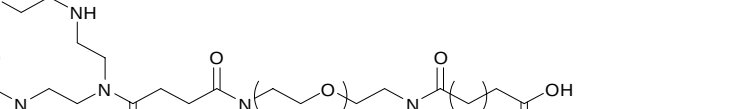


CROSS-REFERENCE

BACKGROUND OF THE INVENTION

SUMMARY OF THE INVENTION

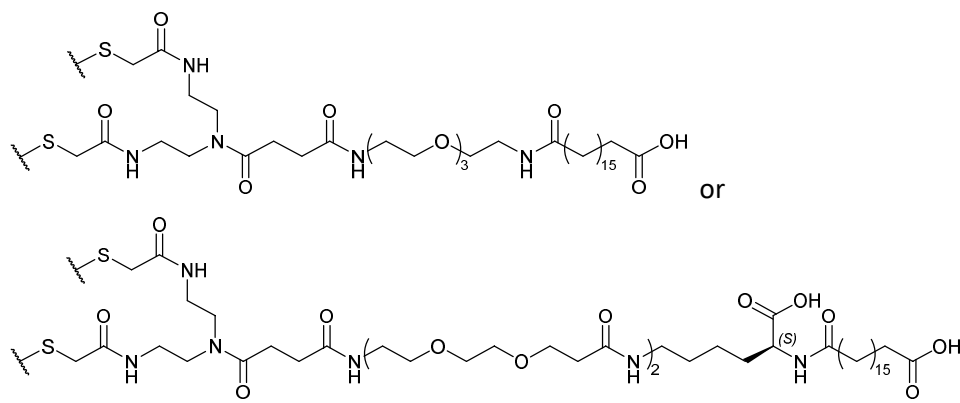


, or



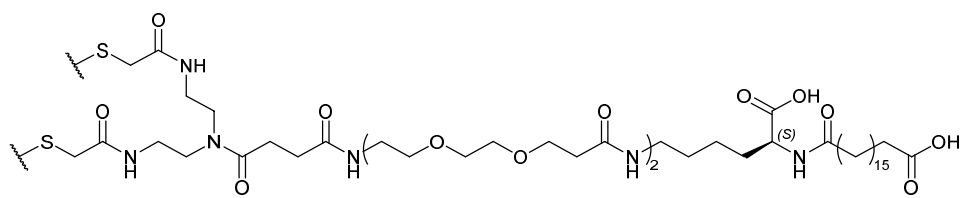
each “S” is a sulfur atom of the first cysteine or the second cysteine.

[0002b] In another aspect, the present disclosure refers to a peptide conjugate comprising: (a) a peptide comprising any one of SEQ ID NOs: 1-3 and 21-23; and (b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure:



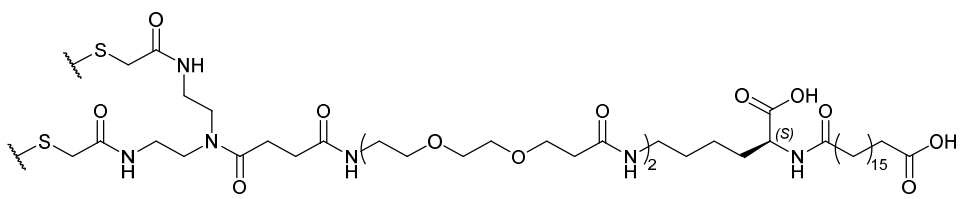
wherein each “S” is a sulfur atom of the first cysteine or the second cysteine.

[0002c] In another aspect, the present disclosure refers to a peptide conjugate comprising: (a) a peptide comprising SEQ ID NO: 1; and (b) a staple attached to the peptide at the first cysteine of SEQ ID NO: 1 and the second cysteine of SEQ ID NO: 1, wherein the staple has the following structure:



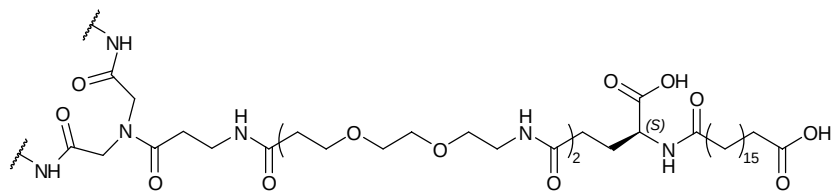
wherein each “S” is a sulfur atom of the first cysteine or the second cysteine.

[0002d] In another aspect, the present disclosure refers to a peptide conjugate comprising: (a) a peptide comprising SEQ ID NO: 2 or 22; and (b) a staple attached to the peptide at the first cysteine of SEQ ID NO: 2 or 22 and the second cysteine of SEQ ID NO: 2 or 22, wherein the staple has the following structure:



wherein each “S” is a sulfur atom of the first cysteine or the second cysteine.

[0002e] In another aspect, the present disclosure refers to a peptide conjugate comprising: (a) a peptide comprising SEQ ID NO: 30 or 10, wherein the amino acid at position 10 is L-Norleucine; and (b) a staple attached to the peptide at a first lysine and a second lysine having the following structure:



wherein each “NH” is an amine of the first lysine or the second lysine.

[0002f] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the peptide conjugate as described herein and a pharmaceutically acceptable excipient.

[0002g] In another aspect, the present disclosure refers to the peptide conjugate as described herein, for use as a medicament in treating a disease or condition in a subject in need thereof.

[0002h] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating diabetes or obesity, or a medical condition associated with diabetes or obesity.

[0002i] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.

[0002j] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating a gastrointestinal (GI) disorder.

[0002k] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein, in the manufacture of a medicament for a subject undergoing chemotherapy.

[0002l] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating radiation-induced GI mucositis.

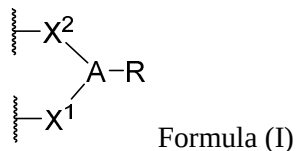
[0002m] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating chemotherapy-induced diarrhea (CID).

[0002n] In another aspect, the present disclosure refers to a use of the peptide conjugate as described herein in the manufacture of a medicament for treating total parenteral nutrition (TPN) induced intestinal atrophy.

[0003] Disclosed herein is a peptide conjugate comprising:

- a) a peptide that modulates the GLP-2 receptor; and
- b) a staple attached to the peptide at a first amino acid and a second amino acid.

[0004] In some embodiments, the staple is of Formula (I):



wherein

A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted -NR³-alkylene-NR³-, or -N-;

X¹ and X² are independently a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene, or -alkylene-C(=O)NR³-, -alkylene-C(=O)NR³-alkylene-;

wherein X¹ is attached to a first amino acid of the peptide, and X² is attached to a second amino acid of the peptide;

R is hydrogen or -(L)_s-Y;

each L is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)-alkylene-, -alkylene-C(=O)-, -NR³-alkylene-, -alkylene-NR³-, -S-alkylene-, -alkylene-S-, -S(=O)-alkylene-, -alkylene-S(=O)-, -S(=O)₂-alkylene-, -alkylene-S(=O)₂-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -NR³C(=O)NR³-, -NR³C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-NR³-, -alkylene-C(=O)NR³-, -C(=O)NR³-alkylene-, -alkylene-NR³C(=O)-, or -NR³C(=O)-alkylene-;

v is 2-20;

+ 3% H ₂ O ₂ + 100 mM Glutathione	92% Met oxidation	Good protection – a little degradation	Good protection – a little degradation
+ 3% H ₂ O ₂ + 0.27% m-cresol	No protection (100% degradation of the peptide)	No protection (100% degradation of the peptide)	No protection (100% degradation of the peptide)
+ 3% H ₂ O ₂ + 1.2 mg/mL NaMBS	92% Met oxidation	Good protection – a little degradation	Good protection – a little degradation

Example I: The long-term stability of the thioether peptides in liquid and in solid forms

[0367] The long-term stability of the thioether peptides was tested in this example.

[0368] The stability of the thioether peptides was measured against wet air oxidation. Met oxidation was observed for GLP2-2G-1-EX4-L5A after 10 days, with 16% degradation observed. GLP2-2G-10Nle-1-EX4-L5A was more stable against wet air oxidation. This indicated that the thioether bridge was stable against oxidation for at least 10 days.

[0369] The powder was stored at 4 C as an HCl salt. There was no sign of Met oxidation for GLP2-2G-1-EX4-L5A (GLP2-L5A) after 4 months. Likewise, there was no sign of Met oxidation for GLP2-2G-1-EX4-L5A (GLP2-L5A) after 7 months.

Example J: The stability of the long-acting GLP2R agonists at different pH values

[0370] The stability of the peptides was measured across a range of pH values and temperatures.

[0371] At pH 3.3 at room temperature, GLP2-2G-1-EX4-L5A (GLP2-L5A) was 100% stable over 4 days. GLP2-2G-10Nle-1K-EX4-K5 was also stable, with 95% of peptides remaining intact by 5 days, as depicted in **FIG. 6A**. GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were less stable at a pH of 3.3 and a temperature of 37 degrees than they were at room temperature, as depicted in **FIG. 6B**. At 37 °C, GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) underwent major hydrolysis at pH 3.4 (-18 Da and -775 Da). Additionally, GLP2-2G-1-EX4-L5A (GLP2-L5A) was not soluble at pH 4.6.

[0372] Both GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were 100% stable for 4 days at pH 7.5 at room temperature, as depicted in **FIG. 6C**. At 37C, GLP2-2G-10Nle-1K-EX4-K5 underwent 1-% degradation and L5A underwent 1% degradation, as depicted in **FIG. 6D**. Both GLP2-2G-10Nle-1K-EX4-K5 and GLP2-2G-1-EX4-L5A (GLP2-L5A) were 100% stable for 4 days at pH 8.9 at room temperature, as depicted in **FIG. 6E**. At 37°C and a pH of 8.9, GLP2-2G-10Nle-1K-EX4-K5 underwent 1-% degradation and GLP2-2G-1-EX4-L5A (GLP2-L5A) underwent 1% degradation, as depicted in **FIG. 6F**.

Example K: The stability of the long-acting GLP2R agonists in hepatocytes

[0373] The hepatocyte stability of the long-acting GLP2R agonists was measured over time. For GLP2-2G-1-EX4-L5A, both the mouse and the MC values were slightly over 100% after 120 minutes, as depicted in **FIG. 7A**. However, for both GLP2-2G-10Nle-1-EX4-L5A and GLP2-2G-10Nle-1K-EX4-

K5, while the mouse values increased to slightly over 100%, the MC values decreased to approximately 60% after 120 minutes, as depicted in **FIGs. 7B-7C**.

[0374] The biological half-lives ($T_{1/2}$) and the intrinsic clearance (CL_{int}) values were calculated for each peptide from the data, as listed in **Table 11**. GLP2-2G-1-EX4-L5A had the highest half-life and the lowest CL_{int} in both hepatocytes and in the liver. GLP2-2G-10Nle-1-EX4-L5A had the lowest half-life and GLP2-2G-10Nle-1-EX4-L5A had the highest CL_{int} values in both the hepatocytes and the liver.

Table 11: Half-lives and CL_{int} values in hepatocytes

Peptide	$T_{1/2}$ (min)	CL _{int} (hep) ($\mu\text{L}/\text{min}/10^6$)	CL _{int} (liver) ($\text{mL}/\text{min}/\text{kg}$)
GLP2-2G-1-EX4-L5A	>289	<4.8	<57
GLP2-2G-10Nle-1-EX4-L5A	153	9.1	107.6
GLP2-2G-10Nle-1K-EX4-K5	178	7.8	92.7

Example L: GLP2-2G-1-EX4-L5A exhibited an extended *in vivo* half-life in mouse

[0375] Male C57BL/6 mice were dosed with GLP2-2G-1-EX4-L5A at 1.5 mg/kg in PBS (pH 7.5, clear solution) and the plasma concentration of agonists was tracked for 96 hours, as depicted in **FIG. 8**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 20 ng/mL. These values were also used to calculate other pharmacokinetic properties of this compound in mice, both for administration of the drug via intravenous injection and subcutaneous injection, as depicted in **Table 12**. A long *in vivo* half-life of around 8.4 hours was observed, similar to the 8-hour half-life of semaglutide in rodents.

Table 12: Pharmacokinetics of GLP2-Met-L5A in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C_0 (ng/mL)	28956	C_{max} (ng/mL)	12933
$T_{1/2}$ (h)	8.37	T_{max} (h)	7.00
Vd_{ss} (L/kg)	0.0966	$T_{1/2}$ (h)	11.0
Cl (mL/min/kg)	0.152	T_{last} (h)	96.0
T_{last} (h)	72.0	$AUC_{0-\text{last}}$ (ng·h/mL)	183645
$AUC_{0-\text{last}}$ (ng·h/mL)	164199	$AUC_{0-\text{inf}}$ (ng·h/mL)	184007
$AUC_{0-\text{inf}}$ (ng·h/mL)	164585	$MRT_{0-\text{last}}$ (h)	13.7
$MRT_{0-\text{last}}$ (h)	10.4	$MRT_{0-\text{inf}}$ (h)	13.9
$MRT_{0-\text{inf}}$ (h)	10.6	AUC_{Extra} (%)	0.197
AUC_{Extra} (%)	0.235	$AUMC_{\text{Extra}}$ (%)	1.59
$AUMC_{\text{Extra}}$ (%)	1.86	Bioavailability (%) ^a	112

Example M: GLP2-2G-1-EX4-L5A exhibited an extended *in vivo* half-life in cyno monkey

[0376] Male cyno monkeys were dosed with GLP2-2G-1-EX4-L5A at 1.0 mg/kg in PBS (pH 7.5, clear solution) and the plasma concentration of agonists tracked for 504 hours, as depicted in **FIG. 9**. Pharmacokinetic properties of GLP2-2G-1-EX4-L5A were analyzed for drug delivers via an IV and via a subcutaneous injection, as listed in **Table 13**. Plasma concentration was analyzed using a LC-MS assay

with a lower limit of quantification of 10 ng/mL. A long *in vivo* half-life of approximately 70 hours was observed, longer than the approximately 50-hour half-life of semaglutide in monkey. This long *in vivo* half-life indicated that potential translation into once-weekly human dosing may be possible.

Table 13: Pharmacokinetic properties of GLP2-2G-1-EX4-L5A in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C ₀ (ng/mL)	34845	2087	C _{max} (ng/mL)	12100	1652
T _{1/2} (h)	68.7	8.05	T _{max} (h)	9.00	1.73
Vd _{ss} (L/kg)	0.0551	0.00244	T _{1/2} (h)	71.9	7.02
Cl (mL/min/kg)	0.0110	0.000748	T _{last} (h)	504	--
T _{last} (h)	504	--	AUC _{0-last} (ng·h/mL)	1102126	157113
AUC _{0-last} (ng·h/mL)	1507007	103313	AUC _{0-inf} (ng·h/mL)	1109413	158218
AUC _{0-inf} (ng·h/mL)	1514090	105816	MRT _{0-last} (h)	90.0	4.40
MRT _{0-last} (h)	80.8	2.53	MRT _{0-inf} (h)	93.4	3.07
MRT _{0-inf} (h)	83.2	3.31	AUC _{Extra} (%)	0.658	0.252
AUC _{Extra} (%)	0.462	0.147	AUMC _{Extra} (%)	4.34	1.80
AUMC _{Extra} (%)	3.33	1.01	Bioavailability (%) ^a	73.3	--

Example N: GLP2-2G-10Nle-1-EX4-L5A exhibited a long *in vivo* half-life in mice

[0377] Male C57BL/6 mice were dosed with GLP2-2G-10Nle-1-EX4-L5A at a concentration of 1.5 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 96 hours after administration of the drug, as depicted in **FIG. 10**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5ng/mL. The pharmacokinetic properties of the drug in mice, including the half-life, was calculated from this data and values are listed in **Table 14**. A long *in vivo* half-life of approximately 8 hours was observed for this drug in mice.

Table 14: Pharmacokinetic properties of GLP2-2G-10Nle-1-EX4-L5A in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C ₀ (ng/mL)	40492	C _{max} (ng/mL)	8963
T _{1/2} (h)	8.07	T _{max} (h)	7.0
Vd _{ss} (L/kg)	0.0823	T _{1/2} (h)	7.97
Cl (mL/min/kg)	0.129	T _{last} (h)	96
T _{last} (h)	96.0	AUC _{0-last} (ng·h/mL)	153773
AUC _{0-last} (ng·h/mL)	193243	AUC _{0-inf} (ng·h/mL)	153830
AUC _{0-inf} (ng·h/mL)	193309	MRT _{0-last} (h)	14.3
MRT _{0-last} (h)	10.6	MRT _{0-inf} (h)	14.3
MRT _{0-inf} (h)	10.6	AUC _{Extra} (%)	0.0369
AUC _{Extra} (%)	0.034	AUMC _{Extra} (%)	0.277
AUMC _{Extra} (%)	0.345	Bioavailability (%) ^a	79.6

Example O: GLP2-2G-10Nle-1-EX4-L5A exhibited an extended half-life in cyno monkeys

[0378] Male cyno monkeys were dosed with GLP2-2G-10Nle-1-EX4-L5A at a concentration of 1.0 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of

agonists was tracked for 504 hours after administration of the drug, as depicted in **FIG. 11**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5ng/mL. The pharmacokinetic properties of the drug in monkeys, including the half-life, was calculated from this data, and values are listed in **Table 15**. A long *in vivo* half-life of approximately 57 hours was observed for this drug in monkeys.

Table 15: Pharmacokinetic properties of GLP2-2G-10Nle-1-EX4-L5A in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C ₀ (ng/mL)	30072	203	C _{max} (ng/mL)	9313	783
T _{1/2} (h)	57.2	7.89	T _{max} (h)	14.7	8.08
Vd _{ss} (L/kg)	0.0784	0.00189	T _{1/2} (h)	49.8	4.72
Cl (mL/min/kg)	0.0231	0.00446	T _{last} (h)	504	--
T _{last} (h)	504	--	AUC _{0-last} (ng·h/mL)	696366	72381
AUC _{0-last} (ng·h/mL)	737816	129904	AUC _{0-inf} (ng·h/mL)	696916	72842
AUC _{0-inf} (ng·h/mL)	738632	130076	MRT _{0-last} (h)	66.5	5.12
MRT _{0-last} (h)	57.2	8.94	MRT _{0-inf} (h)	66.9	5.41
MRT _{0-inf} (h)	57.8	8.94	AUC _{Extra} (%)	0.0751	0.0576
AUC _{Extra} (%)	0.110	0.0165	AUMC _{Extra} (%)	0.626	0.436
AUMC _{Extra} (%)	1.14	0.247	Bioavailability (%) ^a	94.4	--

Example P: GLP2-2G-10Nle-1K-EX4-K5 exhibited a long *in vivo* half-life in mice

[0379] Male C57BL/6 mice were dosed with GLP2-2G-10Nle-1K-EX4-K5 at a concentration of 1.5 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 72 hours after administration of the drug, as depicted in **FIG. 12**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5ng/mL. The pharmacokinetic properties of the drug in mice, including the half-life, was calculated from this data, and values are listed in **Table 16**. A long *in vivo* half-life of approximately 7 hours was observed for this drug in mice.

Table 16: Pharmacokinetic properties of GLP2-2G-10Nle-1K-EX4-K5 in mice

PK Parameters	Mean IV	PK Parameters	Mean SC
C ₀ (ng/mL)	24574	C _{max} (ng/mL)	6760
T _{1/2} (h)	7.16	T _{max} (h)	7.0
Vd _{ss} (L/kg)	0.102	T _{1/2} (h)	7.54
Cl (mL/min/kg)	0.173	T _{last} (h)	72.0
T _{last} (h)	72.0	AUC _{0-last} (ng·h/mL)	104199
AUC _{0-last} (ng·h/mL)	144060	AUC _{0-inf} (ng·h/mL)	104404
AUC _{0-inf} (ng·h/mL)	144210	MRT _{0-last} (h)	12.3
MRT _{0-last} (h)	9.71	MRT _{0-inf} (h)	12.5
MRT _{0-inf} (h)	9.79	AUC _{Extra} (%)	0.196
AUC _{Extra} (%)	0.104	AUMC _{Extra} (%)	1.3
AUMC _{Extra} (%)	0.875	Bioavailability (%) ^a	72.4

Example Q: GLP2-2G-10Nle-1K-EX4-K5 exhibited an extended half-life in cyno monkeys

[0380] Male cyno monkeys were dosed with GLP2-2G-10Nle-1K-EX4-K5 at a concentration of 1.0 mg/kg in PBS (pH 7.5), either subcutaneously (SC) or intravenously (IV). The plasma concentration of agonists was tracked for 504 hours after administration of the drug, as depicted in **FIG. 13**. Plasma concentration was analyzed using a LC-MS assay with a lower limit of quantification of 5ng/mL. The pharmacokinetic properties of the drug in monkeys, including the half-life, was calculated from this data, as listed in **Table 17**. A long *in vivo* half-life of approximately 36 hours was observed for this drug in monkeys.

Table 17: Pharmacokinetic properties of GLP2-2G-10Nle-1K-EX4-K5 in cyno monkeys

PK Parameters	Mean IV	SD	PK Parameters	Mean SC	SD
C ₀ (ng/mL)	27532	4270	C _{max} (ng/mL)	7037	626
T _{1/2} (h)	35.7	1.09	T _{max} (h)	14.7	8.08
Vd _{ss} (L/kg)	0.0723	0.00438	T _{1/2} (h)	31.0	2.5
Cl (mL/min/kg)	0.0294	0.00532	T _{last} (h)	336	--
T _{last} (h)	336	--	AUC _{0-last} (ng·h/mL)	420263	21246
AUC _{0-last} (ng·h/mL)	577542	97811	AUC _{0-inf} (ng·h/mL)	420590	21369
AUC _{0-inf} (ng·h/mL)	578146	98047	MRT _{0-last} (h)	48.7	4.79
MRT _{0-last} (h)	41.2	4.65	MRT _{0-inf} (h)	48.9	4.88
MRT _{0-inf} (h)	41.5	4.75	AUC _{Extra} (%)	0.0768	0.0257
AUC _{Extra} (%)	0.101	0.0367	AUMC _{Extra} (%)	0.590	0.140
AUMC _{Extra} (%)	0.932	0.271	Bioavailability (%) ^a	72.7	--

Example R: GLP2-L5A produced intestinotrophic effects in mice

[0381] 13 week old female CD1 mice were divided into 5 treatment groups as listed: A (Vehicle PBS, SC, QD), B (GLP-C14, 0.05 mg/kg, BID), C (GLP2-2G-1-EX4-L5A, 0.1 mg/kg, QD), D (GLP2-2G-1-EX4-L5A, 1 mg/kg, QD), E (GLP2-2G-10Nle-1-EX4-L5A, 0.1 mg/kg, QD), and F (GLP2-2G-10Nle-1-EX4-L5A, 1 mg/kg, QD). 5 mice were in each group. The mice were administered the relevant dose subcutaneously either daily (QD) or twice a day (BID) using DPBS as the vehicle in a volume of 5 mL/kg and then monitored daily for bodyweight,

[0382] At 10 days after administration of the dose, GI tract measurements were collected. These measurement included collecting terminal bleed; dissecting out the small intestine; and measuring the length and weight of the small intestine; recording the length and weight of the empty large intestine.

[0383] There was a significant increase in the weight of the small intestine in treated mice that received a dose of at least 0.1 mg/kg of either long-acting GLP2R agonist (groups C-F) when compared to untreated mice (group A), as depicted in **FIG. 14A**. The length of the small intestine was increased in all mice that received long-acting GLP2R agonist treatment when compared to untreated mice (group A), and significantly increased in mice that received a treatment of 0.1 mg/kg of GLP2-2G-5-L5A (group E), as depicted in **FIG. 14B**. No treatment groups produced a significant change in bodyweight over 10 days, as depicted in **FIG. 14C**.

Example S: GLP2-2G-10Nle-1-EX4-L5A was effective in treating a mouse model of acute colitis

[0384] This example assessed the intestinotrophic effects of GLP2-2G-10Nle-1-Ex4-L5A in mice.

[0385] 7-8 week old male C57B6 mice were grouped into 6 experimental groups: A (Vehicle PBS, QD); B (teduglutide, 0.5 mg/kg, BID); C (GLP2-2G-10Nle-1K-EX4-K5, 0.03 mg/kg, QD); D (GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg, QD); E (GLP2-2G-10Nle-1K-EX4-K5, 0.3 mg/kg, QD); and F (GLP2-2G-10Nle-1K-EX4-K5, 1 mg/kg, QD). Each treatment group contained 6 mice, except for group A, which contained 4. Mice were administered the treatment subcutaneously either once daily (QD) or twice daily (BID), using FPBS as a vehicle with a dosing volume of 5mL/kg. Bodyweight was monitored daily and after 10 days of dosing, GI tract measurements were collected. These measurement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0386] As depicted in **FIGs. 15C-15D**, all treatment groups (B-F) resulted in a significant increase in small intestine lengths and weights when compared to control groups. Even the lowest dose of GLP2-2G-10Nle-1K-EX4-K5, at 0.03 mg/kg (group C), produced significant effects on both measurements of the small intestine. Furthermore, the 0.1 mg/kg dose of GLP2-2G-10Nle-1-EX4-K5 (group D) showed comparable effects to treatment with teduglutide at 0.5mg/kg (group B).

[0387] Mice that received high doses of GLP2-2G-10Nle-1-EX4-K5 (groups E-F), showed significant increases in the length of the colon when compared to untreated controls (group A). All treatment groups showed a significant increase in colon weight when compared to untreated controls. However, the mice in groups E and F treated with the highest doses of GLP2-2G-10Nle-1-EX4-K5 showed the greatest increase.

Example T: GLP2-2G-1-EX4-L5A was effective in treating a mouse model of acute colitis

[0388] Acute colitis was induced in mice by a single 5-day treatment course with 3% dextran sodium sulfate (DSS). Mice were divided into 4 treatment groups as listed: A (control mice that received no DSS), B (mice that received DSS and a subcutaneous injection of PBS), C (mice that received DSS and a 1mg/kg subcutaneous treatment of GLP2-2G-1-EX4-L5), and D (mice that received DSS and a intraperitoneal treatment of 20 mg/kg of cyclosporin).

[0389] The body weight was measured over 12 days, as depicted in **FIG. 16A**. Mice that received treatment for acute colitis (groups C and D) did not have as great of a decrease in bodyweight when compared to untreated mice with induced colitis (group B). Additionally, mice in group C treated with GLP2-2G-1-EX4-L5A showed a significant increase in both colonic and small intestinal weight, as depicted in **FIGs. 16B-16C**, compared to untreated mice with induced acute colitis (group B). Mice that were treated with GLP2-2G-1-EX4-L5A also showed significant increases in the length of both the colon and the small intestine when compared to untreated controls with induced acute colitis (figure not shown). Treatment with GLP2-2G-1-EX4-L5A also improved the colon and small intestine histopathology in the DSS-induced colitis model. The histopathology of mice that received both DSS and L5A showed a similar crypt depth in the colon as mice that did not received DSS treatment, while mice

that received only DSS had a significant reduction in crypt length, as depicted in **FIG. 16D**. In the jejunal small intestine, the length of jejunum villi was greater in group C mice than in either group A or group B mice, as depicted in **FIG. 16E**. There was a significant increase in the length of the jejunum villi when comparing mice treated with GLP2-2G-1-EX4-L5A to untreated mice. Additionally, the group C mice did not show the villous distortion and abscesses exhibited by the group B mice.

Example U: GLP2-2G-10Nle-1K-EX4-K5 was effective in treating a mouse model of acute colitis

[0390] 8 week old male C57BL/6 mice were divided into 7 treatments groups as listed: A (control mice that received no DSS), B (mice that received DSS and a subcutaneous injection of PBS), C (mice that received DSS and a 0.1 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5), D (mice that received DSS and a 0.3 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5), E (mice that received DSS and a 1 mg/kg subcutaneous treatment of GLP2-2G-10Nle-1K-EX4-K5), F (mice that received DSS and a 0.5 mg/kg subcutaneous treatment of teduglutide), and G (mice that received DSS and a IP treatment of 20 mg/kg of cyclosporin). Each group contained 6 mice, except for group A, which contained 4.

Acute colitis was induced in the mice by a single 5-day treatment course with 3% dextran sodium sulfate (DSS), as depicted in **FIG. 17A**. The animals were treated daily for 11 days with the appropriate dose per treatment group. The body weight was monitored daily. If animals lost more than 20% of their bodyweight, they were euthanized. On days 10-11, samples were collected for pharmacokinetic analysis at 0, 1, 3, 7 and 24 hours after the dose was administered. On day 11, animals were euthanized, and a necropsy was performed. The terminal bleed was collected into a heparinized collection tube and processed into plasma. The small intestine and colon were collected to measure weight and length. GI tissues were collected for histology.

[0391] When examining bodyweight over time, as depicted in **FIG. 17A**, mice in group G treated with cyclosporine showed a greater percent decrease in bodyweight during the DSS treatment than mice in any other treatment groups, but bodyweight increased after DSS treatment ended. Mice that received DSS and no treatment (group B) showed the greatest percent decrease in bodyweight after DSS treatment had ended when compared to all other treatment groups. Mice that had been treated with either GLP2-2G-10Nle-1K-EX4-K5 (groups C-E) or with teduglutide (group F), along with mice that did not received DSS (group A) did not exhibit significant changes in bodyweight during this time.

[0392] Treatment with GLP2-2G-10Nle-1K-EX4-K5 protected the mice both from loss of bodyweight and restored colon shortening. As shown in **FIG. 17B**, Colon length was significantly increased in mice that received high doses of GLP2-2G-10Nle-1K-EX4-K5 or teduglutide (groups D-F), compared to untreated groups (group B). There was no change in colon weight. In the small intestine, both the length and weight were significantly increased in groups that had received either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 (groups C-F) compared to untreated mice, as depicted in **FIGs. 17C-17D**. The lowest dose of GLP2-2G-10Nle-1K-EX4-K5 at 0.1 mg/ml (group C), showed comparable effects to teduglutide at 0.5 mg/kg BID.

[0393] Treatment with GLP2-2G-10Nle-1K-EX4-K5 also affected the histological features of the intestines. All teduglutide and GLP2-2G-10Nle-1K-EX4-K5 treatment groups (groups C-F) showed a significant increase in villus height compared to untreated mice (groups A-B), as seen in **FIG. 17E**. The lowest dose of GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg, administered once daily, showed comparable intestinotrophic effects to Teduglutide at 0.5 mg/kg, administered twice daily.

Furthermore, Ki67 staining showed that there was no increased proliferation in any of the treatment groups, as depicted in **FIG. 17F**. This showed that there was no evidence of abnormal proliferation associated with GLP2-2G-10Nle-1K-EX4-K5 treatment.

[0394] The pharmacokinetic properties of treatment groups C-F are plotted in **FIG. 17G**. Teduglutide was not detectable after 3 hours post treatment. However, all doses of GLP2-2G-10Nle-1K-EX4-K5 were detectable at up to 24 hours after treatment.

Example V: The long-acting GLP2R agonists were effective in treating acute colitis

[0395] Mice were divided into 9 treatment groups as listed: A (Non-DSS: Vehicle), B (DSS: Vehicle (PBS)), C (DSS: GLP2-2G-1-EX4-L5A, 0.03 mg/kg), D (DSS: GLP2-2G-1-EX4-L5A, 0.1 mg/kg), E (DSS: GLP2-2G-10Nle-1-EX4-L5A, 0.03 mg/kg), F (DSS: GLP2-2G-10Nle-1-EX4-L5A, 0.1 mg/kg), G (DSS: GLP2-2G-10Nle-1K-EX4-K5, 0.03 mg/kg), H (DSS: GLP2-2G-10Nle-1K-EX4-K5, 0.1 mg/kg), and I (DSS: Cyclosporine A, 20 mg/kg, IP). Each group contain 6 C57BL/6 male mice aged 8 weeks. Mice were dosed with 3% DSS for 7 days and concurrently dosed with the appropriate treatment for 8 days to induce acute colitis. The animals were all dosed subcutaneously using a volume of 5ml/kg and a vehicle of DPBS, with the except of group I, where the vehicle was olive oil. At days 6-7, pharmacokinetic samples were collected from groups C-H at 0, 1, 3, 7 and 24 hours after dosing. Measurements were taken at day 9. These measurement included collecting the terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0396] All long-acting GLP-2 agonists showed a dose-related protection from body weight loss compared to untreated animals, and this protection was significant at a dose of 0.1 mg/kg. As depicted in **FIG. 18A**, animals treated with either dose of GLP2-2G-10Nle-1-Ex4-L5A (groups C, D) had a greater overall bodyweight than those who received no treatment (group B). As depicted in **FIG. 18B**, animals treated with either dose of GLP2-2G-1-EX4-L5A (groups E,F) had a greater overall bodyweight than those who received no treatment (group B). As depicted in **FIG. 18C**, animals treated with either dose of GLP2-2G-10Nle-1K-Ex4-K5A (groups G,H) had a greater overall bodyweight than those who received no treatment (group B). Furthermore, at a dose of 0.03 mg/kg, GLP2-2G-10Nle-1-Ex4-L5A and GLP2-2G-10Nle-1K-Ex4-K5 were more effective at protecting from bodyweight loss than GLP2-2G-1-EX4-L5A.

[0397] All 3 long acting-GLP-2 agonists increased colon length significantly in the acute DSS-induced colitis model at 0.1 mg/kg, as depicted in **FIG. 18D**. Furthermore, there was a non-significant increasing trend on colon weight when comparing animals treated with long-acting GLP2 agonists to the untreated

DSS animals, as depicted in **FIG. 18E**. Furthermore, all 3 long-acting GLP2 agonists showed dose-related trophic effects on both the weight and length of the small intestine, as depicted in **FIGs 18F-18G**.

[0398] Treatment with GLP2R agonists also increased the size of the gall bladder, as depicted in **FIG. 18H**. Additionally, the quantity of fecal occult blood was measured using a hemocult II test, as depicted in **FIG. 18I**. Several treatment parameters, such as both doses of 1L5A, decreased the hemocult levels compared to the untreated DSS model mice.

[0399] The levels of the long-acting GLP2 agonists were measured over time. At doses of 0.03 mg/kg, the concentrations increased until 7 hours after administration but were still detectable at 24 hours after administration, as depicted in **FIG. 18J**. At doses of 0.1 mg/kg, the concentrations increased until 7 hours after administration and were still detectable at 24 hours after administration, as depicted in **FIG. 18K**. For both doses, GLP2-2G-1-EX4-L5A had the highest levels present, followed by GLP2-2G-10Nle-1-Ex4-L5A, then GLP2-2G-10Nle-1K-Ex4-K5. For all three drugs tested, the higher dose resulted in higher concentrations of the drug present at all tested time points, as depicted in **FIGs. 18L-18N**.

[0400] Significant reduction of mRNA level for inflammatory cytokines was observed in colon tissues.

Example W: GLP2-2G-1-EX4-L5A was effective in treating chronic colitis

[0401] Chronic DSS-induced colitis was induced in C57BL/6 mice (male, age 10-12 weeks) by 3 cycles of administration of 2.5% DSS in drinking water for 5 consecutive days, followed by 7 days of recovery. Animals were treated daily for 7 days during the last DSS-induction cycle. Treatment was administered either subcutaneously (S) or intraperitoneally (IP) either once daily (QD) or twice daily (BID). Mice were treated according to their treatment groups as listed: A (Non-DSS: Vehicle, SC, QD (n = 6)), B (DSS: Vehicle (PBS), SC, QD (n = 8)), C (DSS: GLP2-2G-1-EX4-L5A, 0.1 mg/kg, SC, QD (n = 8)), D (DSS: GLP2-2G-1-EX4-L5A, 0.3 mg/kg, SC, QD (n = 8)), E (DSS: Cyclosporin, 20 mg/kg, IP (n = 6)), and F (DSS: Teduglutide, 0.3 mg/kg, SC, QD (n = 6)).

Bodyweight was monitored 3 times a week. Pharmacokinetic collection occurred 3 and 4 days prior to necropsy. At day 33, a necropsy was performed, and measurements were taken. These measurement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0402] GLP2-2G-1-EX4-L5A was effective in treating weight loss in a mouse model of chronic colitis. The mice which were treated with GLP2-2G-1-EX4-L5A or teduglutide (groups C, D and F) did not show the same loss in percent of bodyweight or in overall bodyweight as seen in untreated mice (group B), as depicted in **FIG. 19A**. The protection from bodyweight loss was dose dependent, with the higher dose resulting in increased protection. Additionally, these effects were equivalent to teduglutide treatment at 0.3mg/kg, QD.

[0403] GLP2-2G-1-EX4-L5A showed a dose-related restoration of colon length when compared to mice that received no treatment, as depicted in **FIG. 19B**. Furthermore, when comparing the 0.3 mg/kg GLP2-2G-1-EX4-L5A treatment to the equivalent dose of teduglutide, the effects of GLP2-2G-1-EX4-L5A were less variable than the effects of teduglutide treatment. Colon weight was also affected by GLP2-2G-

1-EX4-L5A and teduglutide treatment, as seen in **FIG. 19C**. Mice treated with the low dose of GLP2-2G-1-EX4-L5A has a similar colon weight as those treated with teduglutide.

[0404] The higher dose of GLP2-2G-1-EX4-L5A showed a significant increase in small intestinal weight compared to mice that received no treatment, as depicted in **FIG. 19D**. This effect was equivalent to the effect produced by teduglutide.

Example X: GLP2-2G-10Nle-1-Ex4-L5A was effective in treating a mouse model of chronic colitis

[0405] Chronic DSS-induced colitis was induced in C57BL/6 mice (male, age 10-12 weeks) by 3 cycles of administration of 2.5% DSS in drinking water for 5 consecutive days, followed by 7 days of recovery. Animals were treated daily for 7 days during the last DSS-induction cycle. Treatment was administered either subcutaneously (S) or intraperitoneally (IP) either once daily (QD) or twice daily (BID). Mice were treated according to their treatment groups as listed: A (Non-DSS: Vehicle, SC, QD (n = 4)), B (DSS: Vehicle (PBS), SC, QD (n = 6)), C (DSS: GLP2-2G-10Nle-1-L5A, 0.03 mg/kg, SC, QD (n = 6)), D (DSS: GLP2-2G-10Nle-1-L5A, 0.1 mg/kg, SC, QD (n = 6)), E (DSS: GLP2-2G-10Nle-1-L5A, 0.3 mg/kg, SC, QD (n = 6)), F (DSS: GLP2-2G-10Nle-1-L5A, 1 mg/kg, SC, QD (n = 6)), and G (DSS: Teduglutide, 0.5 mg/kg, SC, BID (n = 6)).

[0406] Bodyweight was monitored 3 times a week. Pharmacokinetic collection occurred 3 and 4 days prior to necropsy. At day 33, a necropsy was performed, and measurements were taken. These measurement included collecting terminal bleed; dissecting out the small intestine; measuring the length and weight of the small intestine; and recording the length and weight of the empty large intestine.

[0407] Low doses of GLP2-2G-10Nle-1-Ex4-L5A showed modest effects on body weight loss. Treatment with doses of 0.03 mg/kg and 0.3 mg/kg was protective against bodyweight loss when compared to mice that received no treatment. (figure not shown).

[0408] GLP2-2G-10Nle-1-Ex4-L5A increased both colon length and weight in a chronic DSS-induced colitis model, as depicted in **FIGs. 20A-20B**. Colon length was significantly increased in animals treated with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.1 mg/kg and higher, as well as animals treated with teduglutide (groups D-G), when compared to untreated animals (group B). Colon weight was increased in animals treated with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.3mg/kg or higher, as well as in animals treated with teduglutide, compared to untreated animals.

[0409] GLP2-2G-10Nle-1-Ex4-L5A also significantly affected the small intestine weight and length. Treatment with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.1mg/kg and higher, as well as treatment with teduglutide, resulted in significant increases in small intestine length compared to untreated mice models, as depicted in **FIG. 20C**. Treatment with GLP2-2G-10Nle-1-Ex4-L5A at doses of 0.3 mg/kg or higher resulted in significant increases in small intestine weight compared with untreated mice (not depicted).

Example Y: GLP-2-2G-5-L5A treatment in a NASH model

[0410] 5-week-old C57BL/6 mice were place on either a choline-deficient diet (CDAA, Dyets #518753) or an AA supplemented control diet (CSAA, Dyets # 518754) for a total of 19 weeks. Mice were divided into 3 treatment groups, with 8 mice per group, as listed: a CSAA control diet, treated with vehicle only;

a CDAA diet treated with vehicle (MCT, PO; saline, SC); and a CDAA diet treated with 1 mg/kg subcutaneously of GLP2-2G-5-EX4-L5A. After 15 weeks, the mice were treated with either vehicle or compounds for 4 weeks. Body weight was monitored weekly during the diet induction phase and 3 times a week during the treatment phase. After 19 weeks, the animals were euthanized, and terminal blood and liver samples were harvested for serum panels, histology, and gene expression.

[0411] Chronic treatment with GLP2-2G-5-EX4-L5A improved markers of liver function. In mice that had been fed a choline-deficient diet, there was a significant decrease in both serum ALT and serum AST compared to untreated mice on the same diet, as depicted in **FIGs 21A-21B**. Total serum bilirubin was also decreased in mice that had received GLP2-2G-5-EX4-L5A treatment compared to untreated mice with the same diet. The gall bladder was enlarged in 7/8 of GLP-2 treated mice.

Treatment with GLP2-2G-5-EX4-L5A resulted in a 20% decrease in the liver fibrosis score, as depicted in **FIG. 21C**. Collagen deposition/fibrosis was observed with picosirius red and was graded for severity using the following scale: 0 = absent; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; and 5 = severe. There were no significant effects on body weight with this treatment, indicating that the treatment was tolerated.

[0412] The effects of this treatment on hepatic steatosis and inflammation were also analyzed. Steatosis was analyzed by the percent of hepatocyte vacuolization determined by crisp, round, non-staining lipid vacuoles and assigned a grade based on the listed scale: 0 indicates less than 5%; 1 indicates 5-33%; 2 indicates 33 – 66%; and 3 indicates greater than 66%. Treatment with GLP2-2G-5-EX4-L5A did not significantly affect the steatosis grade in the liver, as depicted in **FIG. 21D**. Lobular inflammation was analyzed by assessment of inflammatory foci for infiltrates of neutrophils, lymphocytes and macrophages. Lobular inflammation was scored using the following scale: 0 indicates no foci; 1 indicates 2 foci/200x field; 2 indicates 2-4 foci/200x field; and 3 indicates more than 4 foci/200x field. Treatment with GLP-2-2G-5-L5A decreased the levels of lobular inflammation compared to untreated animals on the CDAA diet, as depicted in **FIG. 21E**.

This example showed that treatment with GLP2-2G-5-EX4-L5A improved markers of liver injury and prevented worsening of liver fibrosis in a CDAA-NASH model.

Example Z: Long-acting GLP2 agonists treat a mouse model of environmental enteric dysfunction (EED)

[0413] A weaning undernutrition model was used to assess the ability of GLP2-2G-10Nle-1K-EX4-K5 to treat environmental enteric dysfunction (EED). All dams were placed on an isocaloric Northeast Brazil (Regional Basic Diet-RBD), which was moderately deficient in protein, fat and minerals when their pups were 10 days old. At weaning (3 weeks of age), pups were placed on either a standard control diet (CD) or continued on RBD. At 4 weeks of age, weanlings were given drug or placebo (0.1mg/kg formulated in PBS (vehicle)) once a day subcutaneously for 2-3 weeks. Bodyweight and food consumption were measured twice weekly. Stool was collected at weaning, 6 weeks of age, and 8 weeks of age for calorimetry and microbiome. Oral FITC-dextran was used as a measurement of barrier function. At 6

weeks of age, mice were euthanized, and jejunal tissue was collected for morphology, immunohistochemistry, and for chamber analysis of transmucosal resistance and permeability.

There were trends towards greater weight gain in both male and female RBD mice weaned to CD and treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5, as depicted in **FIG. 22A-22B**. However, male and female mice weaned to RBD showed trends towards worsening weight when administered teduglutide or long-acting GLP2 agonist, as depicted in **FIG. 22C-22D**.

[0414] Treatment with both teduglutide and long-acting GLP2 agonists had profound effects on intestinal wet weights and lengths. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated males, as depicted in **FIG. 22E**. CD females treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated females, as depicted in **FIG. 22F**. Furthermore, treatment with GLP2-2G-10Nle-1K-EX4-K5 also resulted in a significant increase when compared to treatment with teduglutide. RBD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet body weight/body weight compared to untreated males. In RBD females, only animals treated with GLP2-2G-10Nle-1K-EX4-K5 showed a significant increase in the small intestine wet weight/bodyweight compared to that of untreated animals.

For both animals weaned to a CD diet and animals weaned to an RBD diet, treatment with either GLP2 or teduglutide resulted in a significant increase in the length of the small intestine when compared to that of untreated animals.

[0415] Treatment with GLP2-2G-10Nle-1K-EX4-K5 also had intestinotrophic effects on the animals. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 had significantly longer villus heights than untreated males. CD females treated with GLP2-2G-10Nle-1K-EX4-K5 also had significantly longer villus lengths than untreated females. The crypt depth of treated and untreated CD animals. Males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 had longer crypt depths than untreated males.

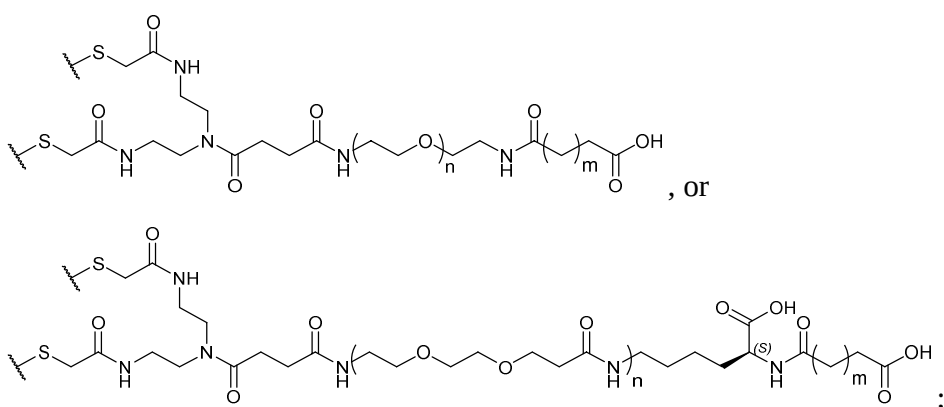
[0416] The intestinal permeability was also measured in these mice, where the greater the FITC-dextran relative fluorescence, the greater the intestinal permeability. CD males treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a trend towards decreased permeability in treated mice compared to untreated mice. CD females treated with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 showed a significant decreases in permeability when compared to untreated CD female mice. Treatment with either teduglutide or GLP2-2G-10Nle-1K-EX4-K5 did not significantly affect the permeability of either RBD females or RBD males when compared to untreated mice.

[0417] Untreated CD mice showed higher levels of intestinal permeability than untreated RBD mice. CD and RBD mice had similar overall levels of permeability when treated with teduglutide. Female might had slightly high levels of permeability when treated with GLP2-2G-10Nle-1K-EX4-K5 when compared to male mice on the same diet.

CLAIMS

What is claimed is:

1. A peptide conjugate comprising:
 - a) a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1-9 and 21-29, or an amino acid sequence having one amino acid addition, deletion, or substitution relative to a sequence selected from the group consisting of SEQ ID NO: 1-9 and 21-29; and
 - b) a staple attached to the peptide at a first cysteine and a second cysteine, wherein the first cysteine has a position i in the peptide and the second cysteine has a position $i + 7$ in the peptide, wherein the staple is:



wherein

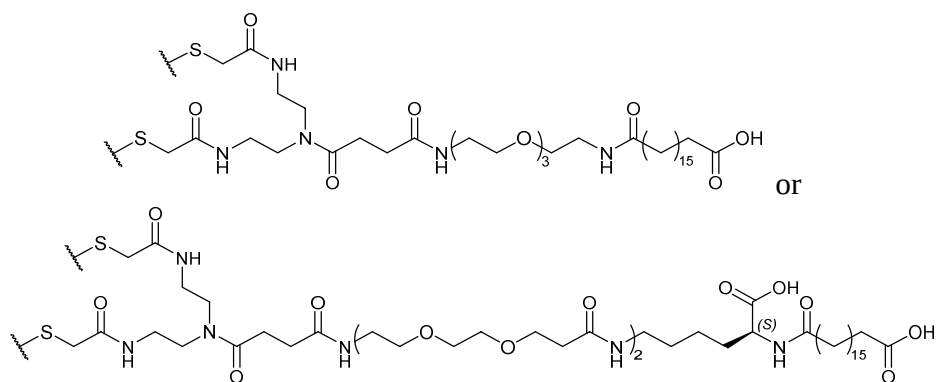
n is 1-4;

m is 6-20; and

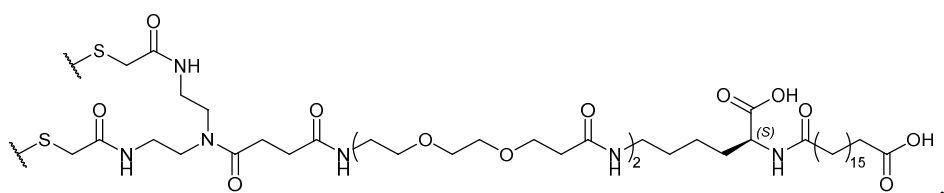
each "S" is a sulfur atom of the first cysteine or the second cysteine.

2. The peptide conjugate of claim 1, wherein the half-life of the peptide conjugate is at least 2-fold greater than the half-life of an unmodified form of the peptide.
3. The peptide conjugate of claim 1, wherein the half-life of the peptide conjugate is at least 5-fold greater than the half-life of an unmodified form of the peptide.

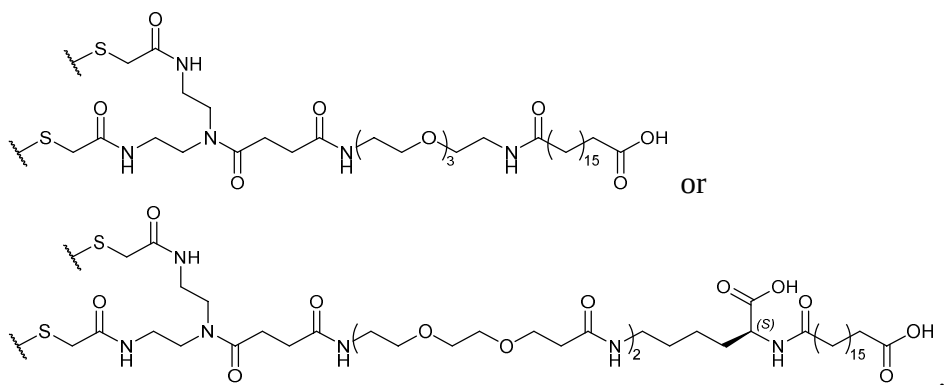
4. The peptide conjugate of claim 3, wherein the half-life of the peptide conjugate is at least 10-fold greater than the half-life of an unmodified form of the peptide.
5. The peptide conjugate of claim 1, wherein the staple is the structure:



6. The peptide conjugate of claim 1, wherein the staple is the structure:

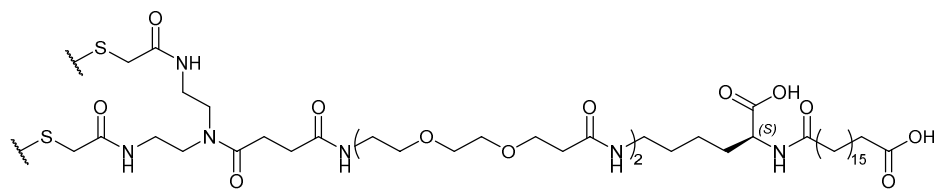


7. A peptide conjugate comprising:
 - a) a peptide comprising any one of SEQ ID NOs: 1-3 and 21-23; and
 - b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure:



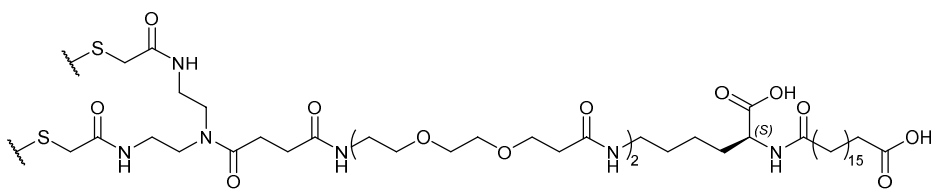
wherein each "S" is a sulfur atom of the first cysteine or the second cysteine.

8. A peptide conjugate comprising:
 - a) a peptide comprising SEQ ID NO: 1; and
 - b) a staple attached to the peptide at the first cysteine of SEQ ID NO: 1 and the second cysteine of SEQ ID NO: 1, wherein the staple has the following structure:



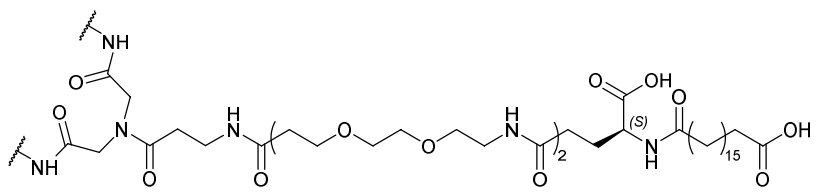
wherein each “S” is a sulfur atom of the first cysteine or the second cysteine.

9. A peptide conjugate comprising:
 - a) a peptide comprising SEQ ID NO: 2 or 22; and
 - b) a staple attached to the peptide at the first cysteine of SEQ ID NO: 2 or 22 and the second cysteine of SEQ ID NO: 2 or 22, wherein the staple has the following structure:



wherein each “S” is a sulfur atom of the first cysteine or the second cysteine.

10. A peptide conjugate comprising:
 - a) a peptide comprising SEQ ID NO: 30 or 10, wherein the amino acid at position 10 is L-Norleucine; and
 - b) a staple attached to the peptide at a first lysine and a second lysine having the following structure:



wherein each “NH” is an amine of the first lysine or the second lysine.

11. A pharmaceutical composition comprising the peptide conjugate of any one of claims 1-10, and a pharmaceutically acceptable excipient.
12. The peptide conjugate of any one of claims 1-10, for use as a medicament in treating a disease or condition in a subject in need thereof.
13. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating diabetes or obesity, or a medical condition associated with diabetes or obesity.
14. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.
15. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating a gastrointestinal (GI) disorder.
16. The use of claim 15, wherein the gastrointestinal (GI) disorder is short bowel syndrome (SBS), inflammatory bowel syndrome (IBS), or inflammatory bowel diseases (IBD).
17. The use of claim 16, wherein the inflammatory bowel diseases (IBD) is Crohn’s disease.
18. The use of claim 16, wherein the inflammatory bowel diseases (IBD) is ulcerative colitis.
19. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for a subject undergoing chemotherapy.
20. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating radiation-induced GI mucositis.
21. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating chemotherapy-induced diarrhea (CID).
22. Use of the peptide conjugate of any one of claims 1-10, in the manufacture of a medicament for treating total parenteral nutrition (TPN) induced intestinal atrophy.