has potent insulinotropic activity and promotes weight loss such that it can be used for the treatment of non-insulin dependent diabetes and/or obesity.

OXM peptides with amino acid substitutions to improve stability and with additional modifications to slow clearance, such as PEGylation or lipidation are disclosed in WO 2008101017, WO2006134340, WO2007100535, and Pocai et al. *Diabetes* 58:2258-2266, 2009. While these OXM-derived peptides may represent a potential improvement over the wild type peptide, the doses required to achieve a sizable weight reduction in a diet-induced obese (DIO) mouse model are typically higher than may be considered feasible for pharmaceutical commercialization. For example, Pocai *et al* (2009) reported an average 11 g (~25 %) weight loss after 13 days of dosing with 1900 nmol/kg (~8 mg/kg) every other day (QOD).

Despite the availability of various OXM peptides and analogues thereof, there is still a need for more potent, stable, long-acting, and well-tolerated OXM peptide analogues having a ratio of GcgR/GLP-1R activity which has been optimized such that the potency and insulinotropic activity of the peptide provides effective treatments for diabetes, preferably type 2 diabetes and related disorders. It is also desirable to provide OXM peptide analogues thereof which provide effective treatments to reduce body weight. Accordingly, the present invention seeks to provide effective treatments for diabetes and/or obesity.

The present ~~invention~~disclosure comprises an OXM peptide analogue with amino acid substitutions introduced to optimize metabolic stability and modulate the relative GcgR/GLP-1R activities while optimizing overall potency. In addition, the OXM peptide analogue of the present ~~invention~~disclosure is PEGylated at selected positions for enhancement of time action thereby allowing for less frequent dosing.

In a first aspect, t~~T~~he present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue comprising the amino acid sequence:

1 5 10

His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-

15 20 25

Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-

30 35

(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala-Xaa_{38}-Xaa_{39} (SEQ ID NO: 5)

wherein Xaa_{38} is Cys, Cys-PEG, or is absent, Xaa_{39} is Cys, Cys-PEG, or is absent, and wherein the C-terminal amino acid is optionally amidated.

The present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue comprising the amino acid sequence:

```
1                5                  10
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-
      15                  20                  25
Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-
        30                  35
(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala (SEQ ID NO: 1).
```

Furthermore, the present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue comprising the amino acid sequence:

```
1                5                  10
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-
      15                  20                  25
Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-
        30                  35
(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala-Cys-Cys (SEQ ID NO: 2)
```

wherein the Cys at position 38 is optionally PEGylated, and wherein the Cys present at position 39 is optionally PEGylated and the carboxyl group of the Cys at position 39 is optionally amidated.

Preferably, the Oxyntomodulin peptide analogue of SEQ ID NO: 2 is PEGylated on either the Cys at position 38 or the Cys at position 39 or both with a 40 kDa PEG molecule covalently linked to the thiol group of the Cys residue at these positions. More preferably the Oxyntomodulin peptide analogue is PEGylated on each Cys residue at both position 38 and position 39 with a 20 kDa PEG molecule covalently linked to each thiol group of each Cys residue at these positions. Optionally, the Cys residue at position 39 may be absent from SEQ ID NO: 2, leaving a single site for PEGylation at position 38.

The more preferred Oxyntomodulin peptide analogue comprises the amino acid sequence:

```
1                5                  10
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-
```

15 20 25

Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-

30 35

(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala-Cys(20kDa PEG)-

Cys(20kDa PEG) (SEQ ID NO: 3)

wherein the carboxyl group of the PEGylated Cys at position 39 is optionally amidated.

The most preferred Oxyntomodulin peptide analogue comprises the amino acid sequence of SEQ ID NO: 3, wherein the carboxyl group of the PEGylated Cys at position 39 is amidated.

The PEG molecule used in the present ~~invention~~disclosure may be linear or branched and is preferably a linear PEG molecule.

In a second aspect, t~~T~~he present ~~invention~~disclosure provides a pharmaceutical composition comprising the Oxyntomodulin peptide analogue as defined above, and a pharmaceutically acceptable carrier, diluent, or excipient. In a third aspect~~Additionally~~, the present ~~invention~~disclosure provides a pharmaceutical composition comprising the Oxyntomodulin peptide analogue as defined above, together with a pharmaceutically acceptable carrier, diluent, or excipient and optionally other therapeutic ingredients.

Furthermore, the present ~~invention~~disclosure provides a method of treating non-insulin-dependent (type 2) diabetes in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of an Oxyntomodulin peptide analogue as defined above.

Additionally, the present ~~invention~~disclosure provides a method of treating insulin-dependent (type 1) diabetes in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of an Oxyntomodulin peptide analogue as defined above.

The present ~~invention~~disclosure includes a method of treating obesity in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of an Oxyntomodulin peptide analogue as defined above.

Furthermore, the present ~~invention~~disclosure includes a method of treating non-insulin-dependent diabetes and obesity in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of an Oxyntomodulin peptide analogue as defined above.

The present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue as defined above for use as a medicament.

Additionally, the present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue as defined above for use in the treatment of non-insulin-dependent diabetes.

Furthermore, the present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue as defined above for use in the treatment of insulin-dependent diabetes.

Furthermore, the present ~~invention~~disclosure provides an Oxyntomodulin peptide analogue as defined above for use in the treatment of obesity.

The present ~~invention~~disclosure includes an Oxyntomodulin peptide analogue as defined above for use in the treatment of non-insulin-dependent diabetes and obesity.

In a fourth aspect, t~~T~~he present ~~invention~~disclosure provides the use of an Oxyntomodulin peptide analogue as defined above in the manufacture of a medicament for treating~~the treatment of~~ non-insulin-dependent diabetes.

Additionally, the present ~~invention~~disclosure includes the use of an Oxyntomodulin peptide analogue as defined above in the manufacture of a medicament for the treatment of insulin-dependent diabetes.

In a fifth aspect~~Furthermore~~, the present ~~invention~~disclosure provides the use of an Oxyntomodulin peptide analogue as defined above in the manufacture of a medicament for treating~~the treatment of~~ obesity.

In a sixth aspect~~Furthermore~~, the present ~~invention~~disclosure provides the use of an Oxyntomodulin peptide analogue as defined above in the manufacture of a medicament for treating~~the treatment of~~ non-insulin-dependent diabetes or~~and~~ obesity.

The OXM peptide analogues of the present invention effectively bind to and activate both the GLP-1 receptor (GLP-1R) and glucagon receptor (GcgR).

It has also been found that the OXM peptide analogues of the present invention are more resistant to degradation by peptidases, in particular dipeptidyl peptidase IV than native human OXM. As a result, the OXM peptide analogues of the present invention possess improved *in vivo* stability versus native human OXM.

Various embodiments according to the present invention are capable of causing a reduction in food intake in overweight and obese subjects.

A particular advantage of the present invention is that the frequency of side-effects, such as nausea, which is commonly associated with GLP-1 based therapy, such as

WE CLAIM:

1. An Oxyntomodulin peptide analogue comprising the amino acid sequence:
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala- Xaa_{38}-Xaa_{39} (SEQ ID NO: 5)
wherein Xaa_{38} is Cys, Cys-PEG, or is absent; Xaa_{39} is Cys, Cys-PEG, or is absent; and wherein the C-terminal amino acid is optionally amidated.

2. An Oxyntomodulin peptide analogue according to Claim 1, comprising the amino acid sequence:
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala-Cys-Cys (SEQ ID NO: 2)
wherein the Cys residue at position 38 is optionally PEGylated; and wherein the Cys residue at position 39 is optionally PEGylated; and the carboxyl group of the Cys at position 39 is optionally amidated.

3. The Oxyntomodulin peptide analogue according to Claim 2, wherein the analogue is PEGylated on the thiol of the Cys residue at either position 38 or position 39 with an approximately 40 kDa PEG molecule.

4. The Oxyntomodulin peptide analogue according to either Claim 1 or 2, wherein the analogue is PEGylated on the thiol of both Cys residues at positions 38 and 39 with an approximately 20 kDa PEG molecule in each case and comprises the amino acid sequence:
His-(D-Ser)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-(1-Nal)-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Ala-Ala-Gln-Glu-Phe-Val-Gln-Trp-Leu-Leu-Asn-(Aib)-Ala-Arg-Asn-Arg-Asn-Asn-Ile-Ala-Cys(PEG20k)-Cys(PEG20k) (SEQ ID NO: 3)
wherein the carboxyl group of the Cys residue at position 39 is optionally amidated.

5. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 4, wherein the PEG molecule is linear.

6. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 5, wherein the carboxyl group of the Cys residue at position 39 is amidated.

7. The Oxyntomodulin peptide analogue according to Claim 1, wherein the Cys residue at position 39 is absent, and the Cys residue at position 38 is PEGylated with an approximately 40 kDa PEG molecule and is optionally amidated.

8. A pharmaceutical composition comprising the Oxyntomodulin peptide analogue of any one of Claims 1 to 7, and a pharmaceutically acceptable carrier, diluent, or excipient.

9. A pharmaceutical composition comprising the Oxyntomodulin peptide analogue of any one of Claims 1 to 7, together with a pharmaceutically acceptable carrier, diluent, or excipient and optionally other therapeutic ingredients.

10. Use of an Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 in the manufacture of a medicament for treating non-insulin-dependent diabetes.

11. Use of an Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 in the manufacture of a medicament for treating obesity.

12. Use of an Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 in the manufacture of a medicament for treating non-insulin-dependent diabetes or obesity.

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13. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 for use as a medicament.

14. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 for use in the treatment of non-insulin-dependent diabetes.

15. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 for use in the treatment of obesity.

16. The Oxyntomodulin peptide analogue according to any one of Claims 1 to 7 for use in the treatment of non-insulin-dependent diabetes or obesity.