What is claimed:

1. An analog of glucagon (SEQ ID NO: 1), comprising:

   a. an amino acid comprising an imidazole side chain at position 1;

   b. an DPP-IV protective amino acid at position 2, optionally, AIB;

   c. an acylated amino acid or alkylated amino acid at any of positions 9, 10, 12, 16, 20, or 37-43, optionally wherein the acyl or alkyl group is linked to the amino acid via a spacer;

   d. an alpha helix stabilizing amino acid at one or more of positions 16-21, optionally, position 16, wherein the analog does not comprise an alpha helix stabilizing amino acid at position 20; and

   e. up to ten additional amino acid modifications relative to SEQ ID NO: 1;

wherein, when the glucagon analog lacks a hydrophilic moiety, the glucagon analog exhibits a GIP percentage potency of at least 0.1%, wherein the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor.

2. The glucagon analog of claim 1, wherein:

   (A) the analog comprises an alpha helix stabilizing amino acid at position 16, optionally, wherein the alpha helix stabilizing amino acid is a negative charged amino acid or an alpha, alpha disubstituted amino acid, optionally, wherein the negative charged amino acid is Glu, optionally, wherein the α,α-disubstituted amino acid comprises R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring; optionally, wherein the alpha, alpha disubstituted amino acid is AIB

(B) the analog comprises at position 18 a small aliphatic amino acid, optionally, Ala, and an Arg at position 17;

(C) the analog is not modified at position 20 compared to SEQ ID NO: 1; or

(D) or a combination thereof.

3. An analog of glucagon (SEQ ID NO: 1), comprising:

a. an amino acid comprising an imidazole side chain at position 1;

b. an DPP-IV protective amino acid at position 2, optionally, AIB;

c. an acylated amino acid or alkylated amino acid at any of positions 9, 10, 12, 16, 20, or 37-43, optionally wherein the acyl or alkyl group is linked to the amino acid via a spacer;

d. an alpha, alpha disubstituted amino acid at position 20; and

e. up to ten additional amino acid modifications relative to SEQ ID NO: 1;

wherein, when the glucagon analog lacks a hydrophilic moiety, the glucagon analog exhibits a GIP percentage potency of at least 0.1%, wherein the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor.

4. The glucagon analog of claim 3, wherein

(A) the α,α-disubstituted amino acid comprises R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring;

(B) the α,α-disubstituted at position 20 is AIB;

(C) the amino acid at position 16 is an alpha helix stabilizing amino acid other than AIB;

(D) the amino acid at position 16 is a charged amino acid, optionally, a negative charged amino acid or a positive charged amino acid

(E) the charged amino acid is Glu or Lys; or

(F) a combination thereof.

5. The glucagon analog of any of claims 1 to 4, wherein:

(A) the glucagon analog comprises (i) an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29 or (ii) the acylated amino acid or alkylated amino acid is located at position 10, 12, or 16;

(B) the amino acid at position 1 is His or a His derivative;

(C) the amino acid at position 2 is an alpha, alpha disubstituted amino acid;

(D) the amino acid at position 2 is an α,α-disubstituted amino acid comprising R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring;

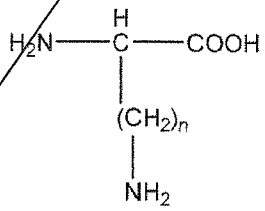
(E) the amino acid at position 2 is AIB;

(F) the glucagon analog comprises an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29; and (i) the amino acid at position 29 is Gly; (ii) the extension comprises an amino acid sequence which forms a Trp cage structure or the extension comprises at least one charged amino acid; (iii) the extension comprises an amino acid sequence

which forms a Trp cage structure and the extension comprises the amino acid sequence of GPSSGAPPPS (SEQ ID NO: 5), or a conservatively substituted sequence thereof (iv) the extension comprises at least one charged amino acid and comprises an amino acid sequence of X1-X2, wherein X1 is a charged amino acid and X2 is a small aliphatic amino acid; optionally, wherein X1 is a positive charged amino acid (e.g., Arg); optionally, wherein the extension comprises Arg-Gly;

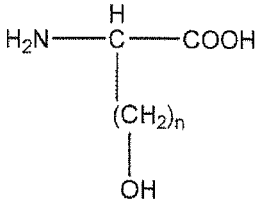
(G) the acylated amino acid or alkylated amino acid is at position 14;

(H) the acyl group or alkyl group is attached to an amino acid comprising a structure of Formula I (optionally, Lys), Formula II (optionally, Cys), or Formula III (optionally, Ser), wherein each of Formulae I, II, and III, is:



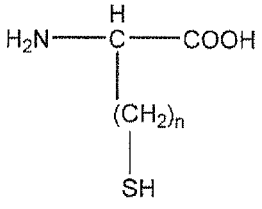
wherein n = 1 to 4

[Formula I];



wherein n = 1 to 4

[Formula II]; and



wherein n = 1 to 4

[Formula III].

or a combination thereof;

(I) the amino acid of the acyl group or alkyl group is attached to amino-Phe or Tyr;

(J) the acyl group or alkyl group is linked to an amino acid via a spacer 3 to 10 atoms in length;

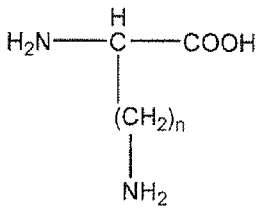
(K) the spacer is an amino acid or dipeptide;

(L) the spacer comprises one or two acidic amino acid residues;

(M) the acylated amino acid or alkylated amino acid is linked to the acyl or alkyl group via a spacer wherein the total length of the spacer and the acyl group is about 14 to about 28 atoms in length;

(N) the acylated amino acid or alkylated amino acid is attached to a C12 to C18 fatty acyl group, optionally, a C14 or C16 fatty acyl group;

(O) the glucagon analog comprises at least one charged amino acid C-terminal to the amino acid at position 27; optionally, wherein the charged amino acid is at position 28, optionally, wherein the charged amino acid is a negative charged amino acid (e.g., Asp); optionally, wherein the charged amino acid is a positive charged amino acid (e.g., an amino acid of Formula I:



wherein n = 1 to 4

[Formula I];

(P) the glucagon analog comprises a Lys at position 28;

(Q) the glucagon analog comprises an amino acid modification at position 27, at position 29, or at both positions 27 and 29;

(R) the glucagon analog comprises Leu, Nle, Val, or Lys at position 27;

(S) the glucagon analog comprseis Gly or Thr at position 29;

(T) the glucagon analog comprises comprising one or more of:

i. a DPP-IV protective amino acid at position 1;

ii. an acidic amino acid, optionally, Glu, at position 3;

iii. an Ile at position 7;

iv. an Ile or Arg at position 12;

v. an acidic amino acid, optionally, Glu, at position 15;

vi. an aliphatic amino acid, optionally, Ala at position 18;

vii. an acidic amino acid, optionally, Glu, at position 21;

viii. an Asn, Ala, or AIB at position 24;

ix. an aliphatic amino acid, optionally, Ala, or Leu, or Nle, at position 27;

x. an acidic amino acid, optionally, Glu, or an aliphatic amino acid, optionally, Ala, at position 28;

xi. an aliphatic amino acid, optionally, Ala, at position 29;

xii. amidation at the C-terminus;

(U) the glucagon analog comprises the amino acid sequence of: (A) any of SEQ ID NOs: 184-199; (B) any of SEQ ID NOs: 28, 29, 31, 37-41,

79, 80, 89, 90, 95, 130, 145-152, 155-167, 171, 176, 177, 180, 203-207, 212, and 230; or (C) any of SEQ ID NOs: 28, 37, 89, 95, 130, 171, and 180; or

(V) or a combination thereof.

6. The glucagon analog of any one of the preceding claims, except for claim 5(A), wherein (i) the amino acid comprising a non-native acyl or alkyl group is located at position 10 or (ii) the glucagon analog comprises an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29 and an acylated amino acid or alkylated amino acid at any of positions 37-43, optionally 40.

7. A peptide comprising the sequence of

(a) SEQ ID NO: 184,

$HX_2X_3GTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}GPSSGX_{35}PPPS$
(SEQ ID NO: 184)

wherein:

X_2 is AIB;

X_3 is Gln or Gln analog;

X_{10} is Tyr or an amino acid covalently attached to a C12 to C18 acyl or alkyl group;

X_{16} is any amino acid, optionally, any amino acid other than Gly, Pro, and Ser;

X_{18} is Arg or Ala;

X_{20} is negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is an acidic amino acid, optionally, Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala or an acidic amino acid (optionally, Asp or Glu);

X_{29} is Ala or Gly;

X_{35} is Ala or a basic amino acid (optionally, Arg or Lys);

wherein, when X_{28} is an acidic amino acid, X_{35} is a basic amino acid;

wherein, when X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and, wherein, optionally, the peptide comprises Gly at position 41,

wherein the C-terminal amino acid of the peptide is amidated;

or

(b) SEQ ID NO: 184 with up to 3 amino acid modifications relative to SEQ ID NO: 184, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor.

8. The peptide of claim 7, wherein:

(A) X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and the peptide optionally comprises Gly at position 41;

or

X_{10} is an amino acid covalently attached to a C12-C18 acyl or alkyl group

(B) X_{20} is Gln, optionally, wherein the amino acid at position 16 is a negative charged amino acid, optionally, wherein the amino acid at position 16 is Glu; optionally, wherein X_{18} is Ala

or

X_{20} is AIB; optionally, wherein X_{16} is any amino acid other than AIB

(C) (i) X_{28} is an acidic amino acid, optionally Asp or Glu, and X_{35} is a basic amino acid, optionally Arg or Lys, (ii) only one of X_{27}, X_{28} and X_{29} is an Ala, (iii) the peptide comprise an amidated Gly at the C-terminus

(D) the up to 3 amino acid modifications are conservative substitutions; or

(E) a combination thereof.

9. A peptide comprising the sequence of

(A) SEQ ID NO: 185,

$HX_2QGTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}GPSSGAPPPS$
(SEQ ID NO: 185)

wherein:

X_2 is AIB;

X_{10} is Tyr or an amino acid covalently attached to a C12 to C18 acyl or alkyl group;

X_{16} is Glu, an alpha, alpha disubstituted amino acid, Lys or

X_{18} is Arg or Ala;

X_{20} is AIB or Gln;

X_{21} is Asp or Glu;

X_{27} is Leu, Nle, or Met;

X_{28} is Ala, Asp or Glu;

X_{29} is Gly of Thr;

and

wherein, when X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and, wherein, optionally, the peptide comprises Gly at position 41,

wherein the C-terminal amino acid of the peptide is amidated;

or

(B) SEQ ID NO: 185 with up to 3 amino acid modifications relative to SEQ ID NO: 185, wherein the peptide exhibits agonist activity at each of the human GIP

receptor, the human GLP-1 receptor and the human glucagon receptor, optionally, wherein the up to 3 amino acid modifications are conservative substitutions

or

(C) SEQ ID NO: 186,

$HX_2X_3GTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}$

(SEQ ID NO: 186)

wherein:

X_2 is AIB;

X_3 is Gln or Gln analog;

X_{10} is Tyr or an amino acid covalently attached to a C10 to C26 acyl or alkyl group;

X_{16} is any amino acid, optionally, any amino acid other than Gly, Pro, and Ser;

X_{18} is Arg or Ala;

X_{20} is a negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is X_{21} is an acidic amino acid, optionally, Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala or an acidic amino acid (optionally, Asp or Glu);

X_{29} is Ala, Gly or Thr; and

wherein the peptide comprises an amino acid covalently attached to a C10 to C26 acyl or alkyl group, optionally, at position 10, and the C-terminal amino acid of the peptide is amidated;

or

(D) SEQ ID NO: 186 with up to 3 amino acid modifications relative to SEQ ID NO: 186, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor; optionally wherein the up to 3 amino acid modifications are conservative substitutions;

or

(E) SEQ ID NO: 187:

$HX_2QGTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}$

(SEQ ID NO: 187)

wherein:

X_2 is AIB;

X_{10} is Tyr or an amino acid covalently attached to a C10 to C26 acyl or alkyl group;

X_{16} is Glu, alpha, alpha-disubstituted amino acid, or Lys;

X_{18} is Arg or Ala;

X_{20} is a negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala, Asp or Glu;

X_{29} is Gly or Thr; and

wherein the peptide comprises an amino acid covalently attached to a C12 to C18 acyl or alkyl group, optionally, at position10, and the C-terminal amino acid of the peptide is amidated;

or

(F) SEQ ID NO: 187 with up to 3 amino acid modifications relative to SEQ ID NO: 187, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor; optionally, wherein the up to 3 amino acid modifications are conservative substitutions

or

(G) SEQ ID NO: 188, or a sequence of SEQ ID NO: 188 with up to 3 amino acid modifications relative to SEQ ID NO: 188, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(H) SEQ ID NO: 189, or a sequence of SEQ ID NO: 189 with up to 3 amino acid modifications relative to SEQ ID NO: 189, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(I) SEQ ID NO: 190, or a sequence of SEQ ID NO: 190 with up to 3 amino acid modifications relative to SEQ ID NO: 190, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(J) SEQ ID NO: 191, or a sequence of SEQ ID NO: 191 with up to 3 amino acid modifications relative to SEQ ID NO: 191, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(K) SEQ ID NO: 192, or a sequence of SEQ ID NO: 192 with up to 3 amino acid modifications relative to SEQ ID NO: 192, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, and optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(L) SEQ ID NO: 193, or a sequence of SEQ ID NO: 193 with up to 3 amino acid modifications relative to SEQ ID NO: 193, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human

GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(M) SEQ ID NO: 194, or a sequence of SEQ ID NO: 194 with up to 3 amino acid modifications relative to SEQ ID NO: 194, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(N) SEQ ID NO: 195, or a sequence of SEQ ID NO: 195 with up to 3 amino acid modifications relative to SEQ ID NO: 195, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor.

10. The peptide of claim 9, part (C) or part (D), comprising SEQ ID NO: 186 or SEQ ID NO: 186 with up to 3 amino acid modifications, relative to SEQ ID NO: 186; wherein:

(A) X_{20} is AIB; optionally, wherein X_{29} is Thr and the peptide does not comprise GPSSGAPPPS (SEQ ID NO: 5); wherein X_{16} is an amino acid other than AIB;

or

X_{20} is Gln; optionally, wherein the amino acid at position 16 is a negative charged amino acid (e.g., Glu); optionally wherein X_{18} is Ala;

(B) X_2 is AIB, X_3 is Gln, X_{10} is an amino acid covalently attached to a C10 to C26 acyl or alkyl group, X_{18} is Arg or Ala, X_{20} is AIB or Gln, X_{21} is Asp or Glu, X_{29} is Gly, and the C-terminal amino acid is amidated, wherein Gly at position 29 is fused to GPSSGAPPPS followed by Lys or Lys-Gly, wherein the Lys is covalently attached to a C10-C26 acyl group; or

(C) or a combination thereof.

11. The peptide of claim 9 part (C) or part (D), or claim 10, excluding wherein (a) X_{20} is AIB, (b) X_{29} is Thr, and (c) the peptide does not comprises SEQ ID NO: 5, wherein the peptide comprises an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29, optionally, wherein the amino acid at position 29 is Gly and/or (i) the extension comprises the amino acid sequence GPSSGAPPPS (SEQ ID NO: 5), or a conservatively substituted sequence thereof, or GPSSGAPPPS (SEQ ID NO: 5) followed by Lys or Lys-Gly, wherein the Lys is covalently attached to an C10 to C26 acyl group or (ii) the extension comprises the sequence X1-X2, wherein X1 is a charged amino acid and X2 is a small aliphatic amino acid, optionally, wherein X1 is a positive charged amino acid (e.g., Arg), optionally wherein the extension comprises or consists of Arg-Gly.

12. The peptide of any one of claims 8 to 11 wherein:

(A) the C12-C18 fatty acyl or alkyl group is a C14 to C16 fatty acyl or alkyl group, optionally attached via a spacer;

(B) the amino acid covalently attached to a C12 to C18 acyl or alkyl group is a Lys or amino-Phe or Tyr or Cys covalently attached to a C12 to C18 acyl or alkyl group;

(C) the spacer is an amino acid or dipeptide, optionally, wherein the spacer comprises one or two acidic amino acid residues;

(D) a combination thereof.

13. A peptide comprising the sequence of SEQ ID NO: 28.

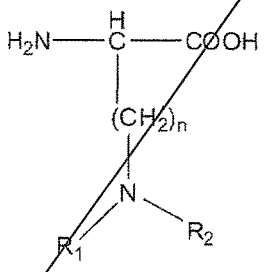
14. A peptide comprising the sequence of SEQ ID NO: 37, SEQ ID NO: 171, or SEQ ID NO: 180.

15. A peptide comprising the sequence of SEQ ID NO: 89.

16. An analog of glucagon (SEQ ID NO: 1) having GIP agonist activity, comprising:

(a) an amino acid comprising an imidazole side chain at position 1,

(b) at position 16, an amino acid of Formula IV:



[Formula IV],

wherein n is 1 to 7, wherein each of R1 and R2 is independently selected from the group consisting of H, C1-C18 alkyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)NH2, (C1-C18 alkyl)SH, (C0-C4 alkyl)(C3-C6)cycloalkyl, (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, and (C1-C4 alkyl)(C3-C9 heteroaryl), wherein R7 is H or OH, wherein optionally the side chain of the amino acid of Formula IV comprises a free amino group,

(c) an α,α-disubstituted amino acid at position 20,

(d) up to ten additional amino acid modifications relative to SEQ ID NO: 1,

wherein, when the analog lacks a hydrophilic moiety, the glucagon analog exhibits at least 0.1% activity of native GIP at the GIP receptor, wherein the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor.

17. The glucagon analog of claim 16, wherein:

(A) the amino acid at position 1 is His or a His derivative;

(B) the amino acid of Formula IV in (b) is homoLys, Lys, Orn, or 2,4-diaminobutyric acid (Dab);

(C) the α,α-disubstituted amino acid comprises R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring; optionally, wherein the α,α-disubstituted amino acid is AIB;

(D) the glucagon analog comprises one or more of:

a. a DPP-IV protective amino acid at position 2; optionally AIB or D-Ser;

b. a large, aliphatic, nonpolar amino acid at position 12, optionally Ile;

c. an amino acid orther than Arg at position 17, optionally Gln;

d. a small aliphatic amino acid at position 18, optionally Ala;

e. an amino acid other than Asp at position 21, optionally Glu;

f. an amino acid other than Gln at position 24, optionally Asn or Ala;

g. an amino acid other than Met at position 27, optionally Leu;

h. an amino acid other than Asn at position 28, optionally Ala;

i. an amino acid other than Thr at position 29, optionally Gly;

j. an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29; and

k. the amino acid sequence set forth as any of SEQ ID NOs: 48, 52, 53, and 74;

(E) or a combination thereof.

18. An analog comprising a parent sequence with a total of up to 3 amino acid modifications relative to the parent sequence, wherein the parent sequence is any of SEQ ID NOs: 27-33, 35-41, 43-46, 76-80, 83-87, 89, 90, 94-100, 102-112, 120-124, and 127-131, or any of SEQ ID NOs: 48, 52, 53, and 74, or any of SEQ ID NOs: 50, 51, 54, 56, 58-60, 62-66, 68-70, 72, 73, 75, 81, 82, 88, 92, 114-119, 125, 126, and 133, wherein the amino acid modifications are selected from the group consisting of:

a DPP-IV protective amino acid at position 2; optionally AIB or D-Ser;

b. a large, aliphatic, nonpolar amino acid at position 12, optionally Ile;

c. an amino acid orther than Arg at position 17, optionally Gln;

d. a small aliphatic amino acid at position 18, optionally Ala;

e. an amino acid other than Asp at position 21, optionally Glu;

f. an amino acid other than Gln at position 24, optionally Asn or Ala;

g. an amino acid other than Met at position 27, optionally Leu;

h. an amino acid other than Asn at position 28, optionally Ala;

i. an amino acid other than Thr at position 29, optionally Gly;

j. an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29; and

k. the amino acid sequence set forth as any of SEQ ID NOs: 48, 52, 53, and 74.

19. The glucagon analog or peptide of any one of the preceding claims, wherein:

(A) the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor;

(B) the EC50 of the glucagon analog at the GIP receptor is within about 50-fold from its EC50 at the GLP-1 receptor;

(C) the EC50 of the glucagon analog at the GIP receptor is within about 40-fold from its EC50 at the GLP-1 receptor;

(D) the EC50 of the glucagon analog at the GIP receptor is within about 30-fold from its EC50 at the GLP-1 receptor;

(E) the EC50 of the glucagon analog at the GIP receptor is within about 20-fold from its EC50 at the GLP-1 receptor;

(F) the EC50 of the glucagon analog at the GIP receptor is within about 10-fold from its EC50 at the GLP-1 receptor;

(G) the EC50 of the glucagon analog at the GIP receptor is within about 5-fold from its EC50 at the GLP-1 receptor;

(H) the glucagon analog exhibits a GIP percentage potency of at least 1%;

(I) the GIP percentage exhibits a GIP percentage potency of at least 10%;

(J) the GIP percentage exhibits a GIP percentage potency of at least 20%;

(K) the GIP percentage exhibits a GIP percentage potency of at least 50%;

(L) the GIP percentage exhibits a GIP percentage potency of at least 100%;

(M) the glucagon analog exhibits a GLP-1 percentage potency of at least 1%;

(N) the glucagon analog exhibits a GLP-1 percentage potency of at least 10%

(O) the glucagon analog exhibits a GLP-1 percentage potency of at least 50%

(P) the glucagon analog exhibits a GLP-1 percentage potency of at least 100%

(Q) the GIP percentage potency is within 10-fold higher or lower than the GLP-1 percentage potency;

(R) the glucagon percentage potency is at least 1%;

(S) the glucagon percentage potency is at least 10%;

(T) the glucagon percentage potency is at least 50%;

(U) the glucagon percentage potency is at least 100%;

(V) the GIP percentage potency is within 10-fold higher or lower than the glucagon percentage potency;

(W) a combination thereof.

20. A dimer or multimer comprising two or more glucagon analogs or peptides of any one of the preceding claims, or a conjugate comprising the glucagon analog or peptide of any one of the preceding claims and a conjugate moiety, optionally, wherein the glucagon analog is fused to a heterologous peptide analog.

21. A pharmaceutical composition comprising a glucagon analog or peptide of any one of claims 1 to 19, a dimer or multimer or conjugate of claim 20, or a combination thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

22. Use of a pharmaceutical composition of claim 21 in the manufacture of a medicament for reducing weight gain or inducing weight loss or for treating obesity.

23. Use of a pharmaceutical composition of claim 21 in the manufacture of a medicament for treating diabetes wherein the medicament is effective to lower blood glucose levels.

What is claimed:

1. An analog of glucagon (SEQ ID NO: 1)comprising:

   a. an amino acid comprising an imidazole side chain at position 1;

   b. an DPP-IV protective amino acid at position 2, optionally, AIB;

   c. an acylated amino acid or alkylated amino acid at any of positions 9, 10, 12, 16, 20, or 37-43, optionally wherein the acyl or alkyl group is linked to the amino acid via a spacer;

   d. an alpha helix stabilizing amino acid at one or more of positions 16-21, optionally, position 16, wherein the analog does not comprise an alpha helix stabilizing amino acid at position 20;

   e. an Arg at position 17 and a small aliphatic amino acid at position 18; and

   f. up to ten additional amino acid modifications relative to SEQ ID NO: 1;

wherein, when the glucagon analog lacks a hydrophilic moiety, the glucagon analog exhibits a GIP percentage potency of at least 0.1%, wherein the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor,

optionally, wherein the analog comprises SEQ ID NO: 184.

2. The glucagon analog of claim 1, wherein:

   (A) the analog comprises an alpha helix stabilizing amino acid at position 16, optionally, wherein the alpha helix stabilizing amino acid is a negative charged amino acid or an alpha, alpha disubstituted amino acid, optionally, wherein the negative charged amino acid is Glu, optionally, wherein the α,α-disubstituted amino acid comprises R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is

independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring; optionally, wherein the alpha, alpha disubstituted amino acid is AIB

(B) the analog is not modified at position 20 compared to SEQ ID NO: 1; or

(C) a combination thereof.

3. The glucagon analog of claim 1 or 2, wherein:

(A) the glucagon analog comprises (i) an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29 or (ii) the acylated amino acid or alkylated amino acid is located at position 10, 12, or 16;

(B) the amino acid at position 1 is His or a His derivative;

(C) the amino acid at position 2 is an alpha, alpha disubstituted amino acid;

(D) the amino acid at position 2 is an α,α-disubstituted amino acid comprising R1 and R2, each of which is bonded to the alpha carbon, wherein each of R1 and R2 is independently selected from the group consisting of C1-C4 alkyl, optionally substituted with a hydroxyl, amide, thiol, halo, or R1 and R2 together with the alpha carbon to which they are attached form a ring;

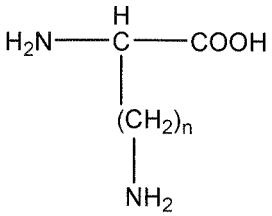
(E) the amino acid at position 2 is AIB;

(F) the glucagon analog comprises an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29; and (i) the amino acid at position 29 is Gly; (ii) the extension comprises an amino acid sequence which forms a Trp cage structure or the extension comprises at least one charged amino acid; (iii) the extension comprises an amino acid sequence

which forms a Trp cage structure and the extension comprises the amino acid sequence of GPSSGAPPPS (SEQ ID NO: 5), or a conservatively substituted sequence thereof (iv) the extension comprises at least one charged amino acid and comprises an amino acid sequence of: X1-X2, wherein X1 is a charged amino acid and X2 is a small aliphatic amino acid; optionally, wherein X1 is a positive charged amino acid; optionally, Arg; optionally, wherein the extension comprises Arg-Gly; (v) or a combination of (i) and (ii) or (iii) or (iv);

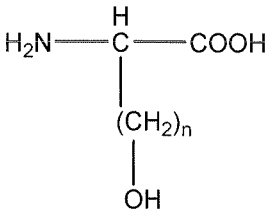
(G) the acylated amino acid or alkylated amino acid is at position 14;

(H) the acyl group or alkyl group is attached to an amino acid comprising a structure of Formula I (optionally, Lys), Formula II (optionally, Cys), or Formula III (optionally, Ser), wherein each of Formulae I, II, and III, is:



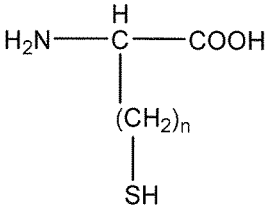
wherein n = 1 to 4

[Formula I];



wherein n = 1 to 4

[Formula II]; and



wherein n = 1 to 4

[Formula III].

or a combination thereof;

(I) the amino acid of the acyl group or alkyl group is attached to amino-Phe or Tyr;

(J) the acyl group or alkyl group is linked to an amino acid via a spacer 3 to 10 atoms in length;

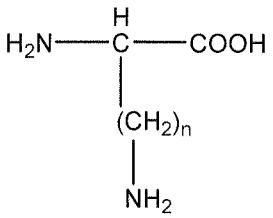
(K) the spacer is an amino acid or dipeptide;

(L) the spacer comprises one or two acidic amino acid residues;

(M) the acylated amino acid or alkylated amino acid is linked to the acyl or alkyl group via a spacer wherein the total length of the spacer and the acyl group is about 14 to about 28 atoms in length;

(N) the acylated amino acid or alkylated amino acid is attached to a C12 to C18 fatty acyl group, optionally, a C14 or C16 fatty acyl group;

(O) the glucagon analog comprises at least one charged amino acid C-terminal to the amino acid at position 27; optionally, wherein the charged amino acid is at position 28, optionally, wherein the charged amino acid is a negative charged amino acid, optionally, Asp; optionally, wherein the charged amino acid is a positive charged amino acid,optionally, an amino acid of Formula I:



wherein n = 1 to 4

[Formula I];

(P) the glucagon analog comprises a Lys at position 28;

(Q) the glucagon analog comprises an amino acid modification at position 27, at position 29, or at both positions 27 and 29;

(R) the glucagon analog comprises Leu, Nle, Val, or Lys at position 27;

(S) the glucagon analog comprseis Gly or Thr at position 29;

(T) the glucagon analog comprises comprising one or more of:

i. a DPP-IV protective amino acid at position 1;

ii. an acidic amino acid, optionally, Glu, at position 3;

iii. an Ile at position 7;

iv. an Ile or Arg at position 12;

v. an acidic amino acid, optionally, Glu, at position 15;

vi. an aliphatic amino acid, optionally, Ala at position 18;

vii. an acidic amino acid, optionally, Glu, at position 21;

viii. an Asn, Ala, or AIB at position 24;

ix. an aliphatic amino acid, optionally, Ala, or Leu, or Nle, at position 27;

x. an acidic amino acid, optionally, Glu, or an aliphatic amino acid, optionally, Ala, at position 28;

xi. an aliphatic amino acid, optionally, Ala, at position 29;

xii. amidation at the C-terminus;

(U) the glucagon analog comprises the amino acid sequence of: (A) any of SEQ ID NOs: 184-199; (B) any of SEQ ID NOs: 28, 29, 31, 37-41, 79, 80, 89, 90, 95, 130, 145-152, 155-167, 171, 176, 177, 180, 203-207, 212, and 230; or (C) any of SEQ ID NOs: 28, 37, 89, 95, 130, 171, and 180; or

(V) a combination thereof.

4. A peptide comprising the sequence of

(a) SEQ ID NO: 184,

$HX_2X_3GTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}GPSSGX_{35}PPPS$

(SEQ ID NO: 184)

wherein:

X_2 is AIB;

X_3 is Gln or Gln analog;

X_{10} is Tyr or an amino acid covalently attached to a C12 to C18 acyl or alkyl group;

X_{16} is any amino acid, optionally, any amino acid other than Gly, Pro, and Ser;

X_{18} is Arg or Ala;

X_{20} is negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is an acidic amino acid, optionally, Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala or an acidic amino acid (optionally, Asp or Glu);

X_{29} is Ala or Gly;

X_{35} is Ala or a basic amino acid (optionally, Arg or Lys);

wherein, when X_{28} is an acidic amino acid, X_{35} is a basic amino acid;

wherein, when X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and, wherein, optionally, the peptide comprises Gly at position 41,

wherein the C-terminal amino acid of the peptide is amidated;

or

(b) SEQ ID NO: 184 with up to 3 amino acid modifications relative to SEQ ID NO: 184, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor,

wherein, optionally:

(A) X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and the peptide optionally comprises Gly at position 41;

or

X_{10} is an amino acid covalently attached to a C12-C18 acyl or alkyl group

(B) X_{20} is Gln, optionally, wherein the amino acid at position 16 is a negative charged amino acid, optionally, wherein the amino acid at position 16 is Glu; optionally, wherein X_{18} is Ala

or

X_{20} is AIB; optionally, wherein X_{16} is any amino acid other than AIB

(C) (i) X_{28} is an acidic amino acid, optionally Asp or Glu, and X_{35} is a basic amino acid, optionally Arg or Lys, (ii) only one of X_{27}, X_{28} and X_{29} is an Ala, (iii) the peptide comprise an amidated Gly at the C-terminus

(D) the up to 3 amino acid modifications are conservative substitutions; or

(E) a combination thereof.

5. A peptide comprising the sequence of

(A) SEQ ID NO: 185,

$HX_2QGTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}GPSSGAPPPS$
(SEQ ID NO: 185)

wherein:

X_2 is AIB;

X_{10} is Tyr or an amino acid covalently attached to a C12 to C18 acyl or alkyl group;

X_{16} is Glu, an alpha, alpha disubstituted amino acid, Lys or

X_{18} is Arg or Ala;

X_{20} is AIB or Gln;

X_{21} is Asp or Glu;

X_{27} is Leu, Nle, or Met;

X_{28} is Ala, Asp or Glu;

X_{29} is Gly of Thr;

and

wherein, when X_{10} is Tyr, the peptide comprises at position 40 an amino acid covalently attached to a C12 to C18 acyl or alkyl group, and, wherein, optionally, the peptide comprises Gly at position 41,

wherein the C-terminal amino acid of the peptide is amidated;

or

(B) SEQ ID NO: 185 with up to 3 amino acid modifications relative to SEQ ID NO: 185, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor, optionally, wherein the up to 3 amino acid modifications are conservative substitutions

or

(C) SEQ ID NO: 186,

$HX_2X_3GTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}$
(SEQ ID NO: 186)

wherein:

X_2 is AIB;

X_3 is Gln or Gln analog;

X_{10} is Tyr or an amino acid covalently attached to a C10 to C26 acyl or alkyl group;

X_{16} is any amino acid, optionally, any amino acid other than Gly, Pro, and Ser;

X_{18} is Arg or Ala;

X_{20} is a negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is X_{21} is an acidic amino acid, optionally, Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala or an acidic amino acid (optionally, Asp or Glu);

X_{29} is Ala, Gly or Thr; and

wherein the peptide comprises an amino acid covalently attached to a C10 to C26 acyl or alkyl group, optionally, at position 10, and the C-terminal amino acid of the peptide is amidated;

or

(D) SEQ ID NO: 186 with up to 3 amino acid modifications relative to SEQ ID NO: 186, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor; optionally wherein the up to 3 amino acid modifications are conservative substitutions;

or

(E) SEQ ID NO: 187:

$HX_2QGTFTSDX_{10}SKYLDX_{16}RX_{18}AX_{20}X_{21}FVQWLX_{27}X_{28}X_{29}$

(SEQ ID NO: 187)

wherein:

X_2 is AIB;

X_{10} is Tyr or an amino acid covalently attached to a C10 to C26 acyl or alkyl group;

X_{16} is Glu, alpha, alpha-disubstituted amino acid, or Lys;

X_{18} is Arg or Ala;

X_{20} is a negative charged amino acid or a charge-neutral amino acid, optionally, AIB or Gln;

X_{21} is Asp or Glu;

X_{27} is Leu, Ala, Nle, or Met;

X_{28} is Ala, Asp or Glu;

X_{29} is Gly or Thr; and

wherein the peptide comprises an amino acid covalently attached to a C12 to C18 acyl or alkyl group, optionally, at position10, and the C-terminal amino acid of the peptide is amidated;

or

(F) SEQ ID NO: 187 with up to 3 amino acid modifications relative to SEQ ID NO: 187, wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor; optionally, wherein the up to 3 amino acid modifications are conservative substitutions

or

(G) SEQ ID NO: 188, or a sequence of SEQ ID NO: 188 with up to 3 amino acid modifications relative to SEQ ID NO: 188, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(H) SEQ ID NO: 189, or a sequence of SEQ ID NO: 189 with up to 3 amino acid modifications relative to SEQ ID NO: 189, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(I) SEQ ID NO: 190, or a sequence of SEQ ID NO: 190 with up to 3 amino acid modifications relative to SEQ ID NO: 190, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(J) SEQ ID NO: 191, or a sequence of SEQ ID NO: 191 with up to 3 amino acid modifications relative to SEQ ID NO: 191, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor

or

(K) SEQ ID NO: 192, or a sequence of SEQ ID NO: 192 with up to 3 amino acid modifications relative to SEQ ID NO: 192, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, and optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(L) SEQ ID NO: 193, or a sequence of SEQ ID NO: 193 with up to 3 amino acid modifications relative to SEQ ID NO: 193, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(M) SEQ ID NO: 194, or a sequence of SEQ ID NO: 194 with up to 3 amino acid modifications relative to SEQ ID NO: 194, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor

or

(N) SEQ ID NO: 195, or a sequence of SEQ ID NO: 195 with up to 3 amino acid modifications relative to SEQ ID NO: 195, wherein the peptide exhibits agonist activity at each of the human GIP receptor and the human GLP-1 receptor, optionally, wherein the peptide exhibits agonist activity at the human glucagon receptor.

6. The peptide of claim 5, part (C) or part (D), comprising SEQ ID NO: 186 or SEQ ID NO: 186 with up to 3 amino acid modifications, relative to SEQ ID NO: 186; wherein:

(A) X_{20} is AIB; optionally, wherein X_{29} is Thr and the peptide does not comprise GPSSGAPPPS (SEQ ID NO: 5); wherein X_{16} is an amino acid other than AIB;

or

X_{20} is Gln; optionally, wherein the amino acid at position 16 is a negative charged amino acid (optionally, Glu); optionally wherein X_{18} is Ala;

(B) X_2 is AIB, X_3 is Gln, X_{10} is an amino acid covalently attached to a C10 to C26 acyl or alkyl group, X_{18} is Arg or Ala, X_{20} is AIB or Gln, X_{21} is Asp or Glu, X_{29} is Gly, and the C-terminal amino acid is amidated, wherein Gly at position 29 is fused to GPSSGAPPPS followed by Lys or Lys-Gly, wherein the Lys is covalently attached to a C10-C26 acyl group; or

(C) or a combination thereof.

7. The peptide of claim 5 part (C) or part (D), or claim 6, excluding wherein (a) X_{20} is AIB, (b) X_{29} is Thr, and (c) the peptide does not comprises SEQ ID NO: 5, wherein the peptide comprises an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29, optionally, wherein the amino acid at position 29 is Gly and/or (i) the extension comprises the amino acid sequence GPSSGAPPPS (SEQ ID NO: 5), or a conservatively substituted sequence thereof, or GPSSGAPPPS (SEQ ID NO: 5) followed by Lys or Lys-Gly, wherein the Lys is covalently attached to an C10 to C26 acyl group or (ii) the extension comprises the sequence X1-X2, wherein X1 is a charged amino acid and X2 is a small aliphatic amino acid, optionally, wherein X1 is a positive charged amino acid (optionally, Arg), optionally wherein the extension comprises or consists of Arg-Gly.

8. The peptide of any one of claims 3 to 7 wherein:

(A) the C12-C18 fatty acyl or alkyl group is a C14 to C16 fatty acyl or alkyl group, optionally attached via a spacer;

(B) the amino acid covalently attached to a C12 to C18 acyl or alkyl group is a Lys or amino-Phe or Tyr or Cys covalently attached to a C12 to C18 acyl or alkyl group;

(C) the spacer is an amino acid or dipeptide, optionally, wherein the spacer comprises one or two acidic amino acid residues; or

(D) a combination thereof.

9. A peptide comprising the sequence of SEQ ID NO: 28, 89, 37, 171 or 180.

10. An analog comprising a parent sequence with a total of 0, 1, 2, or 3 amino acid modifications relative to the parent sequence, wherein the parent sequence is any of SEQ ID NOs: 27, 28, 33, 35-39, 41, 78-80, 83, 84, 87, 89, 90, 94, 95, 97, 98, 100, 102-106, 108, 122-124, 127, 128, 130, 131or any of SEQ ID NOs: 88, wherein the amino acid modifications are selected from the group consisting of:

a DPP-IV protective amino acid at position 2; optionally AIB or D-Ser;

b. a large, aliphatic, nonpolar amino acid at position 12, optionally Ile;

c. an amino acid other than Arg at position 17, optionally Gln;

d. a small aliphatic amino acid at position 18, optionally Ala;

e. an amino acid other than Asp at position 21, optionally Glu;

f. an amino acid other than Gln at position 24, optionally Asn or Ala;

g. an amino acid other than Met at position 27, optionally Leu;

h. an amino acid other than Asn at position 28, optionally Ala;

i. an amino acid other than Thr at position 29, optionally Gly;

j. an extension of 1 to 21 amino acids C-terminal to the amino acid at position 29; and

k. the amino acid sequence set forth as any of SEQ ID NOs: 48, 52, 53, and 74;

wherein the peptide exhibits agonist activity at each of the human GIP receptor, the human GLP-1 receptor and the human glucagon receptor.

11. The glucagon analog or peptide of any one of the preceding claims, wherein:

(A) the glucagon analog has less than 100-fold selectivity for the human GLP-1 receptor versus the GIP receptor;

(B) the EC50 of the glucagon analog at the GIP receptor is within about 50-fold from its EC50 at the GLP-1 receptor;

(C) the EC50 of the glucagon analog at the GIP receptor is within about 40-fold from its EC50 at the GLP-1 receptor;

(D) the EC50 of the glucagon analog at the GIP receptor is within about 30-fold from its EC50 at the GLP-1 receptor;

(E) the EC50 of the glucagon analog at the GIP receptor is within about 20-fold from its EC50 at the GLP-1 receptor;

(F) the EC50 of the glucagon analog at the GIP receptor is within about 10-fold from its EC50 at the GLP-1 receptor;

(G) the EC50 of the glucagon analog at the GIP receptor is within about 5-fold from its EC50 at the GLP-1 receptor;

(H) the glucagon analog exhibits a GIP percentage potency of at least 1%;

(I) the GIP percentage exhibits a GIP percentage potency of at least 10%;

(J) the GIP percentage exhibits a GIP percentage potency of at least 20%;

(K) the GIP percentage exhibits a GIP percentage potency of at least 50%;

(L) the GIP percentage exhibits a GIP percentage potency of at least 100%;

(M) the glucagon analog exhibits a GLP-1 percentage potency of at least 1%;

(N) the glucagon analog exhibits a GLP-1 percentage potency of at least 10%

(O) the glucagon analog exhibits a GLP-1 percentage potency of at least 50%

(P) the glucagon analog exhibits a GLP-1 percentage potency of at least 100%

(Q) the GIP percentage potency is within 10-fold higher or lower than the GLP-1 percentage potency;

(R) the glucagon percentage potency is at least 1%;

(S) the glucagon percentage potency is at least 10%;

(T) the glucagon percentage potency is at least 50%;

(U) the glucagon percentage potency is at least 100%;

(V) the GIP percentage potency is within 10-fold higher or lower than the glucagon percentage potency; or

(W) a combination thereof.

12. A dimer or multimer comprising two or more glucagon analogs or peptides of any one of the preceding claims, or a conjugate comprising the glucagon analog or peptide of any one of the preceding claims and a conjugate moiety, optionally, wherein the glucagon analog is fused to a heterologous peptide analog.

13. A pharmaceutical composition comprising a glucagon analog or peptide of any one of claims 1 to 11, a dimer or multimer or conjugate of claim 12, or a combination thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

14. Use of a pharmaceutical composition of claim 13 in the manufacture of a medicament for reducing weight gain or inducing weight loss in a subject in need thereof, wherein the use comprises that the medicament is to be administered to a patient in need thereof in an amount effective to reduce weight gain or induce weight loss, optionally, wherein the amount effective to treat obesity in the subject in need thereof.

15. Use of a pharmaceutical composition of claim 13 in the manufacture of a medicament for use in treating diabetes, wherein the use comprises that the medicament is to be administered to a patient in need thereof in an amount effective to lower blood glucose levels.