hyperglycemic-related disorders, including kidney damage (e.g., tubule damage or nephropathy), liver degeneration, eye damage (e.g., diabetic retinopathy or cataracts), and diabetic foot disorders; Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary artery disease, cerebrovascular disorders and the like.

[0183] 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.

[0184] As used herein, the term "bile-acid related or associated disorder," when used in reference to a condition of a subject means a transient or chronic abnormal level of a bile acid (one or more bile acids) present in the subject. 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.

[0185] Disclosed herein 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 instances a method of the invention for, for example, modulating bile acid homeostasis or treating a bile-acid related or associated disorder includes contacting or administering a peptide of the invention as set forth herein *(e.g.,* a variant or fusion of FGF19 and/or FGF21 as set forth in Tables 1-10 or the Sequence Listing, for example) in an amount effective to modulate bile acid homeostasis or treat a bile-acid related or associated disorder.

[0186] Further disclosed herein are methods of preventing (e.g., in subjects predisposed to having a particular disorder(s)), slowing or inhibiting the progression of, delaying the onset of, or treating undesirable levels or abnormally low levels of bile acids, all of which, alone or in combination, can lead to, for example, to at a bile-acid related or associated disorder. Such disorders can be due to, for example, genetic predisposition or diet, for example.

[0187] The term "subject" refers to an animal. Typically, the animal is a mammal that would benefit from treatment with a peptide sequence of the invention. Particular examples include primates (e.g., humans), dogs, cats, horses, cows, pigs, and sheep.

[0188] Subjects include those having a disorder, *e.g.,* a bile acid related or associated disorder, 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; or subjects that do not have a disorder but may be at risk of developing the disorder. Subjects at risk of developing a bile acid associated or related disorder include, for example, those whose diet may contribute to development of acute or 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; as well as those which may have a family history or genetic predisposition towards development of a bile acid related or associated disorder, 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.

[0189] As disclosed herein, treatment methods include contacting or administering a peptide of the invention as set forth herein or another variant or fusion of FGF19 and or FGF21 as set forth in Tables 1-10 or the Sequence Listing, for example) in an amount effective to achieve a desired outcome or result in a subject. A treatment that results in a desired outcome or result includes decreasing, reducing or preventing severity or frequency of one or more symptoms of the condition in the subject, e.g., an improvement in the subject's condition or a "beneficial effect" or "therapeutic effect." Therefore, treatment can decrease or reduce or prevent the severity or frequency of one or more symptoms of the disorder, stabilize or inhibit progression or worsening of the disorder, and in some instances, reverse the disorder, transiently (e.g., for 1-6, 6-12, or 12-24 hours), for medium term *(e.g.,* 1-6, 6-12, 12-24 or 24-48 days) or long term *(e.g.,* for 1-6, 6-12, 12-24, 24-48 weeks, or greater than 24-48 weeks). Thus, in the case of a bile acid related or associated disorder, 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; for example, treatment can lower or reduce one or more symptoms or effects of the bile acid associated or related disorder.

[0190] An "effective amount" or a "sufficient amount" for use and/or for treating a subject refer to an amount that provides, in single or multiple doses, alone, or in combination with one or more other compositions (therapeutic agents such as a drug or treatment for hyperglycemia), treatments, protocols, or therapeutic regimens agents, a detectable response of any duration of time (transient, medium or long term), a desired outcome in or an objective or subjective benefit to a subject of any measurable or detectable degree or for any duration of time *(e.g.,* for hours, days, months, years, or cured). Such amounts typically are effective to ameliorate a disorder, or one, multiple or all adverse symptoms, consequences or complications of the disorder, to a measurable extent, although reducing or inhibiting a progression or worsening of the disorder, is considered a satisfactory outcome.

[0191] 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 (*e.g.,* 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; for example, an improvement can be a lowering or a reduction in one or more symptoms or effects of the disorder.

[0192] 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.).*

[0193] Thus, in the case of a disorder treatable by a peptide sequence of the invention, the amount of peptide sufficient to ameliorate a disorder will depend on the type, severity and extent, or duration of the disorder, the therapeutic effect or outcome desired, and can be readily ascertained by the skilled artisan. Appropriate amounts will also depend upon the individual subject (e.g., the bioavailability within the

subject, gender, age, *etc.).* For example, a transient, or partial, restoration of normal bile acid homeostasis in a subject can reduce the dosage amount or frequency of a drug used to treat 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; 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..

[0194] Methods and uses for treating a subject are applicable for prophylaxis to prevent or reduce likelihood of a disorder in a subject, such as a bile acid related or associated disorder. Alternatively, methods and uses can be practiced during or following treatment of a subject. For example, prior to, during or following treatment of a subject to improve bile acid homeostasis using another drug or therapeutic agent, a peptide sequence of the invention can be administered to the subject. In addition, a composition such as a peptide sequence of the invention can be combined with another drug or agent, such as a bile acid stabilizing drug or therapeutic agent, for example.

[0195] Accordingly, methods and uses for treating a subject can be practiced prior to, substantially contemporaneously with or following another treatment, and can be supplemented with other forms of therapy. Supplementary therapies include other glucose lowering treatments, such as insulin, an insulin sensitivity enhancer and other drug treatments, a change in diet (low sugar, fats, *etc.),* weight loss surgery- (reducing stomach volume by gastric bypass, gastrectomy), gastric banding, gastric balloon, gastric sleeve, *etc.* For example, a method or use 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.

[0196] The present disclosure contemplates combination therapy with numerous agents (and classes thereof), including 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 invention methods and uses.

[0198] Peptide sequences of the disclosure including subsequences, sequence variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing), 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 of the disclosure including subsequences, sequence variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing) 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 of the disclosure including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing) 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 disclosure rectally. Peptide sequences of the disclosure including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing) and disclosure methods of the disclosure 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.

[0202] Further disclosed herein are "pharmaceutical compositions," which include a peptide sequence (or sequences) of the disclosure, including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing), and one or more pharmaceutically acceptable or physiologically acceptable diluent, carrier or excipient. In particular embodiments, a peptide sequence or sequences are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in accordance with the invention methods and uses. Thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice treatment methods and uses of the invention.

[0203] Pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. In addition, the pharmaceutical compositions may further comprise other therapeutically active agents or compounds disclosed herein (e.g., 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.

[0204] Pharmaceutical compositions typically comprise a therapeutically effective amount of at least one of the peptide sequences of the disclosure including subsequences, variants and modified forms of the exemplified peptide sequences (sequences listed in Tables 1-10 and the Sequence Listing) and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that could be used in the pharmaceutical compositions and dosage forms used in the invention. Typical buffers include, but are not limited to pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. Buffer components also include water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof.

[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 of the invention may contain still other pharmaceutically-acceptable formulation agents for modifying or maintaining the rate of release of an invention peptide. Such formulation agents include those substances known to artisans skilled in preparing sustained release formulations. For further reference pertaining to pharmaceutically and physiologically acceptable

formulation agents, see, for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712, The Merck Index, 12th Ed. (1996, Merck Publishing Group, Whitehouse, NJ); and Pharmaceutical Principles of Solid Dosage Forms (1993, Technonic Publishing Co., Inc., Lancaster, Pa.). Additional pharmaceutical compositions appropriate for administration are known in the art and are applicable in the methods and compositions of the invention.

[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 invention peptides, including implants (e.g., implantable pumps) and catheter systems, both of which are known to the skilled artisan. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release invention peptides over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. The skilled artisan is familiar with possible formulations and uses of depot injections.

[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 an invention peptide may be in admixture with non-toxic pharmaceutically acceptable excipients suitable for the manufacture of tablets. These excipients include, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or

alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[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, ethylenevinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for preparation of such formulations are known to those skilled in the art and are commercially available.

[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 of the invention may also be in the form of oil-in-water emulsions.

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

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

[0219] Disclosed 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 instance, 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 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 having 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 relation to the invention, evaluation of whether a peptide *(e.g.,* a candidate peptide) exhibits evidence of inducing HCC may be determined *in vivo* by, for example, quantifying HCC nodule formation in an animal model, such as *db*/*db* mice, administered a peptide, compared to HCC nodule formation by wild type FGF19. Macroscopically, liver cancer may be nodular, where the tumor nodules (which are round-to-oval, grey or green, well circumscribed but not encapsulated) appear as either one large mass or multiple smaller masses. Alternatively, HCC may be present as an infiltrative tumor which is diffuse and poorly circumscribed and frequently infiltrates the portal veins.

[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 of the invention may further include assessing a hepatic tissue sample from an *in vivo* animal model *(e.g.,* a *db*/*db* mouse) useful in HCC studies in order to determine whether a peptide sequence exhibits evidence of inducing HCC. By microscopic assessment, a pathologist can determine whether one of the four general architectural and cytological types (patterns) of HCC are present *(i.e.,* fibrolamellar, pseudoglandular (adenoid), pleomorphic (giant cell) and clear cell).

[0224] Also disclosed herein is the generation and use of antibodies, and fragments thereof, that bind the peptide sequences of the disclosure including subsequences, sequence variants and modified forms of the exemplified peptide sequences (including the peptides listed in Tables 1-10 and the Sequence Listing).

[0225] 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.

[0226] 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.

[0227] 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.

[0228] 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.

[0229] 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.

[0230] 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.

[0231] 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.

[0232] The term "Fab" refers to a fragment of an antibody that comprises the constant domain of the light chain and the CHI 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.

[0233] The term "complementarity determining regions" or "CDRs" refers to parts of immunological receptors that make contact with a specific ligand and determine its specificity. The term "hypervariable region" refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" and/or those residues from a "hypervariable loop".

[0234] As used herein, the term "epitope" refers to binding sites for antibodies on protein antigens. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains, as well as specific three dimensional structural and charge characteristics. An antibody is said to bind an antigen when the dissociation constant is ≤1 µM, preferably ≤ 100 nM, and most preferably ≤ 10 nM. An increased equilibrium constant ("K_D") means that there is less affinity between the epitope and the antibody, whereas a decreased equilibrium constant means that there is a higher affinity between the epitope and the antibody. An antibody with a K_D of "no more than" a certain amount means that the antibody will bind to the epitope with the given K_D or more strongly. Whereas K_D describes the binding characteristics of an epitope and an antibody, "potency" describes the effectiveness of the antibody itself for a function of the antibody. There is not necessarily a correlation between an equilibrium constant and potency; thus, for example, a relatively low K_D does not automatically mean a high potency.

[0235] 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.

[0236] 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.

[0237] 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.

[0238] 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.

[0239] Antibodies can be used diagnostically and/or therapeutically. For example, the antibodies can be used as a diagnostic by detecting the level of one or more peptides of the invention in a subject, and either comparing the detected level to standard control level or to a baseline level in a subject determined previously (e.g., prior to any illness). The antibodies can be used as a therapeutic to modulate the activity of one or more peptides of the invention, thereby having an effect on a condition or disorder.

[0240] Disclosed herein are kits including, but not limited to, peptide sequences disclosed herein disclosed herein optionally in combination with one or more therapeutic agents, compositions and pharmaceutical compositions thereof, packaged into suitable packaging material. A kit optionally includes a label or packaging insert including a description of the components or instructions for use *in vitro, in vivo,* or *ex vivo,* of the components therein. Exemplary instructions include instructions for treatment of a bile acid related or associated disorder, 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, *etc.*

[0241] A kit can contain a collection of such components, e.g., two or more peptide sequences alone, or a combination of a peptide sequence with another therapeutically useful composition (e.g., a bile acid homeostasis modulating drug).

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

[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 regimes set forth herein. Exemplary instructions include instructions for treatment or use of a peptide sequence as set forth herein. Kits therefore can additionally

include labels or instructions for practicing any of the methods and uses of the invention described herein including treatment methods and uses.

[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 side effects could also occur when the subject has, will be or is currently taking one or more other medications that may be incompatible with the composition, or the subject has, will be or is currently undergoing another treatment protocol or therapeutic regimen which would be incompatible with the composition and, therefore, instructions could include information regarding such incompatibilities.

[0247] Kits can additionally include other components. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package. Kits can be designed for cold storage. Kits can further be designed to contain peptide sequences of the invention, or that contain nucleic acids encoding peptide sequences. The cells in the kit can be maintained under appropriate storage conditions until ready to use.

[0248] 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.

[0249] For the sake of conciseness, certain abbreviations are used herein. One example is the single letter abbreviation to represent amino acid residues. The amino acids and their corresponding three letter and single letter abbreviations are as follows:

alanine	Ala	(A)
arginine	Arg	(R)
asparagine	Asn	(N)
aspartic acid	Asp	(D)
cysteine	Cys	(C)
glutamic acid	Glu	(E)
glutamine	Gln	(Q)
glycine	Gly	(G)
histidine	His	(H)
isoleucine	Ile	(I)
leucine	Leu	(L)
lysine	Lys	(K)
methionine	Met	(M)
phenylalanine	Phe	(F)
proline	Pro	(P)
serine	Ser	(S)
threonine	Thr	(T)
tryptophan	Trp	(W)
tyrosine	Tyr	(Y)

valine	Val	(V)

Examples

Example 1

[0250] The following is a description of various methods and materials used in the studies herein.

[0251] Animals. *db*/*db* mice were purchased from The Jackson Laboratory (Bar Harbor, ME), Mice were kept in accordance with welfare guidelines under controlled light (12 hr light and 12 hr dark cycle, dark 6:30 pm-6:30 am), temperature (22±4°C) and humidity (50%±20%) conditions. Mice had free access to water (autoclaved distilled water) and were fed *ad libitum* on a commercial diet (Harlan Laboratories, Indianapolis, IN, Irradiated 2018 Teklad Global 18% Protein Rodent Diet) containing 17 kcal% fat, 23 kcal% protein and 60 kcal% carbohydrate. All animal studies were approved by the NGM Institutional Animal Care and Use Committee.

[0252] DNA and amino acid sequences. cDNA of ORF encoding human FGF19 *(Homo sapiens* FGF19, GenBank Accession No. NM_005117.2) variants. Protein sequence encoded by the cDNA (GenBank Accession No. NP_005108.1).

[0253] PCR. FGF19 ORF was amplified with polymerase chain reaction (PCR) using recombinant DNA (cDNA) prepared from human small intestinal tissue. PCR reagents kits with Phusion® high-fidelity DNA polymerase were purchased from New England BioLabs (F-530L, Ipswich, MA). The following primers were used: forward PCR primer:

5' CCGACTAGTCACCatgcggagcgggtgtgtgg (SEQ ID NO:136)

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

[0254] Cyp7a1 repression assay in primary human hepatocytes. Primary human hepatocytes were 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 were treated with FGF19 or variants at 37°C for 6 hours. Cyp7a1 expression was evaluated in triplicate by quantitative RT-PCR (TaqMan® ABI PRISM 7700, Applied Biosystems) and normalized to GAPDH expression.

[0255] Cyp7a1 *in vivo* repression assay. Nine-week-old male *db*/*db* mice (Jackson Laboratories) were injected intraperitoneally with recombinant proteins FGF19 or FGF21 at 0.1 mg/kg, 1 mg/kg, and 10 mg/kg. Animals were euthanized 5 hours post-injection. Liver was harvested and homogenized in TRIzol® reagent (Invitrogen). Total RNA was extracted and treated with DNase (Ambion) followed by quantitative RT-PCR analysis and normalized to GAPDH expression.

[0256] Production and purification of AAV. AAV293 cells (obtained from Agilent Technologies, Santa Clara, CA) were cultured in Dulbeco's Modification of Eagle's Medium (DMEM, Mediatech, Inc. Manassas, VA) supplemented with 10% fetal bovine serum and 1x antibiotic-antimycotic solution (Mediatech, Inc. Manassas, VA). The cells were plated at 50% density on day 1 in 150 mm cell culture plates and transfected on day 2, using calcium phosphate precipitation method with the following 3 plasmids (20 µg/plate of each): AAV transgene plasmid, pHelper™ plasmids (Agilent Technologies) and AAV2/9 plasmid (Gao et al., J. Virol. 78:6381 (2004)). Forty-eight (48) hours after transfection, the cells were scraped off the plates, pelleted by centrifugation at 3000xg and resuspended in buffer containing 20 mM Tris pH 8.5, 100 mM NaCl and 1 mM $MgCl_2$. The suspension was frozen in an alcohol dry ice bath and was then thawed in 37°C water bath. The freeze and thaw cycles were repeated three times; Benzonase® (Sigma-aldrich, St. Louis, MO) was added to 50 units/ml; deoxycholate was added to a final concentration of 0.25%. After an incubation at 37°C for 30 min, cell debris was pelleted by centrifugation at 5000 x g for 20 min. Viral particles in the supernatant were purified using a discontinued iodixanal (Sigma-aldrich, St. Louis, MO) gradient as previously described (Zolotukhin S. et al (1999) Gene Ther. 6:973). The viral stock was concentrated using Vivaspin® 20 (MW cutoff 100,000 Dalton, Sartorius Stedim Biotech, Aubagne, France) and re-suspended in phosphate-buffered saline (PBS) with 10% glycerol and stored at -80°C. To determine the viral genome copy number, 2 µl of viral stock were incubated in 6 µl of solution containing 50 units/ml Benzonase®, 50 mM Tris-HCl pH 7.5, 10 mM $MgCl_2$ and 10 mM $CaCl_2$ at 37°C for 30 minutes.

[0257] Afterwards, 15 µl of the solution containing 2 mg/ml of Proteinase K, 0.5% SDS and 25 mM EDTA were added and the mixture was incubated for additional 20 min at 55°C to release viral DNA. Viral DNA was cleaned with mini DNeasy® Kit (Qiagen, Valencia, CA) and eluted with 40 µl of water. Viral genome copy (GC) was determined by using quantitative PCR.

[0258] Viral stock was diluted with PBS to desirable GC/ml. Viral working solution (200 µl) was delivered into mice via tail vein injection.

[0259] Hepatocellular carcinoma (HCC) assay. Liver specimens were harvested from *db*/*db* mice 24 weeks after AAV injection. HCC scores were 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.

[0260] Serum FGF19/FGF21/variants exposure level assay. Whole blood (about 50 µl/mouse) from mouse tail snips was collected into plain capillary tubes (BD Clay Adams SurePrep™, Becton Dickenson and Co. Sparks, MD). Serum and blood cells were separated by spinning the tubes in an Autocrit™ Ultra 3 (Becton Dickinson and Co. Sparks, MD). FGF19, FGF21, and variant exposure levels in serum was determined using EIA kits (Biovendor) by following the manufacturer's instructions.

[0261] 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.

Example 2

[0262] In order to confirm that FGF19 variants such as those set forth herein repress cyp7a1 expression, inhibition of cyp7a1 expression by wild-type FGF19 was determined following administration of various concentrations. The effects of FGF21 were assessed in a comparable manner.

[0263] Briefly, at time 0, *db*/*db* mice were 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 were harvested, RNA was extracted, and cyp7a1 expression was determined by real-time PCR (QPCR) using GADPH as a normalization control. In each group of mice, n = 3, and cyp7a1 expression values for the various FGF19 and FGF21 concentrations were compared to mice dosed with PBS vehicle control.

[0264] As set forth in FIG. 1, FGF19 dramatically decreased cyp7a1 expression in a concentration-dependent manner. Although administration of FGF21 caused a reduction of cyp7a1 expression, the effect was demonstrably less than that observed with FGF19.

[0265] The effect of variant M70 on cyp7a1 expression in human primary hepatocytes was compared to that of FGF19. As noted in FIG. 2, variant M70 repressed cyp7a1 expression in an amount comparable to that of FGF19.

Example 3

[0266] Using the assays described above, repression of cyp7a1 in primary human hepatocytes was determined for a number of FGF19 variants. As indicated in FIG. 3 - FIG. 5, several variants *(e.g.,* M1, M2, *etc.)* exhibited strong cyp7a1 repression.

[0267] To evaluate effects of some additional FGF19 variants on Cyp7a1 repression, the *in vitro* cell-based assay (primary human hepatocyte) and the *in vivo* assay (protein dosing in *db*/*db* mice) were utilized in which the variants were compared with saline-treated controls. FIG. 5 sets forth the results (IC_{50} and Cyp7a1 (%)) in tabular form. While most FGF19 variants that were evaluated exhibited Cyp7a1-inhibiting activity, a few variants (e.g., M90, M96, M98, M5 and M32) no longer repressed Cyp7a1.

[0268] FGF19 variants 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 might be useful for modulating bile acid metabolism and/or for treating bile acid-related diseases (e.g., bile acid diarrhea

and primary biliary cirrhosis) without causing induction of HCC. The figures set forth data for variants that were evaluated in the HCC assay.

Example 4 **(for reference)**

[0269] The following is a data summary of 25 additional variant peptides analyzed for lipid elevating activity and tumorigenesis. The data clearly show a positive correlation between lipid elevation and tumorigenesis, as determined by HCC formation in *db/db* mice.

[0270] The Tables summarize different variant peptides. Such exemplified variant peptides have FGF19 C-terminal sequence:
PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVR YLCMGADGKMQGL LQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPE EPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:188) at the C-terminal portion, e.g., following the "TSG" amino acid residues. Notably, variant peptides (7 total, including M5) that did not cause a statistically significant elevation of lipids did not induce HCC formation. In contrast, all variant peptides (17 total) that caused a statistically significant elevation of lipids also caused HCC formation in mice. This data indicates that there is a strong positive correlation between lipid elevating activity and HCC formation. Accordingly, lipid elevating activity can be used as an indicator and/or predictor of HCC formation in animals.

Table 1: Elevated Triglyceride and Cholesterol in *db/db* Mice Appears to Positively Correlate With HCC Formation (see SEQ ID NOs:99, 5 and 74 to 81).

	N-terminal Domain	SEQ ID NO.	Core	SEQ ID NO.	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	99 (aa 1-20)	RLRHLYTSG	185	+	+
FGF21	HPIPDSSPLLQ--FGGQV	100 (aa 1-16)	RQRYLYTDD	186	-	-
M5	R-IIPIPDSSPLLQ--FGGQV	5 (aa 1-17)	RLRIILYTSG	185	-	-
M74	R ----------DAGPHVHYGWGDPI	74 (aa 1-15)	RLRHLYTSG	185	+	+
M75	R ---------- VHYGWGDPI	75 (aa 1-10)	RLRHLYTSG	185	-	-
M76	R ---------- GDPI	76 (aa 1-5)	RLRHLYTSG	185	-	-
M77	R ----------	77 (aa 1)	RLRHLYTSG	185	-	-
M78	R ----------AGPIIVIIYGWGDPI	78 (aa 1-14)	RLRIILYTSG	185	+	+
M79	R ---------- GPHVHYGWGDPI	79 (aa 1-13)	RLRHLYTSG	185	+	+
M80	R ---------- PHVHYGWGDPI	80 (aa 1-12)	RLRHLYTSG	185	-	-
M81	R ----------HVHYGWGDPI	81 (aa 1-11)	RLRHLYTSG	185	-	-

Table 2: Elevated Triglyceride and Cholesterol in *db/db* Mice Appears to Positively Correlate with HCC Formation (see SEQ ID NOs:99, 100 and 82 to 98).

	N-terminal Domain	SEQ ID NO.	Core	SEQ ID NO.	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	99 (aa 1-20)	RLRHLYTSG	185	+	+
FGF21	HPIPDSSPLLQ--FGGQV	100 (aa 1-16)	RQRYLYTDD	186	-	-
M82	RPLAFSAAGPHVHYGWGDPI	82 (aa 1-20)	RLRHLYTSG	185	+	+
M83	RPLAFSDAAPHVHYGWGDPI	83 (aa 1-20)	RLRHLYTSG	185	+/-	+/
M84	RPLAFSDAGAHVHYGWGDPI	84 (aa 1-20)	RLRIILYTSG	185	+/-	+/
M85	RPLAFSDAGPHVHYGAGDPI	85 (aa 1-20)	RLRHLYTSG	185	-	-
M86	RPLAFSDAGPHVHYGWGAPI	86 (aa 1-20)	RLRIILYTSG	185	+	+
M87	RPLAFSDAGPHVHYGWGDAI	87 (aa 1-20)	RLRHLYTSG	185	+	+

Table 3: Elevated Triglyceride and Cholesterol in *db/db* Mice Appears to Positively Correlate with HCC Formation (see SEQ ID NOs:99, 100 and 88 to 98)

	N-terminal Domain	Core	SEQ ID NO	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	99 (aa 1-29)	+	+
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	100 (aa 1-25)	-	-

H31A/S141A(M88)	FGF19		+	+
H31A/H142A(M89)	FGF19		+	+
K127A/R129A(M90)	FGF19		+	+

K127A/S141A(M91)	FGF19		+	+
K127A/H142A(M92)	FGF19		+	+
R129A/S141A(M93)	FGF19		+	+
S141A/H142A(M94)	FGF19		+	+
K127A/H142A(M95)	FGF19		+	+
K127A/R129A/S141A(M96)	FGF19		+	+
K127A/R129A/H142A(M97)	FGF19		+	+
K127A/R129A/S141A/H142A(M98)	FGF19		+	+

[0271] M88 (H31A/S141A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPAGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKN RGFLPLAHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:88)

[0272] M89 (H31A/H142A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPAGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKN RGFLPLSAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:89)

[0273] M90 (K127A/R129A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQAQLYKN RGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:90)

[0274] M91 (K127A/S141A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQRQLYKN RGFLPLAHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:91)

[0275] M92 (K127A/H142A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQRQLYKN RGFLPLSAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:92)

[0276] M93 (R129A/S141A):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT

VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQAQLYKN
RGFLPLAHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:93)

[0277] M94 (S141A/H142A):
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKN
RGFLPLAAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:94)

[0278] M95 (K127A/H142A):
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQRQLYKN
RGFLPLSAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:95)

[0279] M96 (K127A/R129A/S141A):
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQAQLYKN
RGFLPLAHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:96)

[0280] M97 (K127A/R129A/H142A):
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQAQLYKN
RGFLPLSAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:97)

[0281] M98 (K127A/R129A/S141A/H142A):
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAAQAQLYKN
RGFLPLAAFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:98)

Example 5

[0282] The following is a data summary of additional FGF19 variant peptides analyzed for glucose lowering activity and lipid elevating activity.

[0283] Table 4 illustrates the peptide "core sequences" of 35 additional FGF19 variants, denoted M5 to M40. Such exemplified variant peptides have FGF19 C-terminal sequence,

[0284] PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGL LQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPE EPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO: 188) at the C-terminal portion, e.g., following the "TSG" amino acid residues of the core sequence. The data clearly show that variants M6, M7, M8, mM38 and M39 have the desired characteristics of glucose lowering activity and not statistically significant lipid elevating activity in *db*/*db* mice.

Table 4: Additional Variants and Fine Mapping of the N-terminal Domain (see SEQ ID NOs:99, 100, and 5 to 40)

	N-terminal Domain	SEQ ID NO of N-term-Domain	Core	SEQ ID NO.	Glucose Lowering	Lipid Elevation
FGF19	RPLAFSDAGPHVHYGWGDPI	99 (aa 1-20)	RLRHLYTSG	185	+	+
FGF21	-HPIPDSSPLLQ--FGGQV	100 (aa 1-16)	RQRYLYTDD	186	+	-
M5	RHPIPDSSPLLQ--FGGQV	5 (aa 1-17)	RLRHLYTSG	185	+	-
M6	R----DSSPLLQ--FGGQV	6 (aa 1-18)	RLRHLYTSG	185	+	-
M7	RPLAFSDSSPLLQ--FGGQV	7 (aa 1-18)	RLRHLYTSG	185	+	-
M8	R-HPIPDSSPLLQ--WGDPI	8 (aa 1-17)	RLRHLYTSG	185	+	-
M9	R-HPIPDSSPLLQFGWGDPI	9 (aa 1-19)	RLRHLYTSG	185	+	+
M10	R-HPIPDSSPHVHYGWGDPI	10 (aa 1-19)	RLRHLYTSG	185	-	+
M11	RPLAFSDAGPLLQ--WGDPI	11 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M12	RPLAFSDAGPLLQFGWGDPI	12 (aa 1-20)	RLRHLYTSG	185	-	+
M13	RPLAFSDAGPLLQ--FGGQV	13 (aa 1-18)	RLRHLYTSG	185	-	-
M14	R-HPIPDSSPHVHYG--GQV	14 (aa 1-17)	RLRHLYTSG	185	-	-
M15	RPLAFSDAGPHVHYG--GQV	15 (aa 1-18)	RLRHLYTSG	185	+	+
M16	RPLAFSDAGPHVH--WGDPI	16 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M17	RPLAFSDAGPHV--GWGDPI	17 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M18	RPLAFSDAGPH--YGWGDPI	18 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M19	RPLAFSDAGP-V-YGWGDPI	19 (aa 1-18)	RLRHLYTSG	185	N/D	N/D

	N-terminal Domain	SEQ ID NO of N-term-Domain	Core	SEQ ID NO.	Glucose Lowering	Lipid Elevation
M20	RPLAFSDAGP-VH-GWGDPI	20 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M21	RPLAFSDAGP-VHY-WGDPI	21 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M22	RPLAFSDAGPHVH-GWGDPI	22 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M23	RPLAFSDAGPH-H-GWGDPI	23 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M24	RPLAFSDAGPH-HY-WGDPI	24 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M25	RPLAFSDAGPHV-Y-WGDPI	25 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M26	RPLAFSDSSPLVH--WGDPI	26 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M27	RPLAFSDSSPHVH--WGDPI	27 (aa 1-18)	RLRHLYTSG	185	N/D	N/D
M28	RPLAFSDAPHV----WGDPI	28 (aa 1-16)	RLRHLYTSG	185	N/D	N/D
M29	RPLAFSDAGPHVHY-WGDPI	29 (aa 1-19)	RLRHLYTSG	185	N/D	N/D
M30	RPLAFSDAGPHVHYAWGDPI	30 (aa 1-20)	RLRHLYTSG	185	N/D	N/D
M31	R-HPIPDSSPLLQ--FGAQV	31 (aa 1-17)	RLRHLYTSG	185	+/-	-
M32	R-HPIPDSSPLLQ-FGIYQV	32 (aa 1-18)	RLRHLYTSG	185	-	-
M33	R-HPIPDSSPLLQ--FGGQV	33 (aa 1-17)	RLRHLYTSG	185	-	-
M34	R-HPIPDSSPLLQ--FGGAV	34 (aa 1-17)	RLRHLYTSG	185	+/-	-
M35	R-HPIPDSSPLLQ--FGGEV	35 (aa 1-17)	RLRHLYTSG	185	+/-	+/
M36	R-HPIPDSSPLLQ--FGGQV	36 (aa 1-17)	RLRHLYTSG	185	+/-	-
M37	R-HPIPDSSPLLQ--FGGUA	37 (aa 1-17)	RLRHLYTSG	185	-	-
M38	R-HPIPDSSPLLQ--FGGQT	38 (aa 1-17)	RLRHLYTSG	185	+	-
M39	R-HPIPDSSPLLQ--FGGQT	39 (aa 1-17)	RLRHLYTSG	185	+	-
M40	R-HPIPDSSPLLQFGWGQP	40 (aa 1-16)	RLRHLYTSG	185	-	+

Table 4a: (see SEQ ID NOs:99, 100, 5, 9, 8, 12, 10, 13, 15, 14, 43, 6 and 7)

	N-terminal Domain Core	SEQ ID NO.	Glucose Lowering	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	99 (aa 1-29)	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	100 (aa 1-25)	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	5 (aa 1-26)	+	-	-
M9	R-HPIPDSSPLLQFGWGDPI RLRHLYTSG	9 (aa 1-28)	+	+	+
M8	R-HPIPDSSPLLQ--WGDPI RLRHLYTSG	8 (aa 1-26)	+	+	+
M12	RPLAFSDAGPLLQFGWGDPI RLRHLYTSG	12 (aa 1-29)	-	+	+
M10	R-HPIPDSSPHVHYGWGDPI RLRHLYTSG	10 (aa 1-28)	-	+	+
M13	RPLAFSDAGPLLQ--FGGQV RLRHLYTSG	13 (aa 1-27)	-	+	+
M15	RPLAFSDAGPHVHYG--GQV RLRHLYTSG	15 (aa 1-27)	-	-	+/-
M14	R-HPIPDSSPHVHYG--GQV RLRHLYTSG	14 (aa 1-26)	-	-	+/-
M43	RPLAFSDAGPHVHYG GD I RLRHLYTSG	43 (aa 1-27)	+	-	+/-
M6	R-----DSSPLLQ--FGGQV RLRHLYTSG	6 (aa 1-22)	+	-	-
M7	RPLAFSDSSPLLQ--FGGQV RLRHLYTSG	7 (aa 1-27)	-	-	-

Table 4b: (see SEQ ID NOs:99, 5 and 31 to 40)

	N-terminal Domain Core	SEQ ID NO.	Glucose Lowering	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	99 (aa 1-29)	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	100 (aa 1-25)	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	5 (aa 1-26)	+	-	-
M31	R-HPIPDSSPLLQ--FGAQV RLRHLYTSG	31 (aa 1-26)	+	-	+
M32	R-HPIPDSSPLLQ--FGDQV RLRHLYTSG	32 (aa 1-26)	+	-	-
M33	R-HPIPDSSPLLQ--FGPQV RLRHLYTSG	33 (aa 1-26)	-	-	+
M34	R-HPIPDSSPLLQ--FGGAV RLRHLYTSG	34 (aa 1-26)	-	-	+
M35	R-HPIPDSSPLLQ--FGGEV RLRHLYTSG	35 (aa 1-26)	-	-	+
M36	R-HPIPDSSPLLQ--FGGNV RLRHLYTSG	36 (aa 1-26)	+	-	+/-
M37	R-HPIPDSSPLLQ--FGGQA RLRHLYTSG	37 (aa 1-26)	-	-	+
M38	R-HPIPDSSPLLQ--FGGQI RLRHLYTSG	38 (aa 1-26)	-	-	+
M39	R-HPIPDSSPLLQ--FGGQT RLRHLYTSG	39 (aa 1-26)	-	-	+
M40	R-HPIPDSSPLLQFGWGQPV RLRHLYTSG	40 (aa 1-28)	-	+	+

Table 4c: (see SEQ ID NOs:99, 100, 5, 52, 54, to 68, 4, 69, 70 and 53)

	N-terminal Domain Core	SEQ ID NO.	Glucose Lowering	Lipid Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI RLRHLYTSG	99 (aa 1-29)	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV RQRYLYTDD	100 (aa 1-25)	+	-	-
M5	R-HPIPDSSPLLQ--FGGQV RLRHLYTSG	5 (aa 1-26)	+	-	-
M52	R-----DSSPLLQ--WGDPI RLRHLYTSG	52 (aa 1-22)	+	+	-
M54	RPLAFSDAGPLLQ--WGDPI RLRHLYTSG	54 (aa 1-27)	-	+	+
M55	RPLAFSDAGPH--YGWGDPI RLRHLYTSG	55 (aa 1-27)	-	+	+
M56	RPLAFSDAGP-V-YGWGDPI RLRHLYTSG	56 (aa 1-27)	-	+	+
M57	RPLAFSDAGP-VT-GWGDPI RLRHLYTSG	57 (aa 1-27)	-	+	+

M57	RPLAFSDAGP-VHY-WGDPI RLRHLYTSG	57 (aa 1-27)	-	+	+
M58	RPLAFSDAGP-VHY-WGDPI RLRHLYTSG	58 (aa 1-27)	-	+	+
M59	RPLAFSDAGPH-H-GWGDPI RLRHLYTSG	59 (aa 1-27)	-	+	+
M60	RPLAFSDAGPH-HY-WGDPI RLRHLYTSG	60 (aa 1-27)	-	+	+
M61	RPLAFSDAGPHV--GWGDPI RLRHLYTSG	61 (aa 1-27)	-	+	+
M62	RPLAFSDAGPHV-Y-WGDPI RLRHLYTSG	62 (aa 1-27)	-	+	+
M63	RPLAFSDAGPHVH--WGDPI RLRHLYTSG	63 (aa 1-27)	+	+	+
M64	RPLAFSDSSPLVH--WGDPI RLRHLYTSG	64 (aa 1-27)	+	+	+
M65	RPLAFSDSSPHVH--WGDPI RLRHLYTSG	65 (aa 1-27)	-	+	+

M66	RPLAFSDAGPHLQ--WGDPI RLRHLYTSG	66 (aa 1-27)	+	+	+
M67	RPLAFSDAGPHV---WGDPI RLRHLYTSG	67 (aa 1-26)	-	-	+/-
M68	RPLAFSDAGPHVHY-WGDPI RLRHLYTSG	68 (aa 1-28)	-	+	-
M4	RPLAFSDAGPHVHYAWGDPI RLRHLYTSG	4 (aa 1-29)	+	+	+
M69	R-----DSSPLVHYGWGDPI RLRHLYTSG	69 (aa 1-24)	+	+	-
M70	MR----DSSPLVHYGWGDPI RLRHLYTSG	70 (aa 1-25)	+	+	-
M53	M-----DSSPLLQ--WGDPI RLRHLYTSG	192 (aa 1-22)	+	+	-

[0285] Table 5 illustrates the peptide sequences of additional variants.

Table 5: Additional Variants (SEQ ID NOs:41, 42 and 44-46)

M41:
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKN RGFLPLSHFLPML**PEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS** (SEQ ID NO:41)
M42:
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIK GVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFL PLSHFLPML**PEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS** (SEQ ID NO:42)
M44:
RPLAFSDAGPHVHYGWGDPI**RQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVI QILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAP RGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS** (SEQ ID NO:44)
M45:
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILG VKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPA RFLPLPGLPPALPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:45)
M46:

RPLAFSDAGPHVHYGWGDPI**RQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVI QILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAP**
RGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYASPMVPEEPEDLRGHLES DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:46)

[0286] Table 6 illustrates the peptide sequences of 3 FGF19 variants, denoted M1, M2 and M69. The data clearly show that these three variants have the desired characteristics of glucose lowering activity in *db*/*db* mice. These three variants appear to elevate lipids in *db*/*db* mice.

Table 6: Additional Variants (SEQ ID NOs:1, 2 and 69)

M1:
RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE AVRSPSFEK (SEQ ID NO:1 or 139)
M2:
RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA VRSPSFEK (SEQ ID NO:2 or 140)
M69:
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP SFEK (SEQ ID NO:69)

Example 6

[0287] The following is a data summary showing that FGF19 reduces body weight in diet-induced obese mice and in *ob*/*ob* mice, and liver tumor formation activity and body weight in *db*/*db* mice.

[0288] Mice were injected with FGF19 or FGF21 in AAV vector. Body weight was recorded 4 weeks after injection.

Table 7: FGF19 reduces body weight in diet-induced obese mice and in *ob/ob* mice (sequences correspond to aa 1-29 of SEQ ID NO:99 and aa 1-25 of SEQ ID NO:100, respectively)

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

Table 8: Correlation of body weight and liver tumor formation of FGF19, FGF21 and selected variants in *db/db* mice (see, *e.g.,* SEQ ID NOs:99, 100, 5, 6, 32, 52 and 69)

	N-terminal Domain	core	SEQ ID NO	Liver Tumor Nodule	Body Weight
FGF19	RPLAFSDAGPHVHYGWGDPI	RLRHLYTSG	99 (aa 1-29)	+	Increased
FGF21	HPIPDSSPLLQ--FGGQV	RQRYLYTDD	100 (aa 1-25)	-	Decreased
M5	R-HPIPDSSPLLQ--FGGQV	RLRHLYTSG	5 (aa 1-26)	-	Increased
M6	R-----DSSPLLQ--FGGQV	RLRHLYTSG	6 (aa 1-22)	-	Decreased
M32	R-HPIPDSSPLLQ--FGDQV	RLRHLYTSG	32 (aa 1-26)	-	Decreased
M52	R-----DSSPLLQ--WGDPI	RLRHLYTSG	52 (aa 1-22)	-	Decreased
M69	R-----DSSPLVHYGWGDPI	RLRHLYTSG	69 (aa 1-24)	-	Increased

Example 7

[0289] The following is a study showing that variant M5 and variant M69 peptides reduce blood glucose.

[0290] Mice *(ob/ob)* were injected (subcutaneously) with M5 (0.1 and 1 mg/kg, s.c.) or FGF19 (1 mg/kg, s.c.), or variant M69 (0.1 and 1 mg/kg, s.c.) or FGF19 (1 mg/kg, s.c.). Plasma glucose levels were measured at 2, 4, 7, and 24 hours after injection. The results of variant M5 and variant M69 showed similar glucose lowering effects as wild type FGF19 (data not shown).

Example 8

[0291] This example sets forth several variant polypeptides and particular characteristics thereof, including the variants' effect on glucose lowering, lipid profile parameters, and HCC formation.

[0292] In particular, Table 9 compares data generated for variants M5 (SEQ ID NO:5), M6 (SEQ ID NO:6) and M50 (SEQ ID NO:50) with data generated for corresponding variant polypeptides (denoted as M144, M145, and M146, respectively) having N-terminal Arg (R) deletions. Only certain sequence domains for each variant are listed: N-terminal domain, Core, and Sheet-8/Loop-8/Sheet-9 region.

Table 9

	N-terminal Domain	Core	Sheet-8/Loop8/Sheet-9 region	Glucose Lowering	Body Weight Reduction	HDL Elevation	Tri-glyceride Elevation	HCC Formation
FGF19	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:99)	RLRHLYTSG (aa 21-29 of SEQ ID NO:99)	//EEIRPDGYNVY// (aa 102-112 of SEQ ID NO:99)	+	-	+	+	+
FGF21	HPIPDSSPLLQ FGGQV (aa 1-20 of SEQ ID NO:100)	RQRYLYTDD (aa 21-29 of SEQ ID NO:100)	//ELLLEDGYNVY// (aa 97-107 of SEQ ID NO:100)	+	+			
M5	R-HPIPDSSPLLQ--FGGQV (aa 1-17 of SEQ ID NO:5)	RLRHLYTSG (aa 18-26 of SEQ ID NO:5)	//EEIRPDGYNVY// (aa 99-109 of SEQ ID NO:5)	+	-	-	-	-
M6	R-------DSSPLLQ--FGGQV	RLRHLYTSG	//EEIRPDGYNVY//	+	-	-	-	-

	(aa 1-14 of SEQ ID NO:6)	(aa 15-23 of SEQ ID NO:6)	(aa 95-105 of SEQ ID NO:6)					
M50	R-HPIPDSSPLLQ--FGDQV (aa 1-17 of SEQ ID NO:50)	RLRHLYTSG (aa 18-26 of SEQ ID NO:50)	//EEIRPDGYNVY// (aa 99-109 of SEQ ID NO:50)	+	+	-	-	-
M144	--HPIPDSSPLLQ--FGGQV (aa 2-17 of SEQ ID NO:5)	RLRHLYTSG (aa 18-26 of SEQ ID NO:5)	//EEIRPDGYNVY// (aa 99-109 of SEQ ID NO:5)	+	-	-	-	-
M145	----DSSPLLQ FGGQV (aa 2-14 of SEQ ID NO:6)	RLRHLYTSG(aa 15-23 of SEQ ID NO:6)	//EEIRPDGYNVY// (aa 95-105 of SEQ ID NO:6)	+	-	-	-	-
M146	--IIPIPDSSPLLQ--FGDQV (aa 2-17 of SEQ ID NO:50)	RLRHLYTSG(aa 18-26 of SEQ ID NO:50)	//EEIRPDGYNVY// (aa 99-109 of SEQ ID NO:50)	+	+	-	-	-

[0293] As the data in Table 9 indicate, the deletion of the N-terminal Arg (R) did not significantly impact glucose lowering, body weight reduction, HDL and triglyceride elevation, and HCC formation.

Example 9

[0294] This example sets forth several variant peptides having amino acid substitutions in the Loop 8 region of FGF19, along with the variants' effect on body weight, certain metabolic parameters, and HCC formation.

[0295] The data in Table 10 are associated with variant polypeptides denoted as M3, M139, M140, M141 and M160. The amino acid sequence for M3 is set forth elsewhere herein, and the amino acid sequences for M139, M140, M141 and M160 are as follows:

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M139) (SEQ ID NO:193);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIREDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M140) (SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILCDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M141) (SEQ ID NO:195); and

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK (M160) (SEQ ID NO:196).

[0296] Only the following sequence domains for each of the aforementioned variants are listed in Table 10: N-terminal domain, Core, and Sheet-8/Loop-8/Sheet-9 region. While the particular amino acid residues making up the Loop 8 region are not universally accepted in the literature, FGF19 residues 127-129 are defined herein as constituting the Loop-8 region.

Table 10

N-terminal Domain	Core	Glucose	Body	HDL	Tri-	HCC

				Lowering	Weight Reduction	Elevation	glyceride Elevation	Formation
FGF19	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:99)	RLRHLYTSG (aa 21-29 of SEQ ID NO:99)	//EEIRPDGYNVY// (aa 102-112 of SEQ ID NO:99)	+	-	+	+	+
FGF21	HPIPDSSPLLQ--FGGQV (aa 1-20 of SEQ ID NO:100)	RQRYLYTDD (aa 21-29 of SEQ ID NO:100)	//ELLLEDGYNVY// (aa 97-107 of SEQ ID NO:100)	-	+	-	-	-
M3	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:3)	RLRHLYTSG (aa 21-29 of SEQ ID NO:3)	//EEILEDGYNVY//(aa 102-112 of SEQ ID NO:3)	+	+	+	+	+/-
M139	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO193)	RLRHLYTSG (aa 21-29 of SEQ ID NO:193)	//EEILPDGYNVY// (aa 102-112 of SEQ ID NO:193)	+	-	+	+	+
M140	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:194)	RLRHLYTSG (aa 21-29 of SEQ ID NO:194)	//EEIREDGYNVY//(aa 102-112 of SEQ ID NO:194)	+	+	+	+	+/-
M141	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:195)	RLRHLYTSG (aa 21-29 of SEQ ID NO:195)	//EEILCDGYNVY// (aa 102-112 of SEQ ID NO:195)	+	-	+	+	+
M160	RPLAFSDAGPHVHYGWGDPI (aa 1-20 of SEQ ID NO:196)	RQRHLYTSG (aa 21-29 of SEQ ID NO:196)	//EEILEDGYNVY//(aa 102-112 of SEQ ID NO:196)	+	+	+	+	-

[0297] Referring to Table 10, the P128E substitution appears necessary to significantly prevent HCC formation, but is insufficient by itself to prevent HCC formation. In particular, an improvement in preventing HCC formation is observed with the P128E substitution in M140. Conversely, by itself the R127L substitution does not prevent HCC formation (see M139). As indicated in comparison to M3, a combination of the R127L and P128E substitutions decreases HCC formation but does not eliminate HCC formation. Surprisingly, however, a combination of the R127L and P128E substitutions along with a substitution of Gln (Q) for Leu (L) in the FGF19 core region does significantly prevent HCC formation (see M160).

[0298] These data indicate that the FGF19 Loop 8 region plays a role in HCC formation. Amino acid residues outside of the Loop 8 region (e.g., substitutions in the core region) may enhance the prevention of HCC formation.

[0299] M1 (SEQ ID NO:1)

RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK

[0300] M2 (SEQ ID NO:2)

RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLS
SAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEA
VRSPSFEK

[0301] M3 (SEQ ID NO:3)

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSL

SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK

[0302] M5 (SEQ ID NO:5)
RHPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK

[0303] M5-R (SEQ ID NO:160)
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK

[0304] M48 (SEQ ID NO:48)
RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K

[0305] M49 (SEQ ID NO:49)
RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVAL
RTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSA
KQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVR
SPSFEK

[0306] M50 (SEQ ID NO:50)
RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK

[0307] M51 (SEQ ID NO:51)
RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK

[0308] M52 (SEQ ID NO:52)
RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAI
KGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ

LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K

[0309] **M53** (SEQ ID NO:192)
MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVA
IKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQ
LYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFE
K

[0310] **M69** (SEQ ID NO:69)
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQ
RQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSP
SFEK

[0311] **M70** (SEQ ID NO:70)
MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALR
TVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAK
QRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRS
PSFEK

[0312] **M71** (SEQ ID NO:71)
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS

[0313] **M72** (SEQ ID NO:72)
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS

[0314] **M73** (SEQ ID NO:73)
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGV
IQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPH
RDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGGEGCHMHPE
NCKTLLTDIDRTHTEKPVWDGITGE

[0315] **M75** (SEQ ID NO:75)
RVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKG
VHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLY
KNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK

[0316] **M76** (SEQ ID NO:76)
RGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVR
YLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFL
PLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK

[0317] **FGF19** (SEQ ID NO:99)
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSL
SSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEK

Example 10:

[0318] This example shows that administration of M70 in human patients results in suppression of 7a-hydroxy-4-cholsten-3-one (C4), a marker of bile acid synthesis.

[0319] Study subjects: Healthy adults in the age range 18-65 years and with normal body weight (body mass index, BMI 20-35) were enrolled in the study. The study protocol was approved by the Human Research Ethics Committee in Australia, and written informed consent was obtained from each subject. For inclusion in the study each subject had to be in good health determined by no clinically significant findings from medical history, physical exam, 12 lead ECG, clinical laboratory findings, and vital signs at screening. Subjects with history or clinical manifestation of any significant metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, GI, neurological, or psychiatric disorder were excluded from enrollment.

[0320] Study Design: The study was a randomized, double-blind, placebo-controlled design. Prescreening of subjects was performed 7-30 days prior to entry, and baseline evaluations were performed before treatment. Each subject was given subcutaneous injection of M70 at doses 3 mg/day in a single bolus dose daily for 7 days. Blood samples were 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 M70 or placebo were analyzed. Serum levels of 7a-hydroxy-4-cholesten-3-one (C4) were used to monitor CYP7A1 enzymatic activity (bile acid synthesis). They were 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).

[0321] Results: The data provided in FIG. 6 show that on days 1 and 7, at both 4.5 hours and 24 hours post-dose, serum levels of C4 were significantly suppressed in the patients, as compared to patients receiving a placebo.

Example 11:

[0322] This example shows activation of mouse FGFR4-β-klotho signaling by FGF19, M3, and M70 in a rat myoblast cell line

[0323] Methods: An ELK luciferase assay was 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 were incubated with ligands for 6 hours before lysed for luciferase activity measurements.

[0324] A cell-based receptor activation assay was 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, was transfected with DNAs encoding FGFR4 and β-klotho from mouse, as well as plasmids containing an Elk1-dependent chimeric transcription factor-based reporter system.

[0325] Following transfection, concentration response of ligand-dependent luciferase expression was analyzed in whole-cell lysates in the presence of luciferin substrate.

[0326] Results: Co-expression of FGFR4 and β-klotho in L6 cells was found to potentiate activation of intracellular signaling pathways by both M3, M70 and FGF19 (EC_{50} = 20, 38 and 53 pM, respectively (see Table 11 and FIG. 7).

Table 11: Co-expression of Mouse FGFR4/β-klotho complex in L6 Cells Potentiates Activation of Intracellular Signaling Pathways by FGF19, M3 and M70.

Ligand	FGFR4 / βklotho	
	EC_{50} (pM)	E_{max} (fold potentiation)
FGF19	52.5 ± 0.01	1.82 ± 0.09
M3	19.8 + 0.04	1.68 + 0.04
M70	38.3 ± 0.12	1.85 ± 0.14
EC_{50} = half-maximal effective concentration; E_{max} = maximum efficacy. Data are expressed as mean ± SD		

[0327] These data 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

[0328]

<110> NGM Biopharmaceuticals, Inc. LING, Lei LUO, Jian

<120> Methods for Modulating Bile Acid Homeostasis and Treatment of Bile Acid Disorders and Diseases

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            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln

        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
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Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu

    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
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Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
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Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Leu Glu Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His

145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
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1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
```

```
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp

                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
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1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys

180                 185                 190
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1               5                   10                  15

His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30

Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45

Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60

Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80

Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95

Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
            100                 105                 110

Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125

Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
    130                 135                 140

Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160

Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175

Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
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1               5                   10                  15

Gln Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
```

```
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro
1               5                   10                  15

Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175
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Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
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1               5                  10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30
```

```
Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
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            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125
```

```
Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
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            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80
```

```
Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
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```
            180                 185                 190
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Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
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1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60
```

```
Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 18

<211> 192

<212> PRT

<213> Homo sapiens

<400> 18

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Tyr Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160
```

```
Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 19

<211> 192

<212> PRT

<213> Homo sapiens

<400> 19

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val Tyr Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 20

<211> 192

<212> PRT

<213> Homo sapiens

<400> 20

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val His Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30
```

```
Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 21

<211> 192

<212> PRT

<213> Homo sapiens

<400> 21

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val His Tyr Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125
```

```
Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 22

<211> 193

<212> PRT

<213> Homo sapiens

<400> 22

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Gly Trp Gly
1               5                   10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 23

<211> 192

<212> PRT

<213> Homo sapiens

<400> 23

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His His Gly Trp Gly Asp
1               5                  10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 24

<211> 192

<212> PRT

<213> Homo sapiens

<400> 24

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His His Tyr Trp Gly Asp
1               5                  10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95
```

```
Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 25

<211> 192

<212> PRT

<213> Homo sapiens

<400> 25

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val Tyr Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 26

<211> 192

<212> PRT

<213> Homo sapiens

<400> 26

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro Leu Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 27

<211> 192

<212> PRT

<213> Homo sapiens

<400> 27

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro His Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60
```

```
Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 28

<211> 191

<212> PRT

<213> Homo sapiens

<400> 28

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val Trp Gly Asp Pro
1               5                   10                  15

Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175
```

```
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 29

<211> 193

<212> PRT

<213> Homo sapiens

<400> 29

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Trp Gly
1               5                   10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 30

<211> 194

<212> PRT

<213> Homo sapiens

<400> 30

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Ala Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
```

```
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 31

<211> 191

<212> PRT

<213> Homo sapiens

<400> 31

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Ala Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
```

```
                115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 32

<211> 191

<212> PRT

<213> Homo sapiens

<400> 32

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Asp Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 33

<211> 191

<212> PRT

<213> Homo sapiens

<400> 33

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Pro Gln
1               5                  10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 34

<211> 191

<212> PRT

<213> Homo sapiens

<400> 34

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Ala

1               5                  10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
```

```
Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 35

<211> 191

<212> PRT

<213> Homo sapiens

<400> 35

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Glu
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly

        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175
```

```
Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 36

<211> 191

<212> PRT

<213> Homo sapiens

<400> 36

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Asn
1               5                  10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala

65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 37

<211> 191

<212> PRT

<213> Homo sapiens

<400> 37

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
1               5                  10                  15

Ala Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45
```

```
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu

            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 38

<211> 191

<212> PRT

<213> Homo sapiens

<400> 38

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
1               5                   10                  15

Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125
```

```
Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 39

<211> 191

<212> PRT

<213> Homo sapiens

<400> 39

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
1               5                   10                  15

Thr Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly

                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 40

<211> 193

<212> PRT

<213> Homo sapiens

<400> 40

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Trp Gly
1               5                   10                  15

Gln Pro Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 41

<211> 182

<212> PRT

<213> Homo sapiens

<400> 41

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
```

```
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp
145                 150                 155                 160

Val Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg
                165                 170                 175

Ser Pro Ser Tyr Ala Ser
            180
```

<210> 42

<211> 178

<212> PRT

<213> Homo sapiens

<400> 42

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val Gly Ser Ser
145                 150                 155                 160

Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser Pro Ser Tyr
                165                 170                 175
```

Ala Ser

<210> 43

<211> 192

<212> PRT

<213> Homo sapiens

<400> 43

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Gly
1               5                   10                  15

Asp Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 44

<211> 185

<212> PRT

<213> Homo sapiens

<400> 44

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln
            20                  25                  30

Thr Glu Ala His Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala
        35                  40                  45
```

```
Ala Asp Gln Ser Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro
    50                  55                  60

Gly Val Ile Gln Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln
65                  70                  75                  80

Arg Pro Asp Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala
                85                  90                  95

Cys Ser Phe Arg Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln
            100                 105                 110

Ser Glu Ala His Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro
        115                 120                 125

His Arg Asp Pro Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro
    130                 135                 140

Gly Leu Pro Pro Ala Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln
145                 150                 155                 160

Pro Pro Asp Val Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser
                165                 170                 175

Gln Gly Arg Ser Pro Ser Tyr Ala Ser
            180                 185
```

<210> 45

<211> 193

<212> PRT

<213> Homo sapiens

<400> 45

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His
            20                  25                  30

Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser
        35                  40                  45

Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln
    50                  55                  60

Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly
65                  70                  75                  80

Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg
                85                  90                  95

Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His
            100                 105                 110

Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro
        115                 120                 125

Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro
    130                 135                 140

Ala Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
```

```
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 46

<211> 232

<212> PRT

<213> Homo sapiens

<400> 46

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln
            20                  25                  30

Thr Glu Ala His Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala
        35                  40                  45

Ala Asp Gln Ser Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro
    50                  55                  60

Gly Val Ile Gln Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln
65                  70                  75                  80

Arg Pro Asp Gly Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala
                85                  90                  95

Cys Ser Phe Arg Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln
            100                 105                 110

Ser Glu Ala His Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro
        115                 120                 125

His Arg Asp Pro Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro
    130                 135                 140

Gly Leu Pro Pro Ala Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln
145                 150                 155                 160

Pro Pro Asp Val Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser
                165                 170                 175

Gln Gly Arg Ser Pro Ser Tyr Ala Ser Pro Met Val Pro Glu Glu Pro
            180                 185                 190

Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu
        195                 200                 205

Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala
    210                 215                 220

Val Arg Ser Pro Ser Phe Glu Lys
225                 230
```

<210> 47

<211> 190

<212> PRT

<213> Homo sapiens

<400> 47

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro Ile
1               5                  10                  15

Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
145                 150                 155                 160

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
                165                 170                 175

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 48

<211> 187

<212> PRT

<213> Homo sapiens

<400> 48

```
Arg Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Leu Arg
1               5                  10                  15

His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30

Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45

Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60
```

```
Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80

Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95

Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
            100                 105                 110

Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125

Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
    130                 135                 140

Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160

Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175

Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 49

<211> 192

<212> PRT

<213> Homo sapiens

<400> 49

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly
1               5                   10                  15

Gln Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
```

```
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 50

<211> 191

<212> PRT

<213> Homo sapiens

<400> 50

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Asp Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Leu Glu Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 51

<211> 191

<212> PRT

<213> Homo sapiens

<400> 51

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Asn
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45
```

```
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 52

<211> 187

<212> PRT

<213> Homo sapiens

<400> 52

```
Arg Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro Ile Arg Leu Arg
1               5                   10                  15

His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30

Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45

Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60

Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80

Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95

Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
            100                 105                 110

Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125

Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
    130                 135                 140
```

```
Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160

Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175

Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 53

<211> 189

<212> PRT

<213> Homo sapiens

<400> 53

```
Met Asp Ser Ser Pro Leu Val His Tyr Gly Trp Gly Asp Pro Ile Arg
1               5                   10                  15

Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe
            20                  25                  30

Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser
        35                  40                  45

Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala
    50                  55                  60

Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly
65                  70                  75                  80

Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu
                85                  90                  95

Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His
            100                 105                 110

Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys
        115                 120                 125

Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met
    130                 135                 140

Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met
145                 150                 155                 160

Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val
                165                 170                 175

Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 54

<211> 192

<212> PRT

<213> Homo sapiens

<400> 54

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Leu Leu Gln Trp Gly Asp
1               5                   10                  15
```

```
Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 55

<211> 192

<212> PRT

<213> Homo sapiens

<400> 55

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Tyr Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
```

```
Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 56

<211> 192

<212> PRT

<213> Homo sapiens

<400> 56

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val Tyr Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 57

<211> 192

<212> PRT

<213> Homo sapiens

<400> 57

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val His Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 58

<211> 192

<212> PRT

<213> Homo sapiens

<400> 58

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Val His Tyr Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95
```

```
Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 59

<211> 192

<212> PRT

<213> Homo sapiens

<400> 59

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His His Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 60

<211> 192

<212> PRT

<213> Homo sapiens

<400> 60

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His His Tyr Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 61

<211> 192

<212> PRT

<213> Homo sapiens

<400> 61

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60
```

```
Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 62

<211> 192

<212> PRT

<213> Homo sapiens

<400> 62

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val Tyr Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
```

```
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 63

<211> 192

<212> PRT

<213> Homo sapiens

<400> 63

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 64

<211> 192

<212> PRT

<213> Homo sapiens

<400> 64

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro Leu Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45
```

```
Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 65

<211> 192

<212> PRT

<213> Homo sapiens

<400> 65

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro His Val His Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140
```

```
Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 66

<211> 192

<212> PRT

<213> Homo sapiens

<400> 66

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Leu Gln Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 67

<211> 191

<212> PRT

<213> Homo sapiens

<400> 67

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val Trp Gly Asp Pro
1               5                   10                  15
```

```
Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 68

<211> 193

<212> PRT

<213> Homo sapiens

<400> 68

Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Trp Gly

```
1               5                   10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110
```

```
Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 69

<211> 189

<212> PRT

<213> Homo sapiens

<400> 69

```
Arg Asp Ser Ser Pro Leu Val His Tyr Gly Trp Gly Asp Pro Ile Arg
1               5                   10                  15

Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe

            20                  25                  30

Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser
        35                  40                  45

Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala
    50                  55                  60

Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly
65                  70                  75                  80

Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu
                85                  90                  95

Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His
            100                 105                 110

Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys
        115                 120                 125

Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met
    130                 135                 140

Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met
145                 150                 155                 160

Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val
                165                 170                 175

Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

180 185

<210> 70

<211> 190

<212> PRT

<213> Homo sapiens

<400> 70

```
Met Arg Asp Ser Ser Pro Leu Val His Tyr Gly Trp Gly Asp Pro Ile
1               5                  10                  15

Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val

    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
145                 150                 155                 160

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
                165                 170                 175

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 71

<211> 181

<212> PRT

<213> Homo sapiens

<400> 71

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                  10                  15

Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His
            20                  25                  30

Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser
        35                  40                  45
```

```
Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln
    50                  55                  60

Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly
65                  70                  75                  80

Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg

                85                  90                  95

Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His
            100                 105                 110

Ser Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro
        115                 120                 125

Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro
    130                 135                 140

Ala Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val
145                 150                 155                 160

Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser
                165                 170                 175

Pro Ser Tyr Ala Ser
            180
```

<210> 72

<211> 181

<212> PRT

<213> Homo sapiens

<400> 72

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His
            20                  25                  30

Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser
        35                  40                  45

Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln
    50                  55                  60

Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly
65                  70                  75                  80

Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg
                85                  90                  95

Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His
            100                 105                 110

Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro

        115                 120                 125

Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro
```

```
    130                 135                 140

Ala Pro Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val
145                 150                 155                 160

Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser
                165                 170                 175

Pro Ser Tyr Ala Ser
            180
```

<210> 73

<211> 212

<212> PRT

<213> Homo sapiens

<400> 73

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His
            20                  25                  30

Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser
        35                  40                  45

Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln
    50                  55                  60

Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly
65                  70                  75                  80

Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg
                85                  90                  95

Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His
            100                 105                 110

Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro
        115                 120                 125

Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro
    130                 135                 140

Ala Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val

145                 150                 155                 160

Gly Ser Ser Asp Pro Leu Ser Met Val Val Gln Asp Glu Leu Gln Gly
                165                 170                 175

Val Gly Gly Glu Gly Cys His Met His Pro Glu Asn Cys Lys Thr Leu
            180                 185                 190

Leu Thr Asp Ile Asp Arg Thr His Thr Glu Lys Pro Val Trp Asp Gly
        195                 200                 205

Ile Thr Gly Glu
    210
```

<210> 74

<211> 189

<212> PRT

<213> Homo sapiens

<400> 74

```
Arg Asp Ala Gly Pro His Val His Tyr Gly Trp Gly Asp Pro Ile Arg
1               5                   10                  15

Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe
            20                  25                  30

Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser
        35                  40                  45

Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala
    50                  55                  60

Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly
65                  70                  75                  80

Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu
                85                  90                  95

Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His
            100                 105                 110

Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys
        115                 120                 125

Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met
    130                 135                 140

Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met

145                 150                 155                 160

Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val
                165                 170                 175

Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 75

<211> 184

<212> PRT

<213> Homo sapiens

<400> 75

```
Arg Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr
1               5                   10                  15

Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala
            20                  25                  30

Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu
        35                  40                  45

Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His
```

```
    50                  55                  60

Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu
65                  70                  75                  80

Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro
                85                  90                  95

Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser
            100                 105                 110

Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu
        115                 120                 125

Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro
    130                 135                 140

Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu
145                 150                 155                 160

Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala
                165                 170                 175

Val Arg Ser Pro Ser Phe Glu Lys

            180
```

<210> 76

<211> 179

<212> PRT

<213> Homo sapiens

<400> 76

```
Arg Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His
1               5                   10                  15

Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp
            20                  25                  30

Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val
        35                  40                  45

Ala Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu
    50                  55                  60

Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu
65                  70                  75                  80

Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val
                85                  90                  95

Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys
            100                 105                 110

Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe
        115                 120                 125

Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly
    130                 135                 140
```

```
His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met
145                 150                 155                 160

Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser
                165                 170                 175

Phe Glu Lys
```

<210> 77

<211> 175

<212> PRT

<213> Homo sapiens

<400> 77

```
Arg Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
1               5                   10                  15

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
            20                  25                  30

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
        35                  40                  45

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
    50                  55                  60

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
65                  70                  75                  80

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
                85                  90                  95

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
            100                 105                 110

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
        115                 120                 125

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
    130                 135                 140

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
145                 150                 155                 160

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
                165                 170                 175
```

<210> 78

<211> 188

<212> PRT

<213> Homo sapiens

<400> 78

```
Arg Ala Gly Pro His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu
1               5                   10                  15

Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu
            20                  25                  30
```

```
Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala
        35                  40                  45

His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile
    50                  55                  60

Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys
65                  70                  75                  80

Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu
                85                  90                  95

Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg
            100                 105                 110

Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn
        115                 120                 125

Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val
    130                 135                 140

Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe
145                 150                 155                 160

Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr
                165                 170                 175

Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 79

<211> 187

<212> PRT

<213> Homo sapiens

<400> 79

```
Arg Gly Pro His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg
1               5                   10                  15

His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30

Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45

Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60

Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80

Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95

Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
            100                 105                 110

Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125

Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
```

```
    130                 135                 140

Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160

Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175

Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 80

<211> 186

<212> PRT

<213> Homo sapiens

<400> 80

```
Arg Pro His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His
1               5                   10                  15

Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile
            20                  25                  30

Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser
        35                  40                  45

Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly
    50                  55                  60

Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln
65                  70                  75                  80

Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile
                85                  90                  95

Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro
            100                 105                 110

Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly
        115                 120                 125

Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu
    130                 135                 140

Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser
145                 150                 155                 160

Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu
                165                 170                 175

Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 81

<211> 185

<212> PRT

<213> Homo sapiens

<400> 81

```
Arg His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu
```

```
1               5                   10                  15

Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg
            20                  25                  30

Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu
        35                  40                  45

Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val
    50                  55                  60

His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly
65                  70                  75                  80

Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg
                85                  90                  95

Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val
            100                 105                 110

Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe
        115                 120                 125

Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu
    130                 135                 140

Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro
145                 150                 155                 160

Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu
                165                 170                 175

Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 82

<211> 194

<212> PRT

<213> Homo sapiens

<400> 82

```
Arg Pro Leu Ala Phe Ser Ala Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110
```

```
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 83

<211> 194

<212> PRT

<213> Homo sapiens

<400> 83

```
Arg Pro Leu Ala Phe Ser Asp Ala Ala Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190
```

Glu Lys

<210> 84

<211> 194

<212> PRT

<213> Homo sapiens

<400> 84

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Ala His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 85

<211> 194

<212> PRT

<213> Homo sapiens

<400> 85

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Ala
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
```

```
Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 86

<211> 194

<212> PRT

<213> Homo sapiens

<400> 86

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Ala Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
```

```
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 87

<211> 167

<212> PRT

<213> Homo sapiens

<400> 87

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Ala Ile Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu
            20                  25                  30

Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His Ser
        35                  40                  45

Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu
    50                  55                  60

Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp
65                  70                  75                  80

Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu
                85                  90                  95

Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro
            100                 105                 110

Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu
        115                 120                 125

Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu
    130                 135                 140

Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val
145                 150                 155                 160

Arg Ser Pro Ser Phe Glu Lys
                165
```

<210> 88

<211> 194

<212> PRT

<213> Homo sapiens

<400> 88

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro Ala Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 89

<211> 194

<212> PRT

<213> Homo sapiens

<400> 89

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro Ala Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95
```

```
Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser Ala Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 90

<211> 194

<212> PRT

<213> Homo sapiens

<400> 90

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Ala Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175
```

```
Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 91

<211> 194

<212> PRT

<213> Homo sapiens

<400> 91

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 92

<211> 194

<212> PRT

<213> Homo sapiens

<400> 92

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
```

```
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser Ala Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 93

<211> 194

<212> PRT

<213> Homo sapiens

<400> 93

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110
```

```
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Ala Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 94

<211> 194

<212> PRT

<213> Homo sapiens

<400> 94

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala Ala Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 95

<211> 194

<212> PRT

<213> Homo sapiens

<400> 95

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser Ala Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 96

<211> 194

<212> PRT

<213> Homo sapiens

<400> 96

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
```

```
                50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Ala Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 97

<211> 194

<212> PRT

<213> Homo sapiens

<400> 97

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Ala Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser Ala Phe Leu
    130                 135                 140
```

```
Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 98

<211> 194

<212> PRT

<213> Homo sapiens

<400> 98

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Ala Gln
        115                 120                 125

Ala Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ala Ala Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 99

<211> 194

<212> PRT

<213> Homo sapiens

<400> 99

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 100

<211> 181

<212> PRT

<213> Homo sapiens

<400> 100

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Gln Arg Tyr Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His
            20                  25                  30

Leu Glu Ile Arg Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser
        35                  40                  45

Pro Glu Ser Leu Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln
    50                  55                  60

Ile Leu Gly Val Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly
```

```
65                  70                  75                  80

Ala Leu Tyr Gly Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg
                85                  90                  95

Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His
            100                 105                 110

Gly Leu Pro Leu His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro
        115                 120                 125

Ala Pro Arg Gly Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro
    130                 135                 140

Ala Leu Pro Glu Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val
145                 150                 155                 160

Gly Ser Ser Asp Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser
                165                 170                 175

Pro Ser Tyr Ala Ser
            180
```

<210> 101

<211> 4

<212> PRT

<213> Homo sapiens

<400> 101

```
Val His Tyr Gly
1
```

<210> 102

<211> 9

<212> PRT

<213> Homo sapiens

<400> 102

```
Asp Ala Ser Pro His Val His Tyr Gly
1               5
```

<210> 103

<211> 9

<212> PRT

<213> Homo sapiens

<400> 103

```
Asp Ser Ser Pro Leu Val His Tyr Gly
1               5
```

<210> 104

<211> 7

<212> PRT

<213> Homo sapiens

<400> 104

```
Asp Ser Ser Pro Leu Leu Gln
1               5
```

<210> 105
<211> 12
<212> PRT
<213> Homo sapiens

<400> 105
Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1 5 10

<210> 106
<211> 5
<212> PRT
<213> Homo sapiens

<400> 106
Arg His Pro Ile Pro
1 5

<210> 107
<211> 4
<212> PRT
<213> Homo sapiens

<400> 107
His Pro Ile Pro

1

<210> 108
<211> 5
<212> PRT
<213> Homo sapiens

<400> 108
Arg Pro Leu Ala Phe
1 5

<210> 109
<211> 4
<212> PRT
<213> Homo sapiens

<400> 109
Pro Leu Ala Phe
1

<210> 110
<211> 6
<212> PRT
<213> Homo sapiens

<400> 110
Met Asp Ser Ser Pro Leu
1 5

<210> 111

<211> 7
<212> PRT
<213> Homo sapiens

<400> 111
Met Ser Asp Ser Ser Pro Leu
1 5

<210> 112
<211> 6
<212> PRT
<213> Homo sapiens

<400> 112
Ser Asp Ser Ser Pro Leu
1 5

<210> 113
<211> 5
<212> PRT
<213> Homo sapiens

<400> 113
Met Ser Ser Pro Leu
1 5

<210> 114
<211> 4
<212> PRT
<213> Homo sapiens

<400> 114
Ser Ser Pro Leu
1

<210> 115
<211> 4
<212> PRT
<213> Homo sapiens

<400> 115
Arg Asp Ser Ser
1

<210> 116
<211> 4
<212> PRT
<213> Homo sapiens

<400> 116
Met Asp Ser Ser
1

<210> 117
<211> 5
<212> PRT
<213> Homo sapiens

<400> 117
Met Arg Asp Ser Ser
1 5

<210> 118
<211> 5
<212> PRT
<213> Homo sapiens

<400> 118
Met Ser Ser Pro Leu
1 5

<210> 119
<211> 6
<212> PRT
<213> Homo sapiens

<400> 119
Met Asp Ser Ser Pro Leu
1 5

<210> 120
<211> 7
<212> PRT
<213> Homo sapiens

<400> 120
Met Ser Asp Ser Ser Pro Leu
1 5

<210> 121
<211> 5
<212> PRT
<213> Homo sapiens

<400> 121
Asp Ser Ser Pro Leu
1 5

<210> 122
<211> 5
<212> PRT
<213> Homo sapiens

<400> 122
Asp Ala Ser Pro His
1 5

<210> 123
<211> 4
<212> PRT
<213> Homo sapiens

<400> 123
Arg Asp Ser Ser
1

<210> 124
<211> 4
<212> PRT
<213> Homo sapiens

<400> 124
Met Asp Ser Ser
1

<210> 125
<211> 5
<212> PRT
<213> Homo sapiens

<400> 125
Met Arg Asp Ser Ser
1 5

<210> 126
<211> 6
<212> PRT
<213> Homo sapiens

<400> 126
Met Asp Ser Ser Pro Leu
1 5

<210> 127
<211> 7
<212> PRT
<213> Homo sapiens

<400> 127
Met Ser Asp Ser Ser Pro Leu
1 5

<210> 128
<211> 5
<212> PRT
<213> Homo sapiens

<400> 128
Met Ser Ser Pro Leu
1 5

<210> 129
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 129
Gly Ser Gly Gly Ser
1 5

<210> 130
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 130
Gly Gly Gly Ser
1

<210> 131
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 131
Gly Gly Ser Gly
1

<210> 132
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 132
Gly Gly Ser Gly Gly
1 5

<210> 133
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 133
Gly Ser Gly Ser Gly
1 5

<210> 134
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 134
Gly Ser Gly Gly Gly

1 5

<210> 135
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker sequence

<400> 135
Gly Ser Ser Ser Gly
1 5

<210> 136
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Forward primer

<400> 136
ccgactagtc accatgcgga gcgggtgtgt gg 32

<210> 137
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Reverse primer

<400> 137
ataagaatgc ggccgcttac ttctcaaagc tgggactcct c 41

<210> 138
<211> 186
<212> PRT
<213> Homo sapiens

<400> 138
Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Leu Arg His
1 5 10 15

Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile
20 25 30

Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser
35 40 45

Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly
50 55 60

```
Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln
65                  70                  75                  80

Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile
                85                  90                  95

Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro
            100                 105                 110

Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly
        115                 120                 125

Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu
    130                 135                 140

Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser
145                 150                 155                 160

Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu
                165                 170                 175

Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 139

<211> 194

<212> PRT

<213> Homo sapiens

<400> 139

```
Arg Pro Leu Ala Phe Ser Asp Ala Ser Pro His Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
```

```
Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 140

<211> 194

<212> PRT

<213> Homo sapiens

<400> 140

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro Leu Val His Tyr Gly Trp
1               5                   10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 141

<211> 188

<212> PRT

<213> Homo sapiens

<400> 141

```
Asp Ser Ser Pro Leu Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu
1               5                   10                  15
```

```
Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu
            20                  25                  30

Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala
        35                  40                  45

His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile
    50                  55                  60

Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys
65                  70                  75                  80

Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu
                85                  90                  95

Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg
            100                 105                 110

Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn
        115                 120                 125

Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val
    130                 135                 140

Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe
145                 150                 155                 160

Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr
                165                 170                 175

Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 142

<211> 193

<212> PRT

<213> Homo sapiens

<400> 142

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Trp Gly
1               5                   10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110
```

```
Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 143

<211> 191

<212> PRT

<213> Homo sapiens

<400> 143

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro
1               5                   10                  15

Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 144

<211> 194

<212> PRT

<213> Homo sapiens

<400> 144

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Leu Leu Gln Phe Gly Trp
1               5                  10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30

Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45

Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60

Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80

Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95

Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
            100                 105                 110

Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125

Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140

Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160

Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175

Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190

Glu Lys
```

<210> 145

<211> 193

<212> PRT

<213> Homo sapiens

<400> 145

```
Arg His Pro Ile Pro Asp Ser Ser Pro His Val His Tyr Gly Trp Gly
1               5                  10                  15

Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60
```

```
Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95

Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu
145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 146

<211> 192

<212> PRT

<213> Homo sapiens

<400> 146

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro Leu Leu Gln Phe Gly Gly
1               5                   10                  15

Gln Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140
```

```
Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 147

<211> 191

<212> PRT

<213> Homo sapiens

<400> 147

```
Arg His Pro Ile Pro Asp Ser Ser Pro His Val His Tyr Gly Gly Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 148

<211> 187

<212> PRT

<213> Homo sapiens

<400> 148

```
Arg Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Leu Arg
1               5                   10                  15
```

```
His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30

Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45

Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60

Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80

Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95

Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
            100                 105                 110

Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125

Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
    130                 135                 140

Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160

Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175

Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 149

<211> 192

<212> PRT

<213> Homo sapiens

<400> 149

```
Arg Pro Leu Ala Phe Ser Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly
1               5                   10                  15

Gln Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110
```

```
Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 150

<211> 191

<212> PRT

<213> Homo sapiens

<400> 150

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Ala Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 151

<211> 191

<212> PRT

<213> Homo sapiens

<400> 151

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Asp Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 152

<211> 191

<212> PRT

<213> Homo sapiens

<400> 152

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Pro Gln
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
```

```
Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 153

<211> 191

<212> PRT

<213> Homo sapiens

<400> 153

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Ala
1               5                   10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

180 185 190

<210> 154

<211> 191

<212> PRT

<213> Homo sapiens

<400> 154

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Glu
1               5                  10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 155

<211> 191

<212> PRT

<213> Homo sapiens

<400> 155

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Asn
1               5                  10                  15

Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser

            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45
```

```
Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 156

<211> 191

<212> PRT

<213> Homo sapiens

<400> 156

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
1               5                   10                  15

Ala Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr

    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140
```

```
Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 157

<211> 191

<212> PRT

<213> Homo sapiens

<400> 157

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
1               5                   10                  15

Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala

                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu
        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 158

<211> 191

<212> PRT

<213> Homo sapiens

<400> 158

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln
```

```
1               5                   10                  15

Thr Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser
            20                  25                  30

Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly
        35                  40                  45

Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr
    50                  55                  60

Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala
65                  70                  75                  80

Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala
                85                  90                  95

Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu
            100                 105                 110

Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu

        115                 120                 125

Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu
    130                 135                 140

Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser
145                 150                 155                 160

Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly
                165                 170                 175

Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 159

<211> 193

<212> PRT

<213> Homo sapiens

<400> 159

```
Arg His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Trp Gly
1               5                   10                  15

Gln Pro Val Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu
            20                  25                  30

Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala
        35                  40                  45

Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu
    50                  55                  60

Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met
65                  70                  75                  80

Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp
                85                  90                  95
```

```
Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg
            100                 105                 110

Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg
        115                 120                 125

Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro
    130                 135                 140

Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu

145                 150                 155                 160

Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro
                165                 170                 175

Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu
            180                 185                 190

Lys
```

<210> 160

<211> 190

<212> PRT

<213> Homo sapiens

<400> 160

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val
1               5                   10                  15

Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
145                 150                 155                 160

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
```

```
                165                 170                 175

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 161

<211> 186

<212> PRT

<213> Homo sapiens

<400> 161

```
Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Leu Arg His
1               5                   10                  15

Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile
            20                  25                  30

Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser
        35                  40                  45

Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly
    50                  55                  60

Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln
65                  70                  75                  80

Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile
                85                  90                  95

Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro
            100                 105                 110

Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly
        115                 120                 125

Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu
    130                 135                 140

Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser
145                 150                 155                 160

Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu
                165                 170                 175

Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 162

<211> 190

<212> PRT

<213> Homo sapiens

<400> 162

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro Ile
1               5                   10                  15

Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
```

```
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
145                 150                 155                 160

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
                165                 170                 175

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 163

<211> 192

<212> PRT

<213> Homo sapiens

<400> 163

```
His Pro Ile Pro Asp Ser Ser Pro Leu Leu Gln Phe Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140
```

```
Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 164

<211> 192

<212> PRT

<213> Homo sapiens

<400> 164

```
His Pro Ile Pro Asp Ser Ser Pro His Val His Tyr Gly Trp Gly Asp
1               5                   10                  15

Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser
            20                  25                  30

Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg
        35                  40                  45

Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg
    50                  55                  60

Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly
65                  70                  75                  80

Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys
                85                  90                  95

Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser
            100                 105                 110

Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln
        115                 120                 125

Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met
    130                 135                 140

Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu
145                 150                 155                 160

Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe
                165                 170                 175

Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 165

<211> 190

<212> PRT

<213> Homo sapiens

<400> 165

```
His Pro Ile Pro Asp Ser Ser Pro His Val His Tyr Gly Gly Gln Val
1               5                   10                  15
```

```
Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
            20                  25                  30

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
        35                  40                  45

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
    50                  55                  60

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
65                  70                  75                  80

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
                85                  90                  95

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
            100                 105                 110

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
        115                 120                 125

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
    130                 135                 140

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
145                 150                 155                 160

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
                165                 170                 175

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185                 190
```

<210> 166

<211> 188

<212> PRT

<213> Homo sapiens

<400> 166

```
Asp Ala Gly Pro His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu
1               5                   10                  15

Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu
            20                  25                  30

Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala
        35                  40                  45

His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile
    50                  55                  60

Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys
65                  70                  75                  80

Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu
                85                  90                  95

Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg
            100                 105                 110
```

```
Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn
        115                 120                 125

Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val
    130                 135                 140

Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe
145                 150                 155                 160

Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr
                165                 170                 175

Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 167

<211> 183

<212> PRT

<213> Homo sapiens

<400> 167

```
Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr
1               5                   10                  15

Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp
            20                  25                  30

Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu
        35                  40                  45

Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His Ser
    50                  55                  60

Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu
65                  70                  75                  80

Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp
                85                  90                  95

Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu
            100                 105                 110

Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro
        115                 120                 125

Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu
    130                 135                 140

Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu
145                 150                 155                 160

Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val
                165                 170                 175

Arg Ser Pro Ser Phe Glu Lys
            180
```

<210> 168

<211> 174

<212> PRT

<213> Homo sapiens

<400> 168

```
Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys
1               5                   10                  15

Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln
            20                  25                  30

Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val
        35                  40                  45

Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp
    50                  55                  60

Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe
65                  70                  75                  80

Glu Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys
                85                  90                  95

His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr
            100                 105                 110

Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro
        115                 120                 125

Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp
    130                 135                 140

Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu
145                 150                 155                 160

Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
                165                 170
```

<210> 169

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 169

```
Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly
 1               5                   10
```

<210> 170

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 170

```
Trp Gly Asp Pro Ile
 1               5
```

<210> 171
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 171
Trp Gly Pro Ile
1

<210> 172
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 172
Trp Gly Asp Pro Val
1 5

<210> 173
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 173
Trp Gly Asp Ile
1

<210> 174
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 174
Gly Asp Pro Ile
1

<210> 175
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 175
Trp Gly Gln Pro Ile
1 5

<210> 176
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 176
Trp Gly Ala Pro Ile
1 5

<210> 177
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 177
Ala Gly Asp Pro Ile
1 5

<210> 178
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 178
Trp Ala Asp Pro Ile
1 5

<210> 179
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 179
Trp Gly Asp Ala Ile
1 5

<210> 180
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 180
Trp Gly Asp Pro Ala
1 5

<210> 181
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 181
Trp Asp Pro Ile
1

<210> 182
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 182
Trp Gly Asp Ile
1

<210> 183
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

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<210> 184
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 184
Phe Gly Asp Pro Ile
1 5

<210> 185
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

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Arg Leu Arg His Leu Tyr Thr Ser Gly
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<210> 186
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> core sequence

<400> 186
Arg Gln Arg Tyr Leu Tyr Thr Asp Asp
1 5

<210> 187
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 187
Ala Gly Pro His Val His Tyr Gly Trp Gly Asp Pro Ile
1 5 10

<210> 188
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<223> FGF19 C-terminal sequence

<400> 188
Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val
1 5 10 15
Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys
20 25 30
Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg
35 40 45
Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr
50 55 60
Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro Asp Gly Tyr
65 70 75 80
Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser
85 90 95
Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser
100 105 110
His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu
115 120 125
Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp
130 135 140
Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser
145 150 155 160

```
Pro Ser Phe Glu Lys
            165
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<210> 189

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker sequence

<400> 189

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Gly Gly Gly Ser Gly
 1               5
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<210> 190

<211> 11

<212> PRT

<213> Homo sapiens

<220>

<223> Sheet-8/Loop-8/Sheet-9 region of FGF19

<400> 190

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Glu Glu Ile Arg Pro Asp Gly Tyr Asn Val Tyr
 1               5                  10
```

<210> 191

<211> 11

<212> PRT

<213> Homo sapiens

<220>

<223> Sheet-8/Loop-8/Sheet-9 region of FGF21

<400> 191

```
Glu Leu Leu Leu Glu Asp Gly Tyr Asn Val Tyr
 1               5                  10
```

<210> 192

<211> 187

<212> PRT

<213> Artificial Sequence

<220>

<223> M53 sequence

<400> 192

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Met Asp Ser Ser Pro Leu Leu Gln Trp Gly Asp Pro Ile Arg Leu Arg
 1               5                  10                  15
His Leu Tyr Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg
            20                  25                  30
Ile Arg Ala Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His
        35                  40                  45
Ser Leu Leu Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys
    50                  55                  60
Gly Val His Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met
65                  70                  75                  80
Gln Gly Leu Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu
                85                  90                  95
Ile Arg Pro Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu
```

```
                100                 105                 110
Pro Val Ser Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg
        115                 120                 125
Gly Phe Leu Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro
    130                 135                 140
Glu Glu Pro Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser
145                 150                 155                 160
Ser Pro Leu Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly
                165                 170                 175
Leu Glu Ala Val Arg Ser Pro Ser Phe Glu Lys
            180                 185
```

<210> 193

<211> 194

<212> PRT

<213> Artificial Sequence

<220>

<223> M139 sequence

<400> 193

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
 1               5                  10                  15
Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60
Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80
Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95
Asp Cys Ala Phe Glu Glu Glu Ile Leu Pro Asp Gly Tyr Asn Val Tyr

            100                 105                 110
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140
Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160
Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175
Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190
Glu Lys
```

<210> 194

<211> 194

<212> PRT

<213> Artificial Sequence

<220>

<223> M140 sequence

<400> 194

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 1               5                  10                  15
Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60
Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80
Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95
Asp Cys Ala Phe Glu Glu Glu Ile Arg Glu Asp Gly Tyr Asn Val Tyr
```

```
            100                 105                 110
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140
Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160
Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175
Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190
Glu Lys
```

<210> 195

<211> 194

<212> PRT

<213> Artificial Sequence

<220>

<223> M141 sequence

<400> 195

```
Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro His Val His Tyr Gly Trp
 1               5                  10                  15

Gly Asp Pro Ile Arg Leu Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60
Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80
Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95
Asp Cys Ala Phe Glu Glu Glu Ile Leu Cys Asp Gly Tyr Asn Val Tyr
            100                 105                 110
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140
Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160
Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175
Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190
Glu Lys
```

<210> 196

<211> 194

<212> PRT

<213> Artificial Sequence

<220>

<223> M160 sequence

<400> 196

```
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 1               5                  10                  15
Gly Asp Pro Ile Arg Gln Arg His Leu Tyr Thr Ser Gly Pro His Gly
            20                  25                  30
Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala Asp Gly Val Val Asp Cys
        35                  40                  45
Ala Arg Gly Gln Ser Ala His Ser Leu Leu Glu Ile Lys Ala Val Ala
    50                  55                  60
Leu Arg Thr Val Ala Ile Lys Gly Val His Ser Val Arg Tyr Leu Cys
65                  70                  75                  80
Met Gly Ala Asp Gly Lys Met Gln Gly Leu Leu Gln Tyr Ser Glu Glu
                85                  90                  95
```

```
Asp Cys Ala Phe Glu Glu Glu Ile Leu Glu Asp Gly Tyr Asn Val Tyr
            100                 105                 110
Arg Ser Glu Lys His Arg Leu Pro Val Ser Leu Ser Ser Ala Lys Gln
        115                 120                 125
Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu Pro Leu Ser His Phe Leu
    130                 135                 140
Pro Met Leu Pro Met Val Pro Glu Glu Pro Glu Asp Leu Arg Gly His
145                 150                 155                 160
Leu Glu Ser Asp Met Phe Ser Ser Pro Leu Glu Thr Asp Ser Met Asp
                165                 170                 175
Pro Phe Gly Leu Val Thr Gly Leu Glu Ala Val Arg Ser Pro Ser Phe
            180                 185                 190
Glu Lys
```

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- US20110104152A1 [0008]
- WO8705330A [0116]
- EP1517921B [0130]
- WO2005118642A [0130]
- WO2006051288A [0130]
- US20070134197A [0136]
- US20060258607A [0136]
- US5700470A [0160]
- US5731172A [0160]
- US5604090A [0160]
- US5501979A [0160]
- US5624820A [0160]
- US5693508A [0160]
- US5674703A [0160]
- US5719054A [0160]
- US5561063A [0160]
- US6013516A [0160]
- US5821235A [0160]
- US6110456A [0160]
- US5721367A [0172]
- US5695977A [0172]
- US5650298A [0172]

- US5614396A [0172]
- US6638513B [0177]
- WO61746499A [0328]
- WO61779604A [0328]
- WO61887129A [0328]

Non-patent literature cited in the description

- **STAELS et al.**Diabetes Care, 2009, vol. 32, 2S237-S245 [0002] [0005]
- **INAGAKI et al.**Cell Metabolism, 2005, vol. 2, 217-25 [0003]
- **ROSE et al.**Cell Metabolism, 2011, vol. 14, 1123-130 [0006]
- **FIORUCCI et al.**Prog Lipid Res., 2009, vol. 49, 2171-85 [0007]
- **LEFEBVRE et al.**Physiol Rev, 2009, vol. 89, 1147-91 [0010]
- **WALTERS et al.**Clin. Gastroenterol Hepatol., 2009, vol. 7, 1189-94 [0014]
- **ROSE et al.**Cell Metabolism, 2011, vol. 14, 1123-30 [0023]
- Peptide and Backbone Modifications**SPATOLA**Chemistry and Biochemistry of Amino Acids, Peptides and ProteinsMarcel Decker19830000vol. 7, 267-357 [0093]
- **ALTSCHUL et al.**J. Mol. Biol., 1990, vol. 215, 403- [0103]
- **PEARSON et al.**Proc. Natl. Acad. Sci. USA, 1988, vol. 85, 2444- [0103]
- **PEARSON**Methods Mol Biol, 2000, vol. 132, 185- [0103]
- **SMITH et al.**J. Mol. Biol., 1981, vol. 147, 195- [0103]
- **BOSTICK et al.**Biochem Biophys Res Commun, 2003, vol. 304, 320- [0103]
- **HRUBY et al.**Synthetic Peptides: A User's GuideBiochem. J., 1990, vol. 268, 249- [0104]
- **TONIOLO C.**Int. J. Peptide Protein Res., 1990, vol. 35, 287- [0104]
- **T. E. CREIGHTON**Proteins: Structure and Molecular PropertiesW.H. Freeman & Co.1983000079-86 [0111]
- **CARUTHERS**Nucleic Acids Res. Symp. Ser., 1980, vol. 215, [0146]
- **BANGA, A.K.**Therapeutic Peptides and Proteins, Formulation, Processing and Delivery SystemsTechnomic Publishing Co.19950000 [0146]
- **ROBERGE**Science, 1995, vol. 269, 202- [0146]
- **MERRIFIELD**Methods Enzymol., 1997, vol. 289, 3- [0146]
- Organic Syntheses Collective VolumesJohn Wiley & Sons, Inc. [0146]
- **BELOUSOV**Nucleic Acids Res., 1997, vol. 25, 3440- [0146]
- **FRENKEL**Free Radic. Biol. Med., 1995, vol. 19, 373- [0146]
- **BLOMMERS**Biochemistry, 1994, vol. 33, 7886- [0146]
- **CARTER et al.**Nucl. Acids Res., 1986, vol. 13, 4331- [0146]
- **ZOLLER et al.**Nucl. Acids Res., 1987, vol. 10, 6487- [0146]
- **WELLS et al.**Gene, 1985, vol. 34, 315- [0146]
- **WELLS et al.**Philos. Trans. R. Soc. London SerA, 1986, vol. 317, 415- [0146]
- **CROYLE et al.**Gene Ther, 1998, vol. 5, 645- [0160]
- **S.J. HENNING**Adv. Drug Deliv. Rev., 1997, vol. 17, 341- [0160]
- **AUSUBEL et al.**Current Protocols in Molecular BiologyGreene Publish. Assoc. & Wiley Interscience19880000vol. 2, [0161]
- **GRANT et al.**Methods in Enzymology19870000vol. 153, 516- [0161]
- **BITTER**Methods in EnzymologyAcad. Press19870000vol. 152, 673- [0161]

- **STRATHERN et al.**The Molecular Biology of the Yeast SaccharomycesCold Spring Harbor Press19820000vol. I,II, [0161]
- **R. ROTHSTEIN**DNA Cloning. A Practical ApproachIRL Press19860000vol. 11, [0161]
- **WIGLER et al.**Cell, 1977, vol. 11, 223- [0162]
- **SZYBALSKA et al.**Proc. Natl. Acad. Sci. USA, 1962, vol. 48, 2026- [0162]
- **LOWY et al.**Cell, 1980, vol. 22, 817- [0162]
- **O'HARE et al.**Proc. Natl. Acad. Sci. USA, 1981, vol. 78, 1527- [0162]
- **MULLIGAN et al.**Proc. Natl. Acad. Sci. USA, 1981, vol. 78, 2072- [0162]
- **COLBERRE-GARAPIN et al.**J. Mol. Biol., 1981, vol. 150, 1- [0162]
- **SANTERRE et al.**Gene, 1984, vol. 30, 147- [0162]
- **HARTMAN et al.**Proc. Natl. Acad. Sci. USA, 1988, vol. 85, 8047- [0162]
- **MCCONLOGUE**Current Communications in Molecular BiologyCold Spring Harbor Laboratory19870000 [0162]
- Remington's Pharmaceutical SciencesMack Publishing Co.199000001435-1712 [0206]
- The Merck IndexMerck Publishing Group19960000 [0206]
- Pharmaceutical Principles of Solid Dosage FormsTechnonic Publishing Co., Inc.19930000 [0206]
- **GAO et al.**J. Virol., 2004, vol. 78, 6381- [0256]
- **ZOLOTUKHIN S. et al.**Gene Ther, 1999, vol. 6, 973- [0256]
- **GALMAN et al.**J Lipid Res., 2003, vol. 44, 4859-66 [0320]

Patentkrav

1. Kimært peptid med en aminosyresekvens bestående af:
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLL
EIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYN
VYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLES
DMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M69) (SEQ ID NO:69), eller
MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHS
LLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDG
YNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGH
LESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK (M70) (SEQ ID NO:70) til anvendelse i en fremgangsmåde til behandling af en galdesyre-relateret eller associeret lidelse (BARD);
hvor nævnte lidelse er kolestase, intrahepatisk kolestase, primær familiær intrahepatisk kolestase (PFIC), progressiv PFIC, gravididetsbetinget intrahepatisk kolestase (PIC), neonatal kolestase, lægemiddel-induceret kolestase, ekstrahepatisk kolestase, primær biliær cirrose (PBC), primær skleroserende kolangitis (PSC), tumorbetinget galdesnitskompression, galdegangsblokade af galdesten, galdesyremalabsorption, galdesyrediarré (BAD) eller galdesyresynteseanormaliteter.

2. Det kimære peptid til anvendelse ifølge krav 1, hvor amino- eller carboxy-terminalen af nævnte peptid er fusioneret med en immunoglobulin-Fc-region.

3. Det kimære peptid til anvendelse ifølge krav 1 eller 2, hvor nævnte lidelse er PFIC.

4. Det kimære peptid til anvendelse ifølge krav 1 eller 2, hvor nævnte lidelse er BAD.

5. Farmaceutisk sammensætning omfattende et kimært peptid som defineret i krav 1 eller 2, til anvendelse i en fremgangsmåde til behandling af en galdesyre-relateret eller associeret lidelse (BARD); hvor nævnte lidelse er kolestase, intrahepatisk kolestase, primær familiær intrahepatisk kolestase (PFIC), progressiv PFIC, graviditetsbetinget intrahepatisk kolestase (PIC), neonatal

kolestase, lægemiddel-induceret kolestase, ekstrahepatisk kolestase, primær biliær cirrose (PBC), primær skleroserende kolangitis (PSC), tumorbetinget galdesnitskompression, galdegangsblokade af galdesten, galdesyre-malabsorption, galdesyrediarré (BAD) eller galdesyresynteseanormaliteter, hvor nævnte farmaceutiske sammensætning yderligere omfatter en farmaceutisk acceptabel bærer.

6. Den farmaceutiske sammensætning til anvendelse ifølge krav 5, hvor nævnte lidelse er PFIC.

7. Den farmaceutiske sammensætning til anvendelse ifølge krav 5, hvor nævnte lidelse er BAD.

DRAWINGS

FIG.1

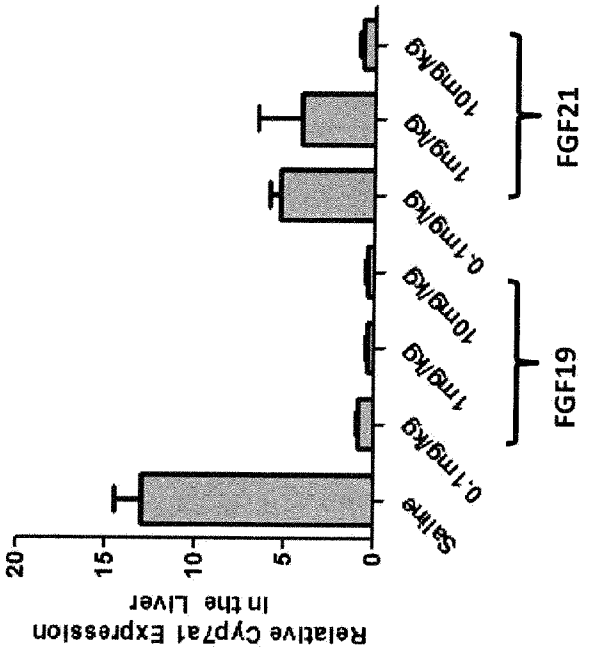


FIG.2A-2D

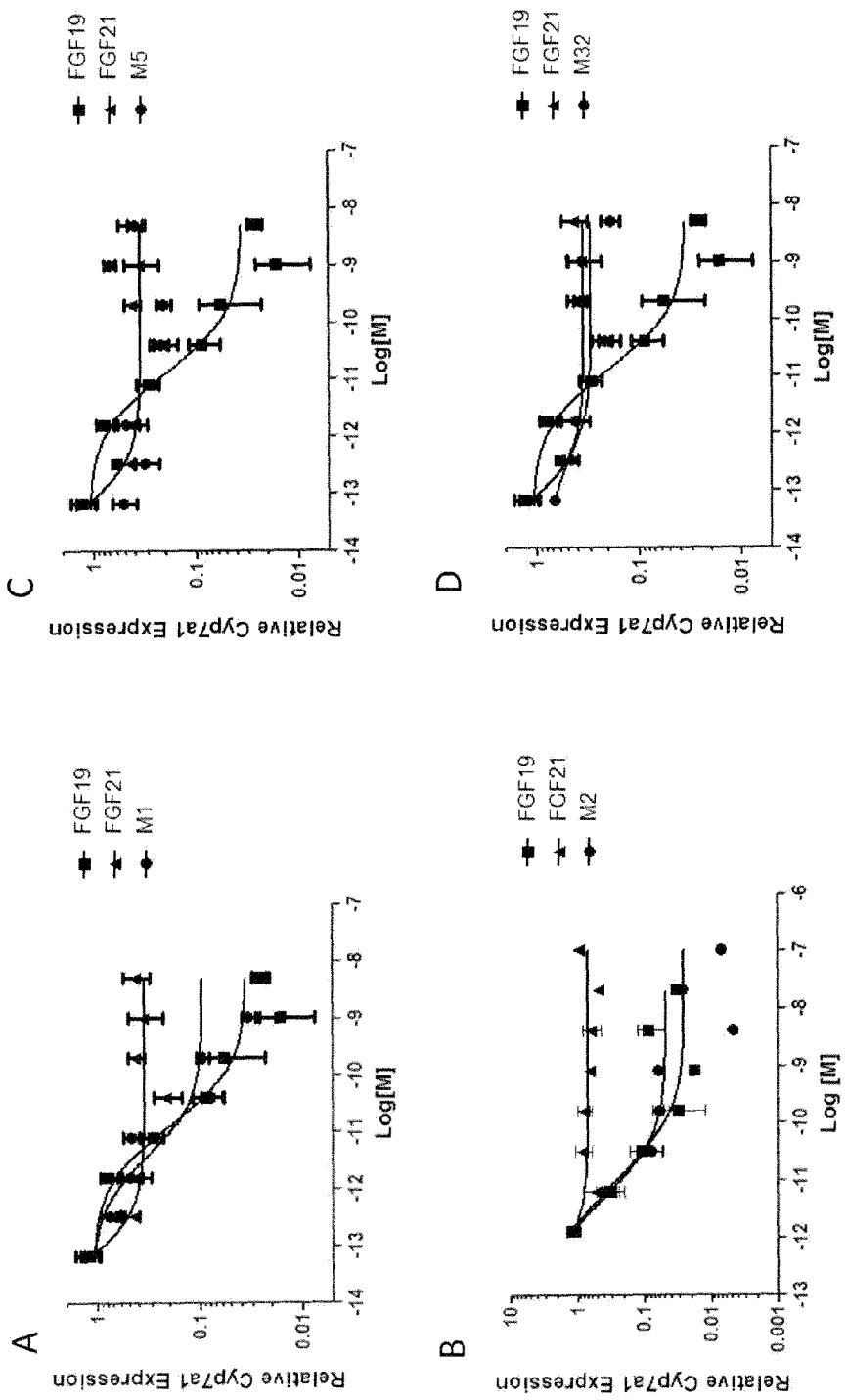

A
FGF19
FGF21
M1
Relative Cyp7a1 Expression
Log[M]
B
FGF19
FGF21
M2
Relative Cyp7a1 Expression
Log [M]
C
FGF19
FGF21
M5
Relative Cyp7a1 Expression
Log[M]
D
FGF19
FGF21
M32
Relative Cyp7a1 Expression
Log[M]

FIG.3A-3D

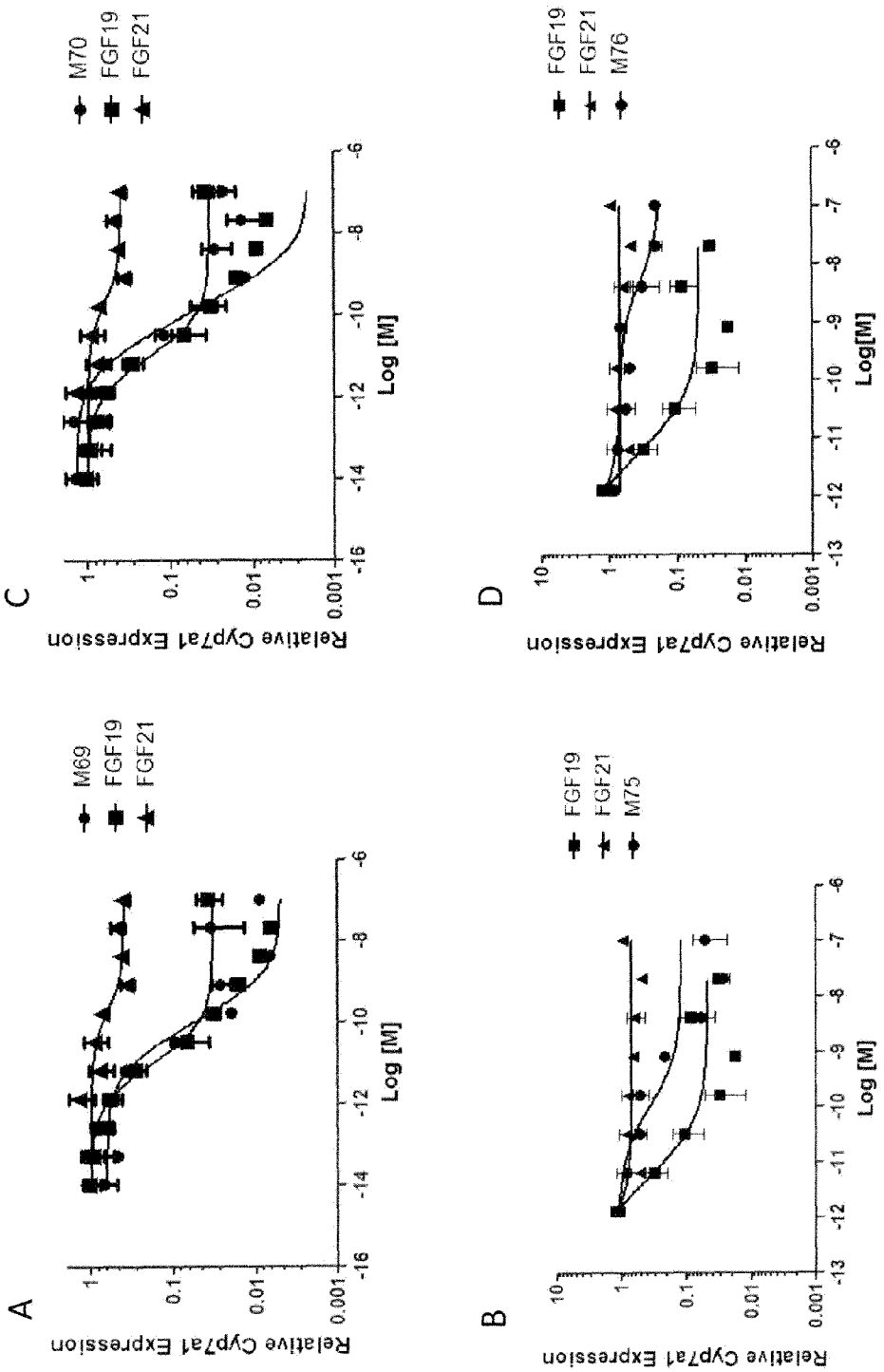

A
M69
FGF19
FGF21
Relative Cyp7a1 Expression
Log [M]
B
FGF19
FGF21
M75
Relative Cyp7a1 Expression
Log [M]
C
M70
FGF19
FGF21
Relative Cyp7a1 Expression
Log [M]
D
FGF19
FGF21
M76
Relative Cyp7a1 Expression
Log[M]

FIG. 4A-4D

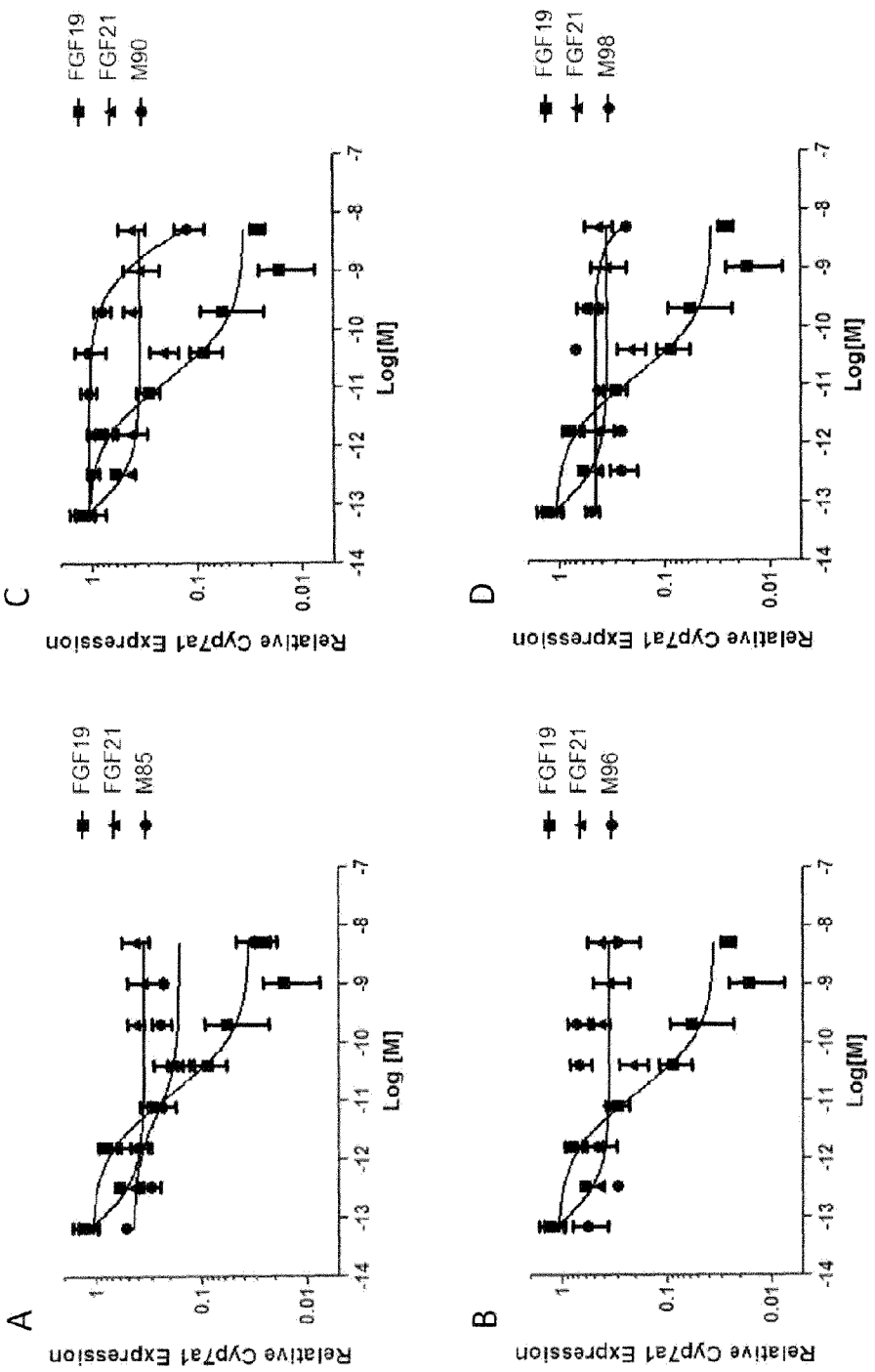

A
FGF19
FGF21
M85
Relative Cyp7a1 Expression
Log [M]
B
FGF19
FGF21
M96
Relative Cyp7a1 Expression
Log[M]
C
FGF19
FGF21
M90
Relative Cyp7a1 Expression
Log[M]
D
FGF19
FGF21
M98
Relative Cyp7a1 Expression
Log[M]

FIG. 5

Variants	Cyp7a1 IC50 (pM)	Relative Cyp7a1 Expression	HCC Score
Saline-treated	n/a	100%	0.00
FGF19	2.3	4%	1.00
FGF21	n/a	35%	0.00
M1	1.1	10%	0.04
M2	0.9	2%	0.06
M5	n/a	100%	0.00
M32	n/a	100%	0.00
M69	8.6	0.5%	0.00
M70	4.8	0.2%	0.00
M75	34	12%	0.00
M76	n/a	17%	0.00
M85	3.6	16%	0.00
M90	859	100%	1.00
M96	n/a	100%	1.00
M98	n/a	100%	1.00

FIG. 6

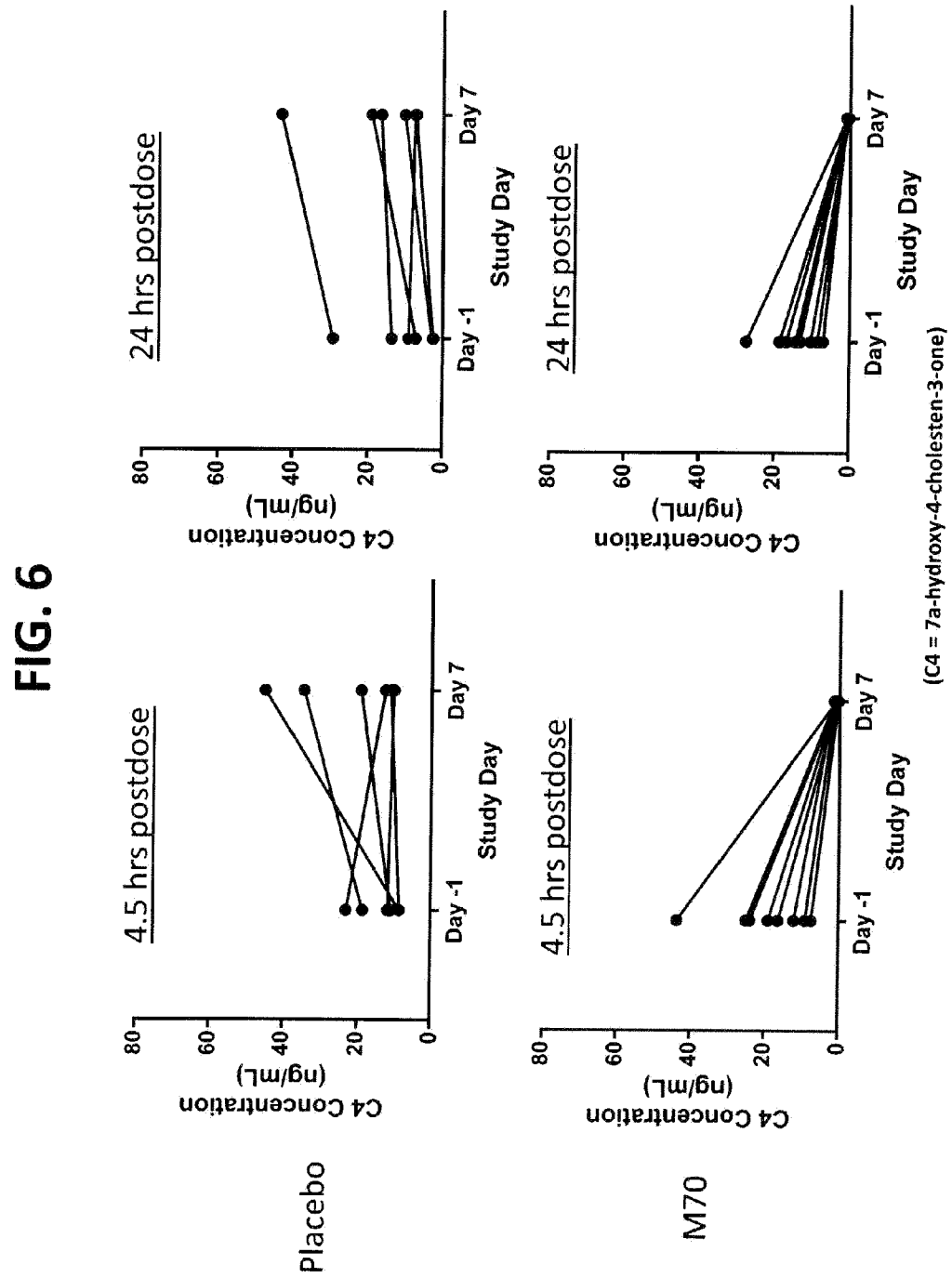
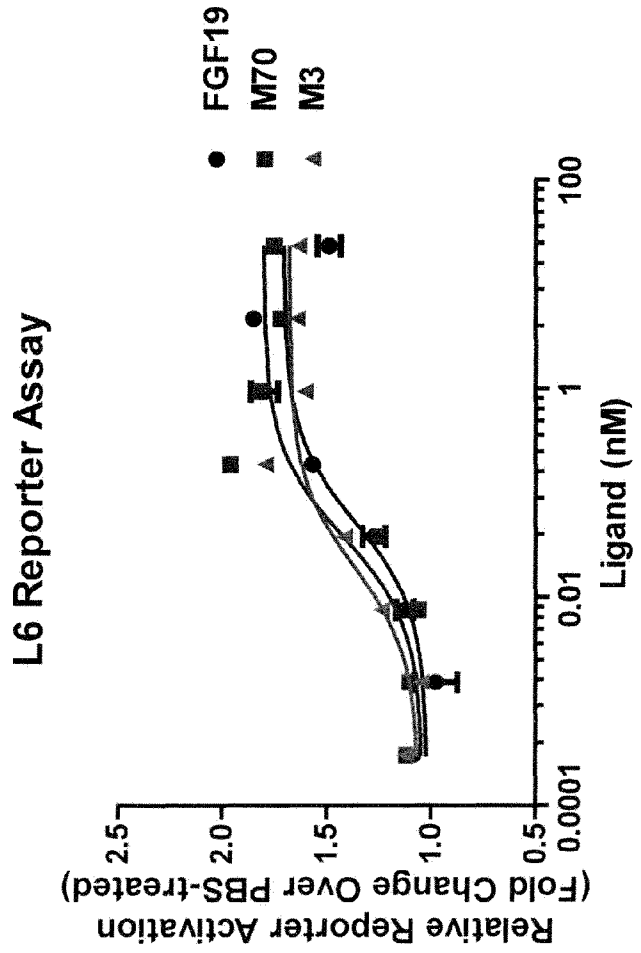

Placebo
M70
4.5 hrs postdose
24 hrs postdose
C4 Concentration (ng/mL)
0
20
40
60
80
Day -1
Day 7
Study Day
(C4 = 7a-hydroxy-4-cholesten-3-one)

FIG. 7


L6 Reporter Assay
Relative Reporter Activation
(Fold Change Over PBS-treated)
2.5
2.0
1.5
1.0
0.5
0.0001
0.01
1
100
Ligand (nM)
FGF19
M70
M3
EC50 (nM)
0.05246
0.03834
0.01979