

CLAIMS

~~What is claimed is:~~

1. An isolated polypeptide, comprising the amino acid sequence of SEQ ID NO: 80:
X₁SHGTFTSX₉YSKYLX₁₅X₁₆X₁₇X₁₈AX₂₀X₂₁FX₂₃X₂₄WX₂₆EX₂₈E-Z-tail-(OH/NH₂) (SEQ ID NO: 80), or a pharmaceutically acceptable salt thereof, wherein:
 - X₁ is Y or acetyl-Y;
 - X₉ is D or E;
 - X₁₅ is D, E, or K;
 - X₁₆ is Aib or K;
 - X₁₇ is K;
 - X₁₈ is K, R, or Y;
 - X₂₀ is E, K, Q, or S;
 - X₂₁ is E or K;
 - X₂₃ is Aib or V;
 - X₂₄ is Aib, E, K, Q, or S;
 - X₂₆ is E, L, or Q;
 - X₂₈ is D, E, K, N, Q, S, or N-methylglutamate;
 - Z-tail is absent or selected from the group consisting of PSSGAPPPS (SEQ ID NO: 90), PSSGEPPPS (SEQ ID NO: 91), PSSGKPPPS (SEQ ID NO: 92), or PSSGSPPPS (SEQ ID NO: 93);
 - wherein when X₁₅, X₁₆, X₁₇, X₁₈, X₂₀, or X₂₁ are K, the lysine residue is optionally covalently bound to a lipophilic substituent, optionally via a spacer,
 - provided that the polypeptide comprises at least one residue covalently bound to a lipophilic substituent, optionally via a spacer; and
 - wherein the isolated polypeptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and an aspartic acid or between the side chains of a lysine and a glutamic acid, wherein the residues that form the lactam bridge are located at positions X₂₀ and X₂₄ or at positions X₂₄ and X₂₈.

2. ~~An~~The isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO: 81:

X₁SHGTFTSDYSKYLX₁₅X₁₆X₁₇X₁₈AX₂₀X₂₁FX₂₃X₂₄WLEX₂₈E-Z-tail-(OH/NH₂) (SEQ ID NO: 81), or a pharmaceutically acceptable salt thereof, wherein:

X₁ is Y or acetyl-Y;

X₁₅ is D or K;

X₁₆ is Aib or K;

X₁₇ is K;

X₁₈ is K or Y;

X₂₀ is E, K, Q, or S;

X₂₁ is E or K;

X₂₃ is Aib or V;

X₂₄ is Aib, E, K, Q, or S;

X₂₈ is D, E, K, N, Q, S, or N-methylglutamate;

Z-tail is absent or selected from the group consisting of PSSGAPPPS (SEQ ID NO: 90), PSSGEPPPS (SEQ ID NO: 91), PSSGKPPPS (SEQ ID NO: 92), or PSSGSPPPS (SEQ ID NO: 93);

wherein when X₁₅, X₁₆, X₁₇, X₁₈, X₂₀, or X₂₁ are K, the lysine residue is optionally covalently bound to a lipophilic substituent, optionally via a spacer,

provided that the polypeptide comprises at least one residue covalently bound to a lipophilic substituent, optionally via a spacer; and

wherein the isolated polypeptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and an aspartic acid or between the side chains of a lysine and a glutamic acid, wherein the residues that form the lactam bridge are located at positions X₂₀ and X₂₄ or at positions X₂₄ and X₂₈.

3. ~~An~~The isolated polypeptide of claim 2, comprising the amino acid sequence of SEQ ID NO: 82:

X₁SHGTFTSDYSKYLDX₁₆X₁₇YAX₂₀X₂₁FX₂₃X₂₄WLEX₂₈E-Z-tail-(OH/NH₂) (SEQ ID NO: 82), or a pharmaceutically acceptable salt thereof, wherein:

X₁ is Y or acetyl-Y;

X₁₆ is Aib or K;

X₁₇ is K;

X₂₀ is E, K, Q, or S;

X₂₁ is E or K;

X₂₃ is Aib or V;

X₂₄ is Aib, E, K, Q, or S;

X₂₈ is D, E, K, N, Q, S, or N-methylglutamate;

Z-tail is absent or selected from the group consisting of PSSGAPPPS (SEQ ID NO: 90), PSSGEPPPS (SEQ ID NO: 91), PSSGKPPPS (SEQ ID NO: 92), or PSSGSPPPS (SEQ ID NO: 93);

wherein when X₁₆, X₁₇, or X₂₁ are K, the lysine residue is optionally covalently bound to a lipophilic substituent, optionally via a spacer,

provided that the polypeptide comprises at least one residue covalently bound to a lipophilic substituent, optionally via a spacer; and

wherein the isolated polypeptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and an aspartic acid or between the side chains of a lysine and a glutamic acid, wherein the residues that form the lactam bridge are located at positions X₂₀ and X₂₄ or at positions X₂₄ and X₂₈.

4. The isolated polypeptide of claim 1 or claim 2, wherein one of X₁₆, X₁₇, or X₂₁ is lysine bound to a lipophilic substituent, optionally via a spacer.

5. The isolated polypeptide of any one of claims 1-3, wherein when X₂₀ is Q, X₁₆ is K, wherein the lysine at residue X₁₆ is covalently bound to a lipophilic substituent, optionally via a spacer; or

X₂₁ is K, wherein the lysine residue at X₂₁ is optionally covalently bound to a lipophilic substituent, optionally via a spacer.

6. The isolated polypeptide of any one of claims 1-3, wherein when X₂₀ is Q, X₂₁ is K, wherein the lysine residue at X₂₁ is optionally covalently bound to a lipophilic substituent, optionally via a spacer.

7. The isolated polypeptide of any one of claims 1-3, wherein when X₂₁ is E, X₂₀ is E, K, or S.
8. The isolated polypeptide of any one of claims 1-3, wherein X₁₆ is Aib or K covalently bound to a lipophilic substituent, optionally via a spacer.
9. The isolated polypeptide of any one of claims 1-3, wherein X₂₄ is Aib or K.
10. The isolated polypeptide of any one of claims 1-3, wherein X₂₈ is D or S.

~~11. The isolated polypeptide of any one of claims 1-3, wherein the lipophilic substituent forms an amide bond between an amino group of the isolated polypeptide and the CO group of the lipophilic substituent.~~

~~12. The isolated polypeptide of claim 11, wherein the lipophilic substituent is of Formula I:~~



Formula I

~~wherein~~

~~Z is CH₃ or CO₂H; and~~

~~m is from 4 to 24.~~

~~13. The isolated polypeptide of claim 12, wherein Z is CO₂H.~~

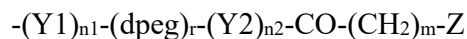
~~14. The isolated polypeptide of claim 12, wherein m is from 14 to 20.~~

~~15. The isolated polypeptide of claim 12, wherein m is 16, 17, or 18.~~

~~16~~11. The isolated polypeptide of any one of claims 1-3, wherein the lipophilic substituent is covalently bound to the isolated polypeptide via a spacer.

~~17. The isolated polypeptide of claim 16, wherein the lipophilic substituent, $\text{CO}-(\text{CH}_2)_m\text{-Z}$, is linked to an amino group of the isolated polypeptide via the spacer, wherein the spacer forms a bridge between the amino group of the isolated polypeptide and the CO group of the lipophilic substituent.~~

~~1812.~~ The isolated polypeptide of claim ~~1611~~, wherein the lipophilic substituent and spacer are of Formula IV:



Formula IV

wherein

Z is $-\text{CH}_3$ or $-\text{CO}_2\text{H}$;

m is from 4 to 24;

Y1 is selected from the group consisting of γGlu , Asp, and Gly;

Y2 is selected from the group consisting of γGlu , Asp, and Gly;

dpeg is $-\text{[CO(CH}_2\text{)O(CH}_2\text{)}_2\text{O(CH}_2\text{)NH]-}$;

r is from 1 to 8;

n1 is from 0 to 10; and

n2 is from 0 to 10.

~~19. The isolated polypeptide of claim 18, wherein Z is CO_2H .~~

~~20. The isolated polypeptide of claim 18, wherein m is from 14 to 20.~~

~~21. The isolated polypeptide of claim 18, wherein m is 16, 17, or 18~~

~~22. The isolated polypeptide of claim 18, wherein Y1 is γGlu .~~

~~23. The isolated polypeptide of claim 18, wherein n1 is 2.~~

~~24. The isolated polypeptide of claim 18, wherein n2 is 0.~~

~~25. The isolated polypeptide of claim 18, wherein r is 1.~~

~~26~~13. An isolated polypeptide comprising the amino acid sequence of any of SEQ ID NOs: 1 to 60, or a pharmaceutically acceptable salt thereof.

~~27~~14. The isolated polypeptide of claim ~~26~~13, comprising the amino acid sequence of any of SEQ ID NOs: 1 to 39, or a pharmaceutically acceptable salt thereof.

~~28~~15. The isolated polypeptide of claim ~~27~~14 comprising the amino acid sequence of SEQ ID NO: 3, or a pharmaceutically acceptable salt thereof.

~~29~~16. The isolated polypeptide of claim ~~27~~14 comprising the amino acid sequence of SEQ ID NO: 6, or a pharmaceutically acceptable salt thereof.

~~30~~17. The isolated polypeptide of claim ~~27~~14 comprising the amino acid sequence of SEQ ID NO: 21, or a pharmaceutically acceptable salt thereof.

~~31~~18. The isolated polypeptide of claim ~~27~~14 comprising the amino acid sequence of SEQ ID NO: 24, or a pharmaceutically acceptable salt thereof.

~~32~~19. A pharmaceutical composition comprising the isolated polypeptide of any one of claims 1-~~3~~
~~or 26-31~~18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

~~33~~20. A pharmaceutical combination comprising the isolated polypeptide of any one of claims 1-~~3~~
~~or 26-31~~18, or a pharmaceutically acceptable salt thereof, and a GLP-1 receptor agonist.

~~34~~21. An osmotic delivery device, comprising the isolated polypeptide of any one of claims 1-~~3~~
~~18 or 26-31~~18.

35. ~~The osmotic delivery device of claim 34, comprising~~
~~an impermeable reservoir comprising interior and exterior surfaces and first and~~
~~second open ends;~~
~~— a semi permeable membrane in sealing relationship with the first open end of the~~
~~reservoir;~~
~~— an osmotic engine within the reservoir and adjacent the semi permeable membrane;~~
~~— a piston adjacent the osmotic engine, wherein the piston forms a movable seal with~~
~~the interior surface of the reservoir, the piston divides the reservoir into a first chamber and a~~
~~second chamber, the first chamber comprising the osmotic engine;~~
~~— a suspension formulation, wherein the second chamber comprises the suspension~~
~~formulation and the suspension formulation is flowable and comprises the isolated~~
~~polypeptide; and~~
~~— a diffusion moderator inserted in the second open end of the reservoir, the diffusion~~
~~moderator adjacent the suspension formulation.~~

3622. ~~A method of treating obesity in a human subject, providing weight loss to the human subject,~~
~~or suppressing appetite in the human subject, comprising administering to the subject~~ Use of a
~~pharmaceutical composition comprising the isolated polypeptide of any one of claims 1-3 or 26-31~~ 18
~~in the preparation of a medicament for treating obesity in a human subject, providing weight loss to~~
~~the human subject, or suppressing appetite in the human subject.~~

3723. ~~A method of treating diabetes in a human subject, comprising administering to the subject~~ Use
~~of a pharmaceutical composition comprising the isolated polypeptide of any one of claims 1-3 or 26-~~
~~31~~ 18 in the preparation of a medicament for treating diabetes in a human subject.

38. ~~The method of claim 37, wherein the diabetes is type 1 diabetes.~~

39. ~~The method of claim 37 wherein the diabetes is type 2 diabetes.~~

4024. ~~A method of treating nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic~~
~~steatohepatitis (NASH) in a human subject, comprising administering to the subject~~ Use of a

pharmaceutical composition comprising the isolated polypeptide of any one of claims 1-3 or 26-31 18
in the preparation of a medicament for treating nonalcoholic fatty liver disease (NAFLD) and/or
nonalcoholic steatohepatitis (NASH) in a human subject.

25. A pharmaceutical composition comprising the isolated polypeptide of any of claims 1-18, or
a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or
vehicle, wherein the pharmaceutical composition is formulated for injection.

26. A pharmaceutical composition comprising the isolated polypeptide of any of claims 1-18, or
a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or
vehicle, wherein the pharmaceutical composition is formulated for oral administration.

27. The use of any one of claims 22-24, wherein the pharmaceutical composition is to be
administered to the subject via injection, via oral administration, or via an osmotic delivery device.